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Improvement of Smoking Abstinence Rates with increased Varenicline Dosage: A Propensity Score Matched Analysis

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Abstract

Purpose/Background—It is unclear whether increasing the dose of varenicline beyond the standard dose of 2 mg/day would improve smoking abstinence.

Methods/Procedures—We examined the effect of 3 mg/day of varenicline on smoking abstinence among smokers who had reduced their smoking by 50% or more in response to 2 mg/day for at least 6 weeks but had not quit smoking. Of 2833 patients treated with varenicline, a subset of 73 smokers were increased to 3 mg/day after 6 weeks. We used a propensity score analysis involving multiple baseline covariates to create a comparative sample of 356 smokers who remained on 2 mg/day. All smokers received concurrent and similar smoking-cessation counseling.

Findings/Results—At 3 months, we found higher 7-day PPA rate in the 3-mg group (26%) than in the 2-mg group (11.5%; $\chi^2=10.60$; $p<0.001$; Risk Ratio (RR)= 2.3 [95% confidence interval, 1.4–3.6]). The difference in abstinence rates remained significant at the 6 months ($p<0.001$; RR= 2.6 [95% confidence interval, 1.6–3.9]) and 9 months follow-up ($p<0.001$; RR= 2.2 [95% confidence interval, 1.4–3.3]).

Implications/Conclusions—We conclude that a relatively small increase in the daily dose of varenicline seems to offer a benefit for those who are not able to achieve total abstinence after ~6 weeks of 2 mg/day.

Keywords

Varenicline; 3 mg; high dose; smoking abstinence; cancer

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INTRODUCTION

Varenicline has been shown to improve smoking cessation in comparison to both bupropion (Odds Ratio, ~2:1)^{1,2} and nicotine replacement therapy (Odds Ratio, ~1.7:1).³ However, even with an effective treatment such as varenicline, 55%–60% of individuals would still fail to achieve abstinence from smoking at the end of treatment.⁴ Initial concerns that varenicline increases the risk for developing neuropsychiatric side effects have not been substantiated in retrospective⁵ and prospective studies;^{6–8} further confirmed in the recently published EAGLES Study, the largest (n=8,000) prospective placebo-controlled smoking-cessation study to date.⁹ These studies have reassured patients and providers regarding the safety profile of varenicline and have encouraged researchers to explore novel ways of maximizing its effectiveness, including combining it with other medications¹⁰ or using it in higher doses.¹¹

Varenicline a novel and selective alpha4-beta2 nicotinic acetylcholine receptor partial agonist was developed for smoking cessation and recommended to be used in divided dosage of 1 mg twice per day, to minimize side effects (e.g. nausea);¹² although it is almost entirely excreted in the kidney with a half-life is 24 hours.¹³ Craving reduction have been associated with increased varenicline concentrations presumably with higher receptor occupancy even in single dose administration,¹⁴ but no studies have examined that effect after weeks of higher dose intake. Patients who fail to quit smoking following medication treatment may be categorized as either (a) favorable responders (i.e., those who had a favorable, albeit incomplete, treatment response by reducing their cigarettes/day [CPD] by half or more) but not quitting, or (b) nonresponders (i.e., those who failed to respond at all or have achieved a smaller reduction in CPD).¹⁵ Two prior studies evaluated increased varenicline doses beyond 2 mg/day but produced conflicting results. The first was a retrospective case series study that showed increasing varenicline from 2 mg/day to 3 mg/day resulted in a 50% increase in abstinence rate among 52 smokers who were “favorable responders” but had not quit after 8 weeks of 2 mg/day varenicline.¹¹ The second study was a randomized placebo-controlled trial involving 200 smokers initially treated for 2 weeks with 2 mg/day of varenicline, who were “nonresponders” as they did not quit and did not reduce smoking by half or more at 2 weeks. They were then randomized to varenicline 3 mg/day or varenicline 2 mg plus a placebo pill as a control. In this study no significant improvement in smoking-abstinence rates was found by increasing the dose beyond 2 mg/day.¹⁶

