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Impact of Early Nausea on Varenicline Adherence and Smoking Cessation

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Abstract

BACKGROUND AND AIMS: Varenicline effectiveness may be related to the level of adherence, which might be reduced by adverse effects such as nausea. The aim of the study was to test a possible effect of nausea on smoking cessation outcomes mediated by adherence.

DESIGN: Mediation path analysis

SETTING: Multiple sites within Canada and the United States.

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Author Contributions

NLB, NLN, JSA, CL and RFT designed the research; NLB, NLN, JSA, CL and RFT performed the research; ARP and WS analyzed the data; ARP and RFT wrote the manuscript. All authors were involved in the revision, review, and approval of the manuscript.

Conflict of Interest

RFT has consulted for Quinn Emanuel, Apotex and Ethismos; she is also a member of several scientific advisory boards (e.g. Health Canada, Quitta, Canadian Centre for Substance Abuse, and Brain Canada). CL and RFT received drug and packaging at no cost for varenicline used in the PNAT2 clinical trial. JSA had consulted with Lucy Gum. NLB is a consultant to Pfizer and Achieve Life Sciences, companies that market or are developing smoking cessation medications, and has served as a paid expert in litigation against tobacco companies. Remaining authors have no conflicts of interest to declare.

Clinical Trial Registration: ,

PARTICIPANTS: Treatment-seeking smokers receiving varenicline from two smoking cessation clinical trials: Quit2Live (; n=449) and Pharmacogenetics of Nicotine Addiction Treatment (PNAT) (; n=421).

MEASUREMENTS: Nausea severity was collected through self-report and adherence was biologically assessed using varenicline concentrations (Quit2Live, plasma sample at Week 4; PNAT, saliva sample at Week 2). In Quit2Live, the endpoints were cotinine-verified abstinence at Weeks 4, 12, and 26. In PNAT, the endpoints were carbon monoxide-verified abstinence at Weeks 2, 12, and 26.

FINDINGS: Early nausea was indirectly associated with lower cessation rates at multiple timepoints (ORs ranging from 0.92–0.94; 95%CI between 0.83–0.99) in a relationship mediated by reduced varenicline adherence (assessed by plasma varenicline concentrations) in the Quit2Live trial. This relationship between nausea, adherence and cessation was similar in direction but weaker in effect size (ORs ranging from 0.98–0.99; 95%CI between 0.90–1.03) in the PNAT trial, where adherence was assessed using salivary varenicline concentrations.

CONCLUSIONS: Early nausea during varenicline treatment may be indirectly associated with lower likelihood of smoking cessation through reducing varenicline adherence.

Introduction

There are currently over a billion active tobacco smokers worldwide, contributing substantially to the global burden of disease (1). Effective treatment for tobacco dependence is necessary to reduce the overall smoking prevalence and attributable disease burden (2). Of the pharmacotherapies approved by the U.S. Food and Drug Administration for smoking cessation, varenicline is the most efficacious in helping smokers achieve long-term cessation (six months or longer). Varenicline has been shown to significantly increase the odds of cessation compared to placebo [odds ratio (OR)=2.88], bupropion (OR=1.59), and nicotine replacement patch (OR=1.51) (3, 4). Even though varenicline is the most efficacious treatment for smoking cessation, up to half of smokers treated with varenicline fail to achieve continuous abstinence in the later stages of the treatment regimen (weeks 9 to 12) (5). Reduced medication adherence to smoking cessation pharmacotherapy is associated with lower abstinence; a third of varenicline-treated smokers are nonadherent by the 2nd week (1 week post dose titration) of the treatment regimen, and nonadherent smokers are significantly less likely to be abstinent at multiple timepoints (6–9). Given the prevalence of varenicline nonadherence and its impact on cessation outcomes, understanding issues that contribute to reduced adherence may provide avenues for enhancing adherence and cessation rates.

In surveys inquiring about discontinuation and nonadherence of varenicline, the most frequently cited reason was adverse events, with nausea being the most common adverse event experienced by varenicline-treated smokers (approximately 25% to 40%) (5, 8). Nausea is usually mild to moderate, begins in the first two weeks of treatment and diminishes over the course of treatment (5, 10). Together, the relationship between nausea and adherence, and the relationship between adherence and cessation outcomes, lead us to hypothesize that early nausea reduces varenicline adherence that in turn, decreases

likelihood of cessation. We sought to test this hypothesis in a large clinical trial. In addition, using a second trial which evaluated adherence using a different biological matrix (saliva vs plasma) at a slightly earlier time (week 2 vs week 4), we looked for a consistency of direction and size of effect. This current study used mediation models to test the potential influence of nausea on adherence, as determined by varenicline drug concentrations, and the subsequent impact on cessation. Mediation models aid in unraveling whether, and how much of, a relationship between an independent variable (i.e. nausea) and an outcome (i.e. cessation) might be predicted by an a priori mediator variable (i.e. varenicline adherence).

Methods

Study Design

Mediation analysis was used to investigate how an independent variable (i.e. nausea severity) affects an outcome variable (i.e. smoking cessation) through a mediator variable (i.e. varenicline adherence) (11). Plasma at week 4 (assessed in Study 1) or saliva at week 2 (assessed in Study 2) varenicline concentration were used as a measure of varenicline adherence (mediator variable). In both studies, the independent variable (i.e. nausea severity) was obtained one to three weeks prior to the assessment of the mediator variable (i.e. varenicline adherence), and 11 weeks prior to the primary outcome variable (i.e. smoking cessation).

Participants

The Study 1 sample was drawn from Quit2Live, a prospective cohort intervention study with a stratified recruitment based on race (African American, Caucasian), age (< 40, ≥ 40), and gender (Male, Female) (); these variables were included as covariates in this analysis (12, 13). Quit2Live was designed to investigate differences in cessation rates between African Americans and Caucasians, and to understand the factors underlying such differences. Treatment-seeking adults (N=449, aged≥18) who self-reported smoking 3–20 cigarettes per day were recruited and received 12 weeks of varenicline treatment in combination with smoking cessation counseling (Figure 1). Individuals were excluded if they had medical contraindications for varenicline, a history of substance abuse, current use of cessation pharmacotherapy, or if they exhibited depressive symptoms as indicated by a score≥3 on the Patient Health Questionnaire 2 - a detailed overview of study procedures with inclusion/exclusion criteria has been previously published (12). Participants provided written informed consent and study procedures were approved by the University of Kansas Medical Center IRB (#00001602).