The equivocal findings of these two studies suggest that further research was needed to determine whether increasing varenicline dosage to 3 mg/day would convey further benefit and whether this increase would benefit a specific group of non-quitters (favorable responders). Here, we conducted an naturalistic and observational study of smokers enrolled in a comprehensive tobacco treatment program at a large cancer center, to evaluate whether increasing varenicline dosage improves abstinence rates among non-quitters who had an initial favorable response. We hypothesized that patients who had a favorable response (i.e., reduced their CPD by half (50%) or more on 2 mg/day of varenicline) would have a higher smoking-cessation rate with an increase to 3 mg/day than those who continued to receive 2 mg/day beyond the initial 6 weeks. We also examined adverse events and explored other

baseline variables that can affect patients' smoking cessation as possible predictors of abstinence outcome.

METHODS

Participants

Of 2833 patients treated with varenicline, our analytic sample included cancer patients and survivors (n=429) who participated in the Tobacco Treatment Program (TTP) at The University of Texas MD Anderson Cancer Center (Houston, TX) from September 2006 through April 2015 who were initially prescribed 2 mg/day of varenicline (Figure 1). On the basis of previously observed clinical success in our practice, we began systematically offering to increase the patients' varenicline dose from 2 mg/day to 3 mg/day if they tolerated the medication and had an initial favorable response (reduced CPD by 50% or more from baseline), but were unable to achieve total abstinence. Based on patients' preference after offering them the option to increase to 3 mg/day, the varenicline dose was either increased to 3 mg/day (3-mg group, n=73) or maintained at 2 mg/day (2-mg group, n=356) for a minimum of an additional 4 weeks. Patients who chose to stay on 2-mg (e.g. some felt they were making progress and want to continue on same dose, others wanted to make an extra behavioral effort and did not want to rely solely on the medication) received a 1-mg tablet twice per day. Patients who agreed to increase to 3-mg received three tablets per day (two tablets of 1 mg in the morning and one tablet of 1 mg in the evening or vice versa, depending on patients' preference).

To reach our analytic sample of n=429 (356+73), we started from a total of 2833 patients in our program were prescribed 2 mg/day of varenicline. We excluded 1280 who took 2 mg/day of varenicline for less than 6 weeks. Of the remaining 1553, 115 were prescribed 3 mg/day and 1438 stayed on 2 mg/day. Among the 1438 that remained on 2 mg/day, 482 were excluded for taking varenicline for more than one episode of care as such there was a gap in their medication in between both episodes, which left 956 patients who were receiving their first treatment of 2 mg/day. We further excluded 91 patients due to lack of baseline assessment data from their initial visit. Of the remaining 865 patients (in 2-mg group), 509 (approximately 60%) had quit smoking at 6 weeks; leaving 356 patients who did not quit but stayed on 2 mg/day and they became our comparator sample. We retrospectively identified 115 patients who had agreed to increase their dose to 3 mg/day; of those we excluded 34 as there was no confirmation of them effectively increasing their dose, and eight patients because they had quit smoking right before the increase to 3 mg (the reason for their dose increase was due to high cravings and fear of relapse) or had taken 3 mg for less than 1 week, leaving 73 smokers at the 3 mg/day dose eligible for analysis (Figure 1). Among all our patients, 43% did not have cancer, while the most common cancer diagnoses were lung and hematologic-oncologic ones. Note, that this is a retrospective analysis of data collected from a comprehensive tobacco treatment program.

The MD Anderson Institutional Review Board had approved a 15-year repository of clinical data to be collected through our program for quality improvement and future dissemination of pertinent findings. The requirement for written informed consent was waived owing to the

program following standard clinical procedures; patients' verbal consent was obtained and documented in their medical record before increasing their dose to 3 mg/day.