Our mediation findings from Quit2Live were extended into Pharmacogenetics of Nicotine Addiction Treatment (PNAT; Study 2), a double-blind placebo-controlled randomized clinical trial with a stratified recruitment based on rate of nicotine metabolism (Nicotine Metabolite Ratio, NMR) (); NMR was included as a covariate in this analysis (14). PNAT investigated whether NMR, a genetically informed biomarker of nicotine clearance, predicts treatment response to smoking cessation treatments (15). Treatment-seeking individuals (N=421, aged≥18) who self-reported smoking more than 10 cigarettes per day, and confirmed by carbon monoxide≥10ppm, received 12 weeks of varenicline treatment in

combination with behavioural counselling. The exclusion criteria were comparable to those of Quit2Live – detailed inclusion/exclusion criteria have been previously published (14). Participants from both studies received varenicline under the recommended dosing regimen (0.5 mg once daily for three days, 0.5 mg twice daily for four days, and 1.0 mg twice daily for the remainder of the twelve-week treatment, figure 1) (16). Participants provided written informed consent and the protocol was approved by the institutional review boards.

Nausea and Varenicline Adherence Assessment

Nausea severity data were collected through self-report at multiple timepoints in the Quit2Live (Weeks 1, 4, and 8) and PNAT (Weeks 1 and 2) trials; nausea was examined on a 4-point scale (0 to 3) as previously described in varenicline randomized clinical trials (17–26). Adherence was biologically assessed at Week 4 (Quit2Live, plasma sample) and Week 2 (PNAT, saliva sample) using varenicline concentrations analyzed by LC-MS/MS (limit of quantification = 0.05 ng/ml for plasma, 1 ng/ml for saliva) (6, 27, 28). Adherence was determined based on varenicline concentrations instead of self-report pill counts as the varenicline concentrations were more predictive of cessation outcomes, while self-report pill counts tended to overestimate adherence, and were less predictive of cessation outcomes (6, 7, 29).

Within Quit2Live (Study 1), variations of the nausea severity variable were tested, specifically, a) including all individuals (N=355) who filled out the nausea questionnaire (i.e. including those who reported ‘no nausea’) and b) limiting the analyses to the individuals (N=125) who reported nausea. Similarly, variations of the plasma varenicline concentration variable were tested, specifically, a) comprising all including participants (N=404) including those who did not provide a sample (varenicline concentration assigned 0 ng/ml) and b) limiting the analyses to participants (N=381) who provided a plasma sample for varenicline concentrations assessments.

Outcome Assessment

In Quit2Live, the primary endpoint was cotinine-verified 7-day point prevalence smoking abstinence at Week 12 (end of varenicline treatment); secondary endpoints were cotinine-verified 7-day point prevalence smoking abstinence at Week 4, and 26 (13). Abstinence was defined by recommended cut-points of 15 ng/ml for salivary cotinine (30). In PNAT, the primary endpoint was carbon monoxide-verified 7-day point prevalence smoking abstinence at Week 12 (end of varenicline treatment); secondary endpoints were carbon monoxide-verified 7-day point prevalence smoking abstinence at Week 2, and 26 (14). Abstinence was defined by recommended cut-points of 8 ppm for carbon monoxide (30). An intent-to-treat approach was utilized in the outcome assessment (i.e. participants who were absent at an outcome assessment session were considered as smoking in the analyses).

Statistical Analyses

Chi-Square Tests for Independence and Mann-Whitney U Tests (2-tailed) were used to compare subject characteristics between Week 12 abstinent and smoking individuals. To test a potential mediation effect, indirect effects of early nausea on the primary outcome (i.e. Week 12 abstinence) mediated by adherence (i.e. plasma/salivary varenicline concentrations)

were estimated in SPSS Statistics (Version 22, IBM Corporation) using the PROCESS macro (31). When estimating potential indirect effects, varenicline concentrations were standardized to Z-scores (i.e. number of standard deviations from the mean) as varenicline concentrations were different in plasma vs. saliva. A bias-corrected bootstrapping method was used in the indirect pathway modelling, and 10,000 replications were used in estimating the 95% confidence intervals (CIs). Factors upon which the trials were stratified were added as covariates a priori, regressed against both the mediator and the outcome. In Quit2Live, age (<40, ≥40), gender (Male, Female) and race (African American, Caucasian) were entered as covariates in the mediation models to reduce confounding. The potential effect of adding NMR as a covariate in Q2L was also examined as NMR was previously shown to be associated with smoking cessation outcomes (14, 32, 33). In PNAT, NMR (<0.31, ≥0.31) was entered as covariate to reduce confounding. The potential effects of adding age, gender and race as covariates in PNAT was also examined to parallel the covariates in Q2L.

Results

Quit2Live - Study 1 Sample

Of the N=449 participants enrolled into a cohort intervention trial to varenicline treatment, N=381 provided a plasma sample at Week 4 for varenicline sampling. Of the participants who provided a plasma sample, abstinent individuals at Week 12 (the primary outcome) were more likely to be Caucasian, and to have higher Week 4 plasma varenicline concentrations (Table 1) compared to smoking individuals. Between individuals who were abstinent and those who were smoking at Week 12, there were no significant differences in self-reported nausea severity at Weeks 1, 4 and 8 (Figure 1).

Testing the Mediation Pathway and Potential Effects of Covariates

Path analyses demonstrated that greater Week 1 nausea severity was associated with lower Week 4 plasma varenicline concentration [Beta(a) = −0.16, p=**0.04**)], and higher Week 4 plasma varenicline concentration was associated with increased abstinence at Week 4, 12, and 26 [ORs (b) ranged from 1.43 to 1.64, p≤**0.01**] (Figure 2). In the path model, the indirect (mediation) pathway (a b) was statistically significant for all three outcome timepoints (abstinence at Week 4, 12 and 26) examined, suggesting that increased Week 1 nausea was associated with lower abstinence rates, mediated via decreased Week 4 plasma varenicline concentration (Figure 2). This indirect pathway was also significant when plasma varenicline concentrations were unstandardized (Suppl. Figure 1), when NMR was included as an additional covariate (Suppl. Figure 2), and when different grouping strategies of the nausea severity scale and/or plasma varenicline variables were utilized (Suppl. Figure 3). There was no association between Week 1 nausea severity and abstinence at Week 4, 12, or 26 directly [ORs (c) ranged from 0.91 to 1.02, p≥0.63] and within the pathway model [ORs (c') ranged from 0.98 to 1.07, p≥0.74] (Figure 2). The lack of direct association [(c) pathway] between nausea and abstinence outcomes is no longer thought to be an impediment to conducting mediation analyses and the interpretation of the indirect effects (34) (see Discussion).

Testing Alternative Interpretations

Suppl. Table 1 illustrates the additional Quit2Live analyses that were completed to support the mediation pathway observed in Figure 2. To reduce the potential for confounding in the mediation pathway tested in Figure 2, race, gender and age (Quit2Live stratification recruitment variables, see Methods) were included as covariates. Additionally, race, gender and age were tested as potential moderators at the (a) and (b) pathways; they were not significant moderators at any of the three outcome timepoints ($p \geq 0.17$). To test whether nausea severity and plasma varenicline had independent effects on abstinence outcomes, potential interactions between nausea severity and plasma varenicline on abstinence outcome were tested; there were no significant interactions at any of the three outcome timepoints ($p \geq 0.56$). To test possible bidirectional (reciprocal) causal effects between nausea and plasma concentration, and to strengthen support for the hypothesized pathway, we tested whether there was an indirect effect of Week 4 plasma varenicline on abstinence outcomes mediated by Week 1 nausea; there was no significant indirect effect. To test the temporality assumption of mediation modelling, we tested whether there was an indirect effect of Week 4 and 8 nausea severity on abstinence outcomes, mediated by Week 4 plasma varenicline; there was no significant indirect effect.

PNAT – Study 2 Sample

The impact of early nausea severity on abstinence outcomes mediated through changes in plasma varenicline concentration observed in the final Quit2Live mediation model (Figure 2) was then tested in PNAT, which did not collect plasma samples, but did collect salivary samples at Week 2 for varenicline analyses. Of the N=421 participants randomized to the varenicline treatment arm, N=376 provided a salivary sample for varenicline concentration analysis. Of the N=376 participants who provided a salivary sample, those who were abstinent at Week 12 (the primary outcome) were more likely be a normal metabolizer of nicotine (NMR≥0.31) and have higher Week 2 salivary varenicline concentrations (Table 2) than those who were smoking. There were no significant differences in self-reported nausea severity at Weeks 1 or 2 between abstinent and smoking individuals at Week 12.

Testing the Mediation Pathway and Potential Effects of Covariates

To reduce the potential for confounding in the mediation pathway tested in Figure 3, the addition of NMR as a covariate was included (PNAT was randomized on NMR, see Methods). Although the direction (i.e. negative effect of nausea on adherence) and effect size between nausea severity and varenicline concentrations were similar to those observed in Quit2Live [Figure 2, Beta(a) = −0.16, p=**0.04**], independent path analyses demonstrated that Week 1 nausea severity was not significantly associated with Week 2 salivary varenicline concentrations [Figure 3; Beta(a) = −0.12, p=0.26)]; nor were salivary varenicline concentrations significantly associated with Week 2, 12, and 26 abstinence [ORs (b) ranged from 0.97 to 1.17, $p \geq 0.16$]. Although, the direction of the indirect effects (a b) on outcome were similar to that observed in Quit2Live [Figure 2, ORs (a b) ranged from 0.92 to 0.94], they were not significant for all three outcome timepoints (abstinence at Week 2, 12 and 26) examined in PNAT. This was found when NMR was entered as the only covariate (Suppl. Figure 4), when Week 2 nausea severity was tested as the independent variable

(Suppl. Figure 5A), and when race, gender, sex as well as NMR were covariates in this model (Suppl. Figure 5B).

Exploratory Analyses

The robustness of the main mediation models in Quit2Live (Figure 2) and PNAT (Figure 3) was explored by including additional covariates which have been found to impact abstinence outcomes (13). Of the baseline variables that were significant predictors of Week 26 abstinence, plasma cotinine was available in both trials. Baseline plasma cotinine did not alter the interpretation of the indirect nausea effect at any of the three abstinence timepoints in Quit2Live [ORs (a b) ranging from 0.91 to 0.93] or in PNAT [ORs (a b) ranging from 0.98 to 1.00]. Lastly, in an effort to address the growing interest in gender-stratified analyses, the main mediation models in Quit2Live (Figure 2) and PNAT (Figure 3) were stratified by gender instead of covarying for gender, providing estimates of gender-stratified effect sizes for future studies (Suppl. Figure 6 and 7).

Discussion

One aspect of improving cessation outcomes for varenicline-treated smokers is to enhance adherence. This study provided some evidence for a role of early nausea on varenicline adherence and its impact on cessation outcomes. Specifically observed in the Quit2Live (Study 1) dataset, increased severity of early nausea was associated with reduced varenicline adherence (e.g. plasma varenicline concentrations, Figure 2), which mediated an effect of nausea on lower cessation rates at both short and long term timepoints [Figure 2; ORs (a b) ranged from 0.92 to 0.94]. The indirect pathway suggests that for every increase in nausea severity of 1 (from 0 to 3), plasma concentrations decrease by 0.16 standard deviation of the mean (e.g. approximately 0.7 ng/ml plasma varenicline), and the odds of cessation decrease by 0.92 to 0.94 - an effect that is mediated by lower varenicline adherence.