Procedures

Patients in both the 2-mg and 3-mg groups were motivated to quit smoking and participated in 6 or more sessions (15–30 minutes each) of smoking-cessation counseling in addition to receiving varenicline. These treatments were free of charge to all patients. Most follow-up counseling sessions were conducted by telephone (~90%). At baseline (an in person visit consisting of the first consult at our program), we administered the following standardized questionnaires: Center for Epidemiologic Studies Depression Scale (CES-D),¹⁷ the Patient Health Questionnaire (PHQ),¹⁸ the Brief Sleep Scale (BSS),¹⁹ the Fagerström Test for Nicotine Dependence (FTND),²⁰ the Wisconsin Smoking Withdrawal Scale (WSWS),²¹ and the Positive and Negative Affect Schedule (PANAS).²² Those were administered to screen for depression, anxiety, alcohol, insomnia, nicotine dependence, nicotine withdrawal, and negative affect, respectively. We also assessed motivation to quit on a one-item Likert scale (Table 1): “How motivated are you to quit smoking?” The baseline values of these assessments were used as covariates to calculate the propensity scores to match the two treatment groups, as described below.

We recorded the CPD at each session using the timeline follow-back method (TLFB),²³ and, in a small group (n=11) who attended in-person sessions, we measured exhaled carbon monoxide (CO) levels. Further details about our treatment program are reported elsewhere.²⁴ In addition to total abstinence, reduction in CPD by 50% or more has been used as a criterion for treatment response in studies evaluating the importance of switching treatment approaches (i.e., switch to other treatments including varenicline, nicotine replacement therapies, or bupropion).^{15,25} In this study, we used TLFB data to establish the 50% reduction in CPD as criteria for a favorable response. In addition, we were interested in the robust reduction in smoking to 5 cigarettes or less/day, especially among those who smoked more than 10 CPD at baseline. The latter being a possible easy measure of a “robust response”, while on varenicline at 2 mg/day, that could be used as proxy or marker of a substantial benefit in increasing the varenicline dose further.

Data Analysis

All data analyses were conducted using R statistical software (version 3.3.0; <http://www.r-project.org/>). Baseline group differences were identified using chi-squared analysis. The effect of treatment group on smoking abstinence was estimated using the cumulative incidence ratio or risk ratio (RR), along with odds ratios (OR).

Propensity Score Matching—Given the quasi-experimental nature of the study and to account for possible differences in the baseline characteristics between the two groups, we used the propensity score-matching method.^{26,27} A propensity score is the probability that a patient will be assigned to the 3 mg/day group as opposed to the 2 mg/day group given each patient's measured characteristics. A matched set consists of a patient in the 3 mg/day group and at least one patient from the control group with similar propensity (probability) scores. The aim of this method is to approximate or simulate randomization by eliminating

confounding due to individual differences. We matched 142 patients who were initially treated and continued on 2 mg/day (out of the 356 described above) with the 73 patients who were increased to 3 mg/day.

The propensity score in this study was estimated using a multivariate logistic regression model, with varenicline dose/day as the dependent variable and the baseline characteristics outlined above and in Table 1 as covariates. In the propensity score–matching procedure, we reached the best compromise of balance and sample size with a matching of 1:3 using a greedy nearest-neighbor–matching algorithm with a caliper width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. The greedy nearest-neighbor–matching algorithm selects a subject from the 3 mg/day group and then selects a subject from the 2 mg/day group whose propensity score is closest to that of the 3 mg/day subject. The caliper of 0.2 constraints the selection of the matched subject to be within 0.2 units of the propensity score. We estimated both unadjusted and adjusted RRs using a logistic regression model and compared the average expected values for each patient as the varenicline dose was increased from 2 mg to 3 mg. After estimating the propensity score, we performed a series of matching algorithms to extract the optimal balanced sample. We used R package MatchIt²⁸ software to perform the propensity score matching and Zelig²⁹ software to estimate the parameters of the models (Figure 2).