The mediation of the effect of early nausea on cessation outcomes through varenicline adherence was supported through a number of analyses to ensure that key assumptions for claiming mediation were met (Suppl. Table 1) (35). For example, 1) potential confounding was minimized by including a priori covariates (race, gender, and age); 2) the lack of interaction between early nausea (i.e. exposure) and varenicline adherence (i.e. mediator) on cessation outcomes (i.e. outcome) was confirmed; 3) the assumption that early nausea affected varenicline adherence and not vice versa (i.e. bidirectionality) was tested and confirmed; and 4) the assumption that early nausea came before varenicline adherence (i.e. temporality) was tested and confirmed. Furthermore, it is important to note that nonsignificant direct effects of nausea on abstinence outcomes observed in Quit2Live [Figure 2; (c) pathway, $p \geq 0.63$] and PNAT [Figure 3; (c) pathway, $p \geq 0.26$] are not impediments to conducting mediation analyses. While the classical mediation approach by Baron and Kenny required a significant direct effect [i.e. (c) pathway] (36), more recent work suggest that this requirement is too restrictive and not necessary to conduct mediation analyses (11, 34, 37).

When findings from the final Quit2Live mediation model (Figure 2) were extended into PNAT (Study 2), the effect of early nausea on cessation outcomes mediated through

varenicline concentrations was consistent in direction and magnitude, albeit lacking statistical significance. A number of reasons may have contributed to this, including the use of a different biological matrix (plasma in Quit2Live vs. salivary in PNAT) to assess varenicline adherence. Plasma varenicline concentrations are ideal for adherence measures due to varenicline's favorable pharmacokinetic profile (i.e. minimal metabolism where over 90% varenicline is excreted as the parent compound, and long elimination half-life of approximately 24 hours) (38, 39). In contrast, a number of factors contribute noise to the salivary varenicline concentrations that may have weakened the associations in PNAT. For example, salivary drug concentrations can be affected by salivary flow rate, salivary pH, and specific protein and electrolyte composition of saliva that vary based on diet, age, sex and time of day (40). Despite using standardized varenicline concentrations in the analyses, variation in salivary varenicline concentrations in PNAT may have contributed to noisier mediation effect (similar direction and magnitude of effect, but statistical insignificance) compared to that observed in Quit2Live where plasma varenicline concentrations were measured to determine varenicline adherence. Within Quit2Live, a subset of participants (N=160) provided both a plasma and saliva sample, and while they were correlated (Spearman correlation=0.77, $p<$**0.001**), there was greater variation in salivary compared to plasma varenicline concentrations [$Mean_{salivary}$ (SD)=15.5 ng/ml (23.9) vs. $Mean_{plasma}$ (SD)=5.7 ng/ml (4.2)] (6). Currently, a correction factor between saliva and plasma varenicline concentration has not been determined nor prospectively tested. Therefore, further replication of the Quit2Live findings, either in a larger dataset, or in another dataset with plasma sampling, is warranted.

The results of the first study suggest that improved management of early nausea during varenicline treatment may positively impact smoking cessation success through increasing varenicline adherence. Varenicline-induced nausea is thought to be generated through both peripherally and/or centrally-mediated systems. Varenicline can cause nausea due to its effects at the α4, α5, α7, β2 and β2 containing nicotinic acetylcholine receptors in the small intestine neurons which project into the area postrema (within the medulla oblongata that controls nausea and vomiting) (i.e. peripheral mechanism) or its direct effects into the area postrema (i.e. central mechanism) (41, 42). Potential management strategies for varenicline-induced nausea could include: 1) extending the titration period and/or allow the participants to self-titrate the dose between the starting dose (0.5 mg once daily) and the maintenance dose (1.0 mg twice daily); 2) remaining at a lower dose (0.5 mg twice daily) for the duration of the treatment period; 3) increasing participants' understanding of the potential for nausea, its diminishment over time, and the evidence for adherence on cessation; and/or 4) supplementing an antiemetic agents such as 5-hydroxytryptamine$_3$ (5-HT$_3$) or neurokinin$_1$ receptor (NK$_1$) antagonists during the early course of varenicline treatment (41, 43, 44).

There are some limitations to this study. First, varenicline adherence as determined by varenicline concentrations was collected only at one timepoint in each of the two studies examined (Quit2Live and PNAT) and this may have restricted our ability to examine the effect of early nausea on varenicline adherence over time, and its impact on cessation outcomes. Second, self-reported nausea may have been prone to response and social desirability bias and thus not truly representative of nausea experienced. Third, PNAT (the

extension study) was not identical to Quit2Live (the primary study) in terms of recruitment, data collection timepoints, proportion of participants reporting mild to severe nausea at Week 1, proportion of participants who were abstinent at the various timepoints, type of biological sample collected for varenicline concentration analysis, and method of biochemical verification of cessation which may have contributed to the differences in robustness of effects and prevented direct pooling of data.

In conclusion, this study demonstrated a potentially important effect of early nausea on cessation outcomes through predicting adherence in a population of varenicline-treated smokers. While the study confirmed the hypothesis that greater nausea predicted lower cessation, mediated by poorer adherence, the effect was relatively small; other factors related to varenicline adherence need to be identified and addressed. Previously, probable indirect effects of varenicline adverse effects, such as nausea, on cessation outcomes have not been extensively examined; this study clarified an effect on varenicline adherence as one mechanism underlying the relationship between nausea and short- and long-term smoking cessation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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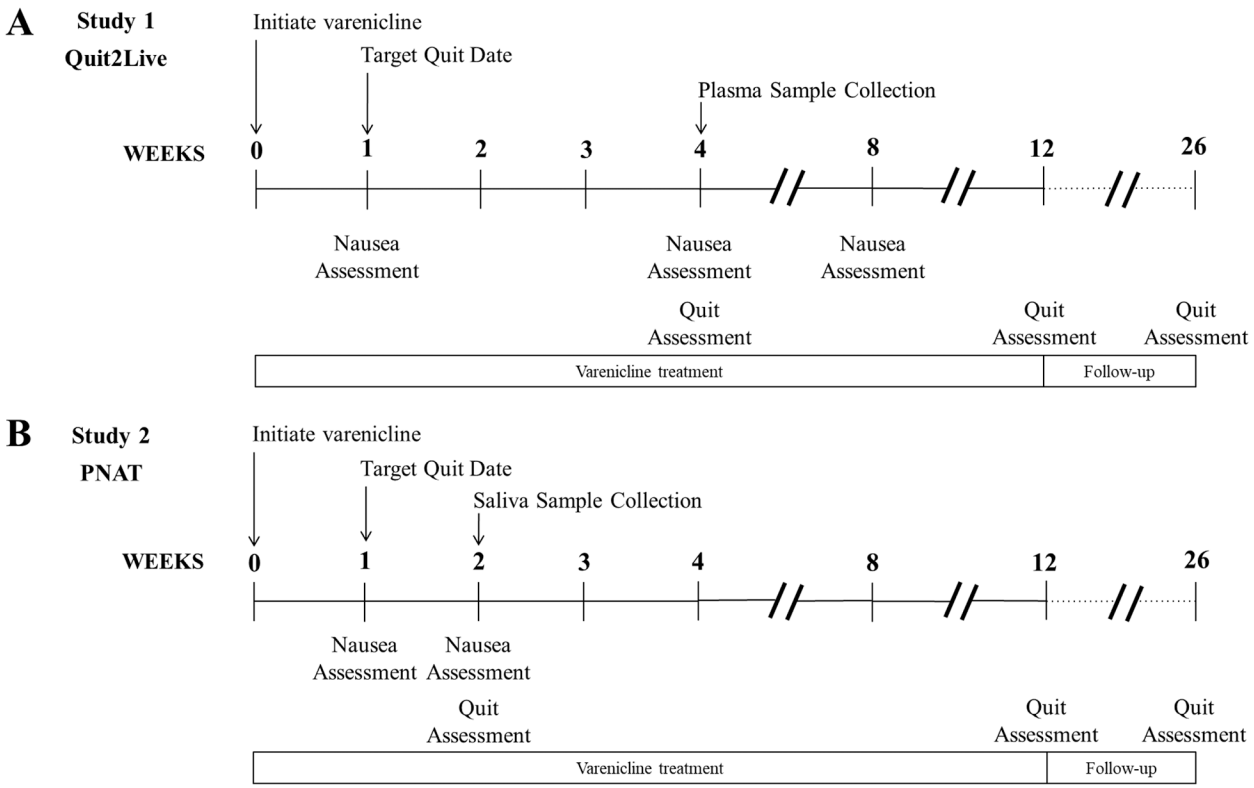

Figure 1. (A) Study 1 - Quit2Live and (B) Study 2 - PNAT trial timelines.

Participants were prescribed varenicline under the recommended dosing schedule for 12 weeks (0.5mg once daily for three days, 0.5mg twice daily for four days, and 1.0mg twice daily for the remainder of the twelve weeks). Nausea Assessment= collection of self-reported nausea incidence and severity; Quit Assessment= biochemically-verified quit.

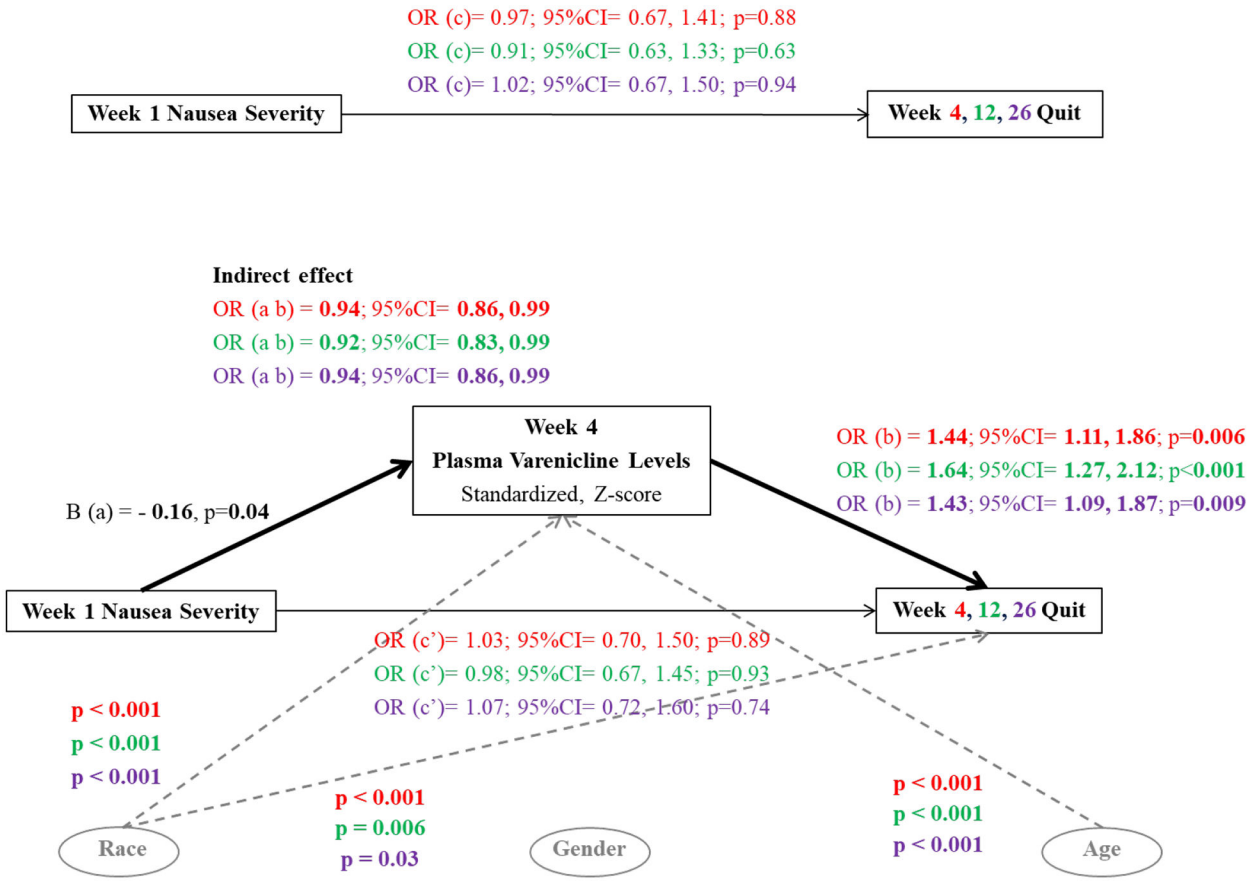

Figure 2 –. Quit2Live mediation path model. Association between Week 1 nausea and quit outcomes via standardized Week 4 plasma varenicline levels.