Missing Data—Prior to running the propensity score analysis, we used multiple imputation to impute (substitute) missing values in the covariates and minimize potential bias due to missingness using the program Amelia II.³⁰ Multiple imputation is an analytical technique for missing data which consists of three steps: a) imputation of missing values for a predetermined number of data sets (in this paper we created 10 imputed sets); b) separate analysis in each data set; c) pooling and averaging the results from each imputed set. In the final models of the matched samples, we also included all covariates to adjust for potential imbalance not eliminated from our matching procedure. Amelia II software uses expectation-maximization with a bootstrapping algorithm, which is well suited for multivariate analysis of categorical or mixed data.³¹ Expectation-maximization is an iterative method to find the best solution by maximizing the likelihood of the data given the parameters. Each iteration of the expectation-maximization algorithm uses random sampling. The percentages of missing data for the covariates ranged from 2% to 32%. To evaluate the imputation results, we imputed 10 datasets and examined the imputation diagnostics. We then performed the propensity score–matching algorithm on each imputed dataset separately. We proceeded by averaging the results using Rubin's²⁶ rules for combining results from multiple imputed datasets to account for the uncertainty of the logistic regression results produced from each imputed and matched dataset and to derive point estimates and confidence intervals (CI) for the parameters of interest.

Sensitivity Analysis—Because of the lack of random assignment between the two treatment groups, we used a sensitivity analysis to estimate the effect of possible confounding variables (e.g., selection bias or placebo effect).³² For this analysis, we assumed that an unobserved confounder (or several unobserved confounders) had an OR of

2 with smoking abstinence and an OR of 2 with exposure to 3 mg/day of varenicline, both considerably higher than most of the observed covariate effects shown in Table 1.

We also considered different assumed prevalence levels of the unobserved covariate in the population ranging from 1% to 30%. Briefly, we used the associations between exposure to 3 mg/day of varenicline to the outcome and the unobserved confounder to estimate the bias factor, which we then used to obtain the estimate of the relationship between the outcome and the exposure, adjusted for both the observed and the unobserved covariates.³³

Decrease in CPD by > 50% versus < 5 CPD

Our data analysis seem to suggest that those who smoked more than 10 cig/day at baseline *and* reduced to 5 cig/day or less while on varenicline 2 mg/day had a particular advantage with the further increase in dose of varenicline. However, the numbers in each sub-group (Table 2) are too small to make firmer conclusion; therefore the decrease in CPD by 50% or more seems to be a simple and reasonable predictor of response to higher dose that clinicians could use to identify patients who may benefit from this strategy.

RESULTS

Baseline Characteristics

Before propensity score matching, our patients were highly dependent on nicotine, with a mean FTND of 5.0 (Table 1). Before the imputation and matching analysis, we found that at 3 months after the “increase or stay same” visit, 41 of 356 patients (11.5%) in the 2-mg group and 19 of 73 patients (26%) in the 3-mg group achieved 7-day point prevalence smoking abstinence (PPA). As shown in Table 3 (Unadjusted model with no imputation) patients in the 3-mg group were significantly more likely to report 7-day PPA at the first outcome point (3 months) than those in the 2-mg group ($\chi^2=10.60$; $p<0.001$; RR, 2.3 [95% CI, 1.4–3.6]). The difference remained significant regardless if the sample was adjusted, matched with imputation, or none of the above. Similar statistically significant effects were observed for 7-day PPA at 6 months ($p<0.001$; RR= 2.6 [95% confidence interval, 1.6–3.9]) and 9 months follow-up ($p<0.001$; RR= 2.2 [95% confidence interval, 1.4–3.3]).

Selecting Case Controls Using Propensity Score Matching

Table 1 shows the observed mean differences between the groups for each baseline characteristic before and after matching. The final matched 2-mg and 3-mg groups consisted of 142 patients and 72 patients, respectively (1 of the patients from the 3-mg group did not have a matching control) and the mean differences were reduced by this matching. The adjusted models with imputation and matching (Table 4) are the final models and are considered “doubly robust” to confounding because we preprocessed the data to match patients on the basis of covariates and because we controlled for covariates in the estimation of the final parameters.²⁸ After matching, all but two (PANAS-positive affect and PHQ-depression) of the standardized mean differences between the 2-mg and 3-mg groups were smaller than 0.10 (Table 1), which has been recommended as a maximum limit of differences between two groups to be treated as equivalent.³⁴

Smoking Abstinence

We next compared the proportion of patients in each matched treatment group who had quit smoking at 3, 6, and 9 months. The RRs of efficacy varied from 2.1 to 2.9. The adjusted and unadjusted RRs (with 95% CIs) of achieving 7-day PPA are presented in Table 3, showing that patients who received the 3-mg dose had a significantly higher probability of 7-day PPA in all models than those who stayed on the 2-mg dose.