N=355 had available self-report Week 1 nausea data and provided a Week 4 plasma sample for varenicline level testing. Thin solid arrows indicate non-significant pathways; thick solid arrows indicate significant pathways ($p < 0.05$). The mediating effects of Week 4 plasma varenicline levels (standardized, Z-score) on Week 4 quit (red), Week 12 quit (green) and Week 26 quit (purple) are denoted by (a b) pathway. (a) pathway indicates the relationship between Week 1 nausea severity and Week 4 plasma varenicline. (b) pathway indicates the relationship between Week 4 plasma varenicline and quit outcomes. (c) pathway is the direct effect adjusted for covariates; (c') pathway is the direct effect adjusted for covariates as well as indirect effect tested. Significant covariate (included based on study design) effects n mediators or outcomes are shown in grey (dotted line), with p-values shown. B = beta; OR = odds ratio; CI = confidence interval; p = p-value

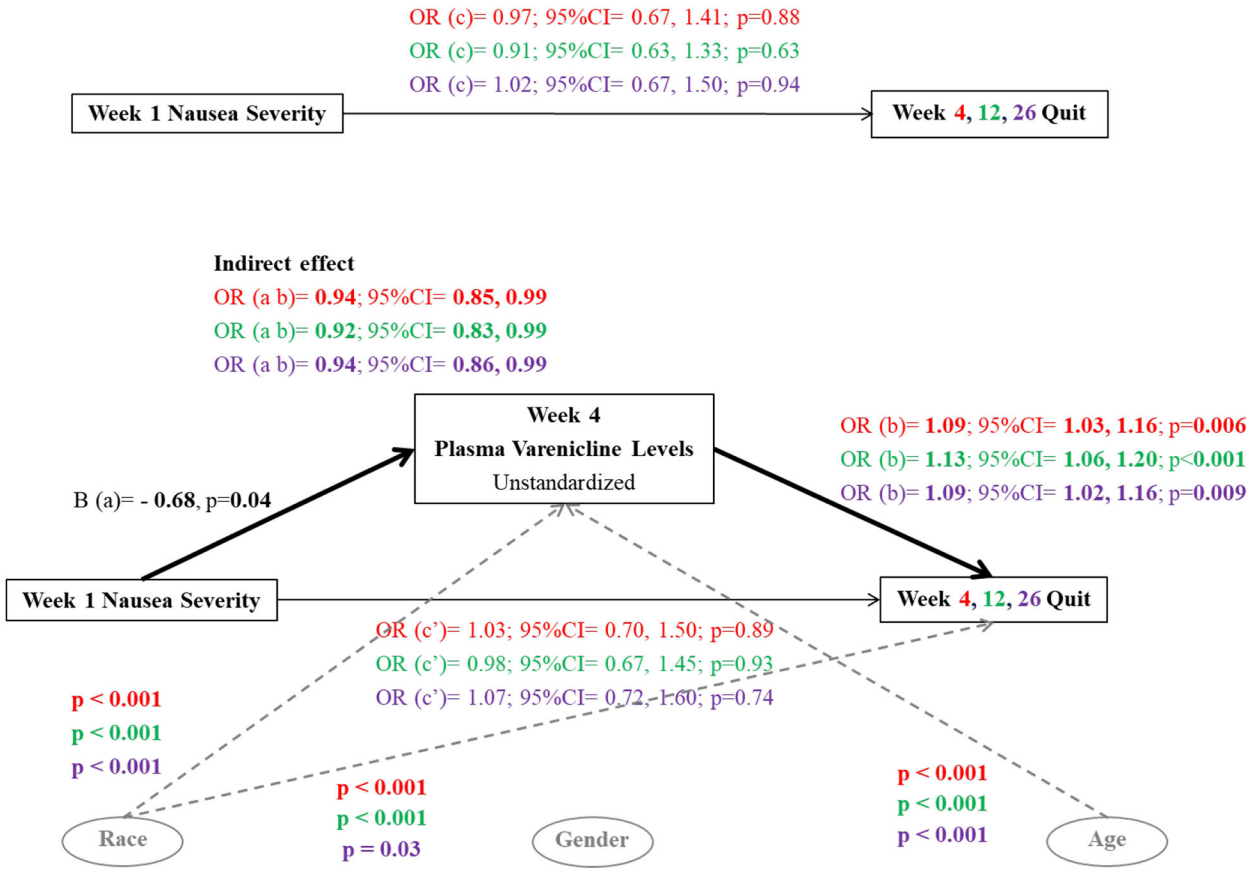

Figure 3 –. Quit2Live mediation path model. Association between Week 1 nausea and quit outcomes via unstandardized Week 4 plasma varenicline levels.