In the sensitivity analysis results (Table 5) none of the confidence intervals crossed 1.0, suggesting that the significant relationship between the 3-mg dose and smoking abstinence was not sensitive to an unobserved confounder, which was modeled as if associated with approximately 2-fold increase in being in the 3-mg group and 2-fold increase in smoking abstinence. We further examined the smoking-abstinence rates for the patients in the 3-mg and 2-mg groups categorized according to two parameters before increasing varenicline to 3 mg: 1) reduced smoking by 50% or more from baseline visit and/or 2) reduced CPD (5 CPD) after the initial 6 weeks of 2 mg/day. Those who met both criteria seem to have the most robust response by increasing to 3 mg/day, they would be patients who were smoking 10 CPD or more at baseline and reduced to 5 CPD or less while on 2 mg/day before the increase in dose (Table 2).

For patient convenience and to accommodate patients who must travel some distance to return to MD Anderson, we conduct the majority (90%) of our counseling follow-up sessions over the phone. As such there is no opportunity to conduct an expired CO assessment on these visits. However we do measure exhaled CO levels for those patients who attended in-person follow-up visits. In this sample, we identified 11 patients attending an in-person follow-up: four reported abstinence from smoking, and all had CO levels below 2 ppm (4 ppm or lower is the cutoff for abstinence), indicating 100% congruence between the self-report of smoking abstinence and the CO levels. Further, most of the seven patients who reported that they had not quit smoking had CO levels that were substantially higher than 4 ppm. While this is a small number of the sample, the high congruence is consistent with the accuracy in self-report on tobacco use in the literature,^{35,36} and it does provide confidence in the veracity of self-reported abstinence of our patients.

Adverse Events

At least one adverse event was reported by 146 (34%) patients in both groups (total sample of 429 patients). No significant difference in the presence or absence of at least one adverse effect was found between the 2-mg and 3-mg groups. Specifically, 23 patients (31.5%) in the 3-mg group experienced an adverse event compared with 123 patients in the 2-mg group (34.5%; $\chi^2=0.25$; $p=0.617$). We also compared the number of adverse events for only patients who had experienced one or more adverse events in both groups (2 and 3 mg/day). The mean number of adverse effects was 2.2 (SD=1.9) for the 2-mg group and was 3.2 (SD=3.3) for the 3-mg group; however, this difference was not statistically significant ($p=0.062$). No severe or serious adverse events we reported, almost all the adverse events were mild (or grade I), except few that were moderate (grade II). Those grade II were: 4 occasions of nausea (3-mg group) and 2 occasions (2-mg group), as well as 4 occasions of insomnia/vivid dreams in each of the two groups. The most frequently reported adverse

events in our study were nausea, abnormal dreaming, insomnia, and headache, which are the most frequent varenicline-related adverse events reported in placebo-controlled trials.^{1,2}

Sensitivity Analysis

We examined the sensitivity of our results to unobserved confounding variables, as defined above, which may have determined selection into the 3-mg group vs. the 2-mg group. The results in Table 4 show that patients in the 3-mg group had an OR of 2.67 (95% CI, 1.06–6.7) of 7-day PPA at 3 months relative to patients in the 2-mg group. Similarly, the ORs of 7-day PPA were 2.96 at 6 months (95% CI, 1.23–7.12) and 3.24 at 9 months (95% CI, 1.3–3.9) for patients in the 3-mg group compared with the 2-mg group. Our sensitivity analysis indicate that the effect of 3 mg of varenicline on smoking abstinence is robust and is not the result of unobserved confounding variables.

DISCUSSION

Our data supports the hypothesis that increasing the dose of varenicline to 3 mg/day is associated with significant increase in 7-day PP abstinence rates. This benefit was observed among patients who reduce their smoking (50% or more) but fail to quit following an initial 6 weeks of varenicline at 2 mg/day and later increased to 3 mg/day. The impetus for trying a higher dose is to enhance cessation rates among those who fail to quit after an initial treatment exposure before they get discouraged and may give up on trying to quit. Therefore, in the program we have used innovative techniques, such as combining medications or increasing medication dose beyond the maximum recommended dose (as in this sample) to enhance the treatment effect.²⁴ This favorable outcome was achieved with a relatively small increase in varenicline (30% difference in the daily dose), which suggests that a subgroup of patients may need a higher than the 2 mg/day dose to achieve total abstinence.

We found no significant differences in adverse events, by treatment group. This was probably due to the prolonged habituation period of 6 weeks on the 2-mg dose (i.e., most adverse events likely occurred early, while receiving the 2 mg/day and those who did not tolerate varenicline would have stopped taking it). Therefore a tailored increase in varenicline dosage among people who initially tolerated it can lead to an increased efficacy (abstinence from smoking) with no increase in adverse events.

A possible limitation is that the improved 7-day PPA rate in the 3-mg group could be attributed to a higher motivation to quit because these patients agreed to try this dose. However, we did assess motivation to quit at baseline, and no differences were found between the two groups. Another possible explanation is expectancy or “placebo effect”, as patients in the 3-mg group took three tablets per day instead of two tablets and knew that they were taking a higher dose than the patients in the 2-mg group. Therefore, while the strength of this study is the real world effectiveness in a natural setting, on the flip side of that is its major limitation as being a non-randomized and open-label design, which could have resulted in a selection bias for patients in the 3-mg group. We tried to mitigate this possible bias by conducting a sensitivity analysis³² that assumed up to a 2-fold chance of an “unobserved covariate” between the two groups, such as a variable that we did not measure or account for (e.g. placebo effect), yet our results did not change. Nevertheless, only a

randomized controlled trial, using a placebo tablet versus varenicline as “add on”, among those who have an initial favorable response can eliminate the possibility of a selection bias or a placebo effect.

In conclusion, increasing varenicline to 3 mg/day appears to improve 7-day PPA rates at 3, 6, and 9 months from the onset of the possible change of treatment among those who previously received a 2-mg dose for 6 weeks and who had reduced CPD by 50% or more. Furthermore, the increased dose of varenicline did not increase the incidence of adverse events and was found to be safe in our study.

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Figure 1.
Consort Diagram

Figure 2. Propensity score distributions of the two treatment groups. A high degree of overlap, indicating that the two groups are well-balanced given the observed covariates

Table 1

Mean Baseline Characteristics of Patients with Cancer Who Received Varenicline (2 mg or 3 mg) for Smoking Cessation Before and After Propensity Score Matching*

Characteristic	Before matching			After matching [†]		
	3 mg (n=73)	2 mg (n=356)	Standardized difference %	3 mg (n=72)	2 mg (n=142)	Standardized difference %
Age, years	52.64	54.07	-16	52.92	52.39	6
Female sex ratio	1.49	1.52	-6	1.50	1.45	9
FTND score	5.02	4.97	2	5.02	5.04	-1
CPD	20.64	18.99	15	20.65	21.16	-5
CES-D score	13.30	12.62	6	13.28	13.30	0
Sleep score	10.67	9.13	25	10.61	10.70	-2
PANAS score						
Positive	29.77	30.70	-12	29.83	30.71	-11
Negative	21.38	19.77	19	21.30	21.37	-1
WSWS score						
Anxiety	8.62	8.21	11	8.53	8.49	1
Craving	10.86	10.73	4	10.89	10.66	7
PHQ (# Diagnosed)						
Anxiety	16	21	-12	17	16	1
Alcohol	12	12	2	13	13	-1
Panic	3	7	-26	3	2	6
Depression	14	13	3	14	9	13
Motivation item ^{††}	4.05	3.95	11	4.04	4.05	-1
CPD (7-day PP) [‡]	5.98	8.70	-50	6.03	6.42	-7

Abbreviations: CPD, cigarettes/day; FTND, Fagerström Test for Nicotine Dependence; CES-D, Center for Epidemiologic Studies Depression Scale; PANAS, Positive and Negative Affect Schedule; WSWS, Wisconsin Smoking Withdrawal Scale; PHQ, Patient Health Questionnaire; CPD (7-day PPA), cigarettes per day as 7-day point prevalence abstinence.