N=355 had available self-report Week 1 nausea data and provided a Week 4 plasma sample for varenicline level testing. Thin solid arrows indicate non-significant pathways; thick solid arrows indicate significant pathways ($p < 0.05$). The mediating effects of Week 4 plasma varenicline levels (unstandardized) on Week 4 quit (red), Week 12 quit (green) and Week 26 quit (purple) are denoted by (a b) pathway. (a) pathway indicates the relationship between Week 1 nausea severity and Week 4 plasma varenicline. (b) pathway indicates the relationship between Week 4 plasma varenicline and quit outcomes. (c) pathway is the direct effect adjusted for covariates; (c') pathway is the direct effect adjusted for covariates as well as indirect effect tested. Significant covariate effects on mediators or outcomes are shown in grey (dotted line), with p-values shown. B = beta; OR = odds ratio; CI = confidence interval; p = p-value

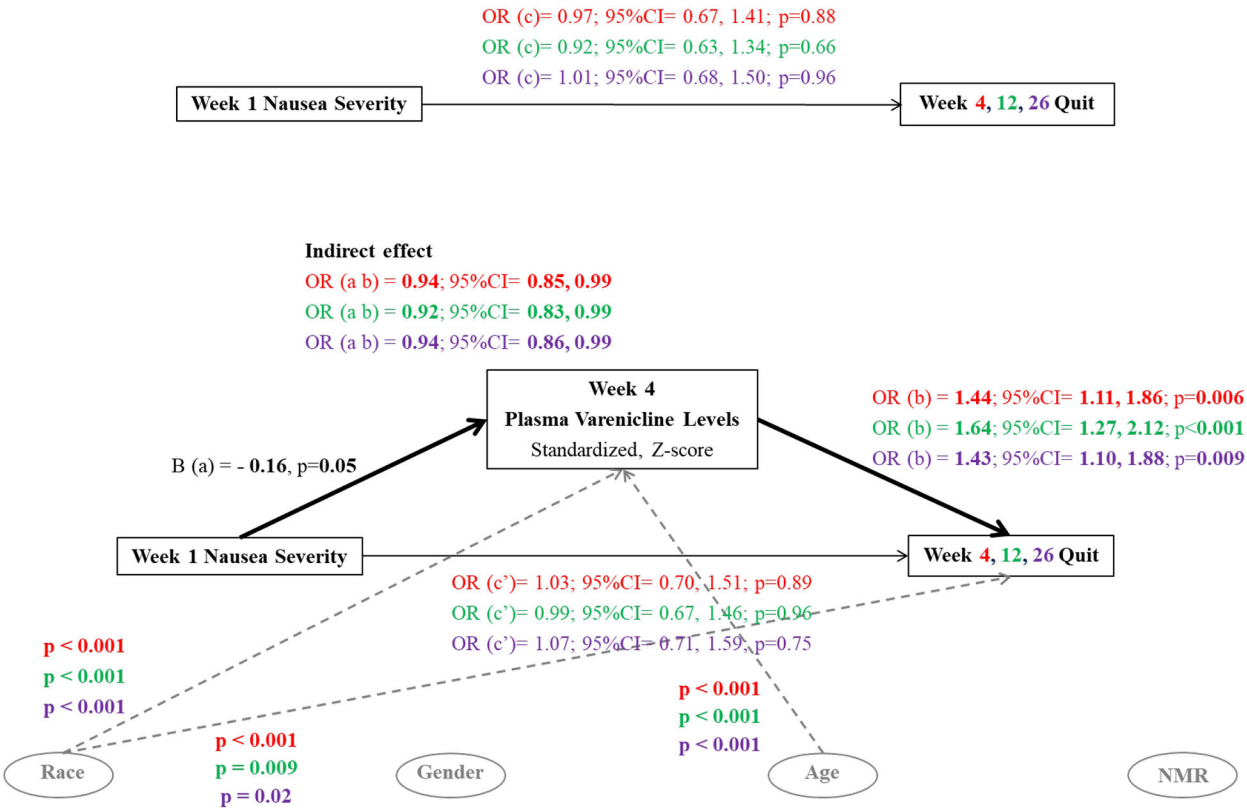

Figure 4 –. Quit2Live mediation path model. Association between Week 1 nausea and quit outcomes via standardized Week 4 salivary varenicline levels.

N=355 had available self-report Week 1 nausea data and provided a Week 4 plasma sample for varenicline level testing. Thin solid arrows indicate non-significant pathways; thick solid arrows indicate significant pathways ($p < 0.05$). The mediating effects of Week 4 plasma varenicline levels (unstandardized) on Week 4 quit (red), Week 12 quit (green) and Week 26 quit (purple) are denoted by (a b) pathway. (a) pathway indicates the relationship between Week 1 nausea severity and Week 4 plasma varenicline. (b) pathway indicates the relationship between Week 4 plasma varenicline and quit outcomes. (c) pathway is the direct effect adjusted for covariates; (c') pathway is the direct effect adjusted for covariates as well as indirect effect tested. Significant covariate effects on mediators or outcomes are shown in grey (dotted line), with p-values shown. NMR = nicotine metabolite ratio; B = beta; OR = odds ratio; CI = confidence interval; p = p-value