*The standardized differences are reported as percentages; a difference of less than 10.0% indicates a relatively small imbalance.

[‡]Sample size for the 2-mg and 3-mg groups after matching, varied by imputed dataset. The ranges of the sample size were 135–145 for the 2-mg group and 68–73 for the 3-mg group.

^{††}Motivation was assessed on a Likert scale of one item: How motivated are you to quit smoking? Not Motivated=1, Somewhat Motivated=2, Neutral=3, Motivated=4, and Very Motivated=5

CPD is based on 7-day PP of smoked cigarettes, before patients chose to increase to 3 mg or to maintain the 2-mg dose

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Smoking-Abstinence Rates for the Varenicline Groups (2 mg or 3 mg) for Patients Who Had Reduced CPD 50% or more from Baseline and/or for Those Who Smoked 5 or Fewer CPD Before the Intervention

Table 2

CPD	50% decrease in CPD % (n)			P- value	5 CPD % (n)			P- value	50% decrease in CPD and >5 CPD % (n)			P- value	50% decrease in CPD and 5 CPD % (n)			P- value	50% decrease in CPD and 5 CPD % (n)			P- value
	3 mg	2 mg			3 mg	2 mg			3 mg	2 mg			3 mg	2 mg			3 mg	2 mg		
3-month	32 (19)	14 (26)	0.002		36 (17)	17 (22)		0.010	13 (2)	9 (6)	0.567		20 (2)	0 (0)	0.400		39 (17)	17 (20)	0.005	
6-month	36 (21)	16 (30)	0.001		43 (20)	17 (21)		<0.001	13 (2)	16 (11)	0.816		20 (2)	33 (1)	0.631		43 (19)	17 (19)	<0.001	
9-month	31 (18)	20 (38)	0.113		34 (16)	21.6 (27)		0.093	20 (3)	17 (12)	0.792		10 (1)	33 (1)	0.326		34 (15)	22 (26)	0.139	

Abbreviations: CPD: cigarettes per day in past 7-days before patients increased dose to 3 mg or to maintained the 2-mg dose

Table 3

Estimated Effect Sizes (Risk Ratios) of Varenicline Dose on 7-day PPA Smoking Abstinence Outcomes at Three Time Points According to Different Models

Model	Risk Ratio	95% CI	P-value
<u>3-month</u>			
Unadjusted (no imputation or matching)	2.3	1.4–3.6	<0.001
Adjusted with imputation and no matching	2.1	1.1–3.7	0.016
Unadjusted with imputation and matching	2.3	1.2–4.1	0.008
Adjusted with imputation and matching	2.9	1.1–4.7	0.004
<u>6-month</u>			
Unadjusted (no imputation or matching)	2.6	1.6–3.9	<0.001
Adjusted with imputation and no matching	2.5	1.4–4.1	<0.001
Unadjusted with imputation and matching	2.4	1.3–4.3	0.008
Adjusted with imputation and matching	2.5	1.1–5.2	0.02
<u>9-month</u>			
Unadjusted (no imputation or matching)	2.2	1.4–3.3	<0.001
Adjusted with imputation and no matching	2.5	1.1–3.9	<0.001
Unadjusted with imputation and matching	2.3	1.3–3.9	0.003
Adjusted with imputation and matching	2.7	1.2–5.2	0.008

Abbreviations: 7-day PPA, 7-day point prevalence abstinence. CI, confidence interval.

Table 4
Adjusted ORs of the Final Imputed and Matched Models for 7-Day PPA at Three Time Points

Covariate	3 months			6 months			9 months					
	OR	5%	95 % value	OR	5%	95 % value	OR	5%	95 % value			
Varenicline (3 mg)	2.67	1.06	6.70	0.033	2.96	1.23	7.12	0.013	3.24	1.37	7.66	0.007
Age (mean)	1.00	0.95	1.06	0.955	1.03	0.97	1.09	0.286	1.03	0.98	1.07	0.279
Sex (female)	1.12	0.38	3.28	0.831	1.40	0.47	4.14	0.539	1.05	0.38	2.86	0.929
FTND (mean score)	0.83	0.60	1.15	0.255	0.94	0.65	1.36	0.748	0.96	0.65	1.42	0.841
CPD (mean #)	1.06	0.98	1.15	0.174	1.01	0.93	1.10	0.743	0.97	0.89	1.05	0.461
CES-D (mean score)	0.94	0.83	1.07	0.348	0.96	0.87	1.07	0.448	0.94	0.83	1.06	0.336
Sleep (mean score)	0.98	0.89	1.09	0.753	1.01	0.92	1.11	0.835	0.97	0.87	1.08	0.537
PANAS (mean score)												
Positive	0.95	0.87	1.03	0.183	0.99	0.92	1.07	0.842	0.96	0.89	1.04	0.357
Negative	1.00	0.91	1.10	0.945	0.95	0.87	1.05	0.308	0.98	0.90	1.07	0.675
WSWS (mean score)												
Anxiety	1.04	0.84	1.28	0.741	1.09	0.87	1.38	0.445	1.05	0.88	1.24	0.587
Craving	1.09	0.90	1.30	0.368	1.13	0.95	1.36	0.167	1.09	0.87	1.36	0.442
PHQ (Diagnosis)												
Anxiety	0.96	0.26	3.48	0.944	0.42	0.05	3.88	0.446	0.76	0.18	3.29	0.715
Alcohol	0.24	0.02	2.71	0.241	0.58	0.11	2.94	0.5	0.83	0.18	3.76	0.807
Panic	0.01	0.01	10.8	0.993	0.01	0.01	5.99	0.997	0.67	0.00	3.24	0.999
Depression	3.58	0.32	39.5	0.293	0.87	0.09	8.34	0.902	0.90	0.06	13.4	0.940
MOTIVATION*	0.97	0.47	1.99	0.932	1.23	0.60	2.54	0.571	1.04	0.54	1.97	0.911
CPD (7-day PP)‡	0.82	0.69	0.97	0.023	0.89	0.76	1.03	0.122	1.00	0.91	1.10	0.974

Abbreviations: OR, odds ratio; 7-Day PPA, 7-day point prevalence abstinence; CPD, cigarettes/day; FTND, Fagerström Test for Nicotine Dependence; CES-D, Center for Epidemiologic Studies Depression Scale; PANAS, Positive and Negative Affect Schedule; WSWS, Wisconsin Smoking Withdrawal Scale; PHQ, Patient Health Questionnaire

* Motivation was assessed on a Likert scale of one item: How motivated are you to quit smoking? Not Motivated=1, Somewhat Motivated=2, Neutral=3, Motivated=4, and Very Motivated=5.

‡ CPD (7-day PP), cigarettes per day as 7-day point prevalence, before patients chose to increase dose to 3 mg or to maintain the 2-mg dose

Sensitivity Analysis with Estimated Effects and ORs (95% CI) of Varenicline Dose on Abstinence Controlling for Unobserved Covariates with a Varying Population Prevalence of a Possible Confounder

Table 5

Prevalence	0.01% OR (95% CI)	10% OR (95% CI)	15% OR (95% CI)	20% OR (95% CI)	25% OR (95% CI)	30% OR (95% CI)
Treatment effect						
3-month abstinence	2 (1.2–4.1)	2.1 (1.1–3.8)	2.1 (1.1–3.7)	2.1 (1.1–3.7)	2.1 (1.1–3.7)	2 (1.1–3.6)
6-month abstinence	2.4 (1.3–4.3)	2.2 (1.2–4)	2.2 (1.2–3.9)	2.2 (1.2–3.9)	2.1 (1.2–3.8)	2.1 (1.2–3.8)
9-month abstinence	2.3 (1.3–3.9)	2.1 (1.2–3.6)	2.1 (1.2–3.6)	2.1 (1.2–3.5)	2.1 (1.2–3.5)	2 (1.2–3.5)

Abbreviations: OR, odds ratio; CI, confidence interval.