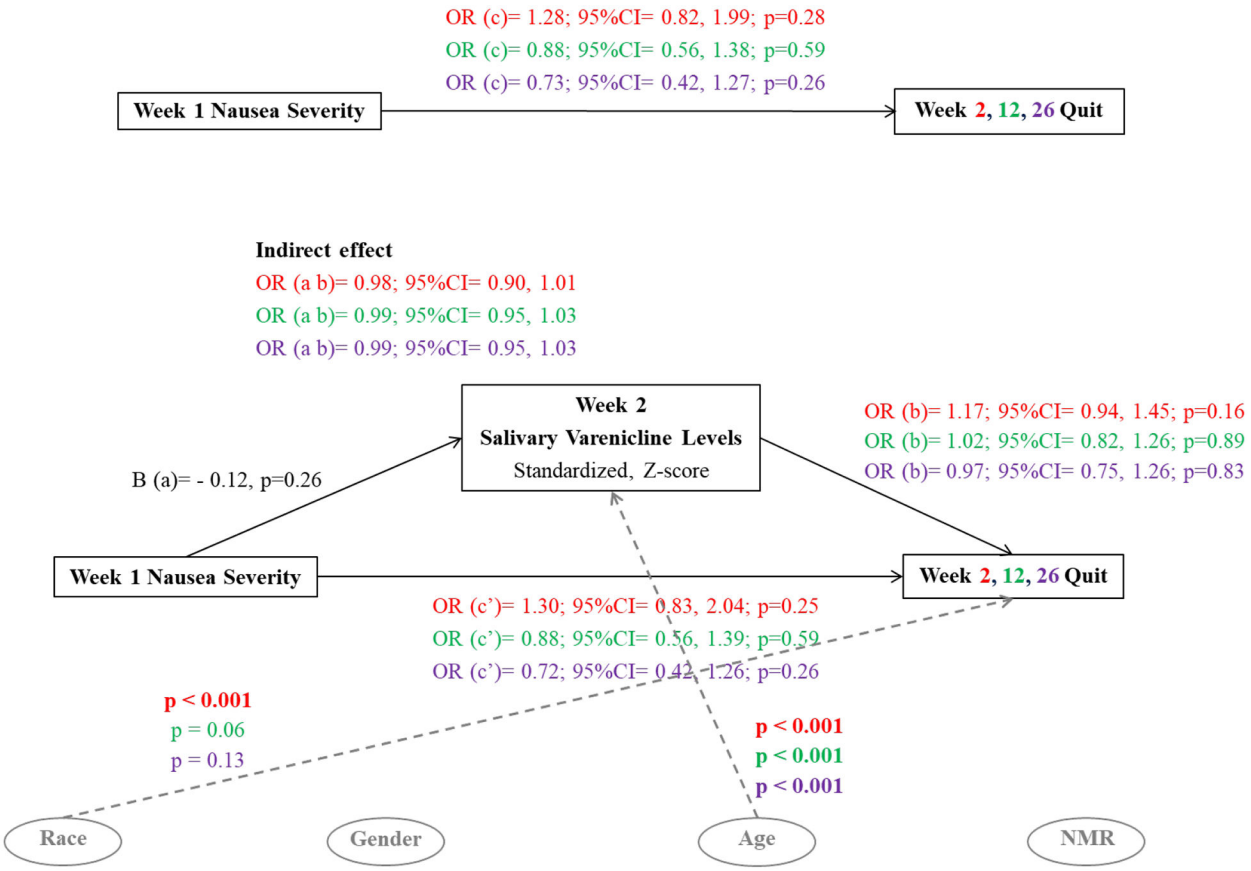

Figure 5 –. PNAT mediation path model. Association between Week 1 nausea and quit outcomes via standardized Week 2 salivary varenicline levels.

N=363 had available self-report Week 1 nausea data and provided a Week 2 salivary sample for varenicline level testing. Thin solid arrows indicate non-significant pathways; thick solid arrows indicate significant pathways ($p < 0.05$). The mediating effects of salivary varenicline levels (standardized, Z-score) on Week 2 quit (red), Week 12 quit (green) and Week 26 quit (purple) are denoted by (a b) pathway. (a) pathway indicates the relationship between Week 1 nausea severity and Week 2 salivary varenicline. (b) pathway indicates the relationship between Week 2 salivary varenicline and quit outcomes. (c) pathway is the direct effect adjusted for covariates; (c') pathway is the direct effect adjusted for covariates as well as indirect effect tested. Significant covariate (NMR included due to PNAT trial design) effects on mediators or outcomes are shown in grey (dotted line), with p-values shown. NMR = nicotine metabolite ratio; B = beta; OR = odds ratio; CI = confidence interval; p = p-value

Table 1.

Characteristics of Quit2Live according to Week 12 (primary end-of-treatment outcome) abstinence

Characteristics	**Smoking (N=273)** N (% of Total) or Mean (SD)	**Abstinent**[a] **(N=108)** N (% of Total) or Mean (SD)	**Total**[b] **(N=381)** N or Mean (SD)	**P-Value**[c]
Gender				
Male	129 (70)	54 (30)	183	.65
Female	144 (73)	54 (27)	198	
Age (years)	41.8 (11.6)	44.2 (11.8)	42.4 (11.7)	.06
Race				
Caucasian	114 (62)	69 (38)	183	**< .001**
African American	159 (80)	39 (20)	198	
BMI (Body Mass Index; kg/m^2)	29.9 (7.9)	30.6 (7.8)	30.1 (7.8)	.36
Baseline NMR (nicotine metabolite ratio)				
Slow Metabolizers <0.31	134 (77)	41 (23)	175	.05
Normal Metabolizer ≥0.31	139 (67)	67 (33)	206	
Week 4 Plasma Varenicline Concentration (ng/ml)	4.8 (4.2)	7.1 (3.6)	5.5 (4.2)	**< .001**
Week 1 Nausea[d]				
No incidence/Does not bother at all	192 (72)	74 (28)	266	.10
Mild	43 (61)	27 (39)	70	
Moderate	9 (75)	3 (25)	12	
Severe	7 (100)	0 (0)	7	
Week 4 Nausea[e]				
No incidence/Does not bother at all	158 (71)	65 (29)	223	.21
Mild	71 (68)	33 (32)	104	
Moderate	29 (76)	9 (24)	38	
Severe	14 (93)	1 (7)	15	
Week 8 Nausea[f]				
No incidence/Does not bother at all	176 (69)	79 (33)	255	.49
Mild	31 (63)	18 (37)	49	

Characteristics	Smoking (N=273) N (% of Total) or Mean (SD)	Abstinent[a] (N=108) N (% of Total) or Mean (SD)	Total[b] (N=381) N or Mean (SD)	P-Value[c]
Moderate	13 (72)	5 (28)	18	
Severe	1 (33)	2 (67)	3	

[a] Abstinence based on COT-verified point-prevalence, COT≤15ng/ml (intent-to-treat);

[b] Limited to N=381 participants who provided a Week 4 plasma sample for varenicline testing;

[c] P-values derived from Mann-Whitney U tests or Chi-Square Test for Independence (comparing smoking against abstinent);

[d] N=355 completed the survey and provided a Week 4 plasma sample;

[e] N=380 completed the survey and provided a Week 4 plasma sample;

[f] N=325 completed the survey and provided a Week 4 plasma sample.

Table 2 –

Characteristics of PNAT according Week 12 (primary end-of-treatment outcome) abstinence

Characteristics	Smoking (N=232) N (% of Total) or Mean (SD)	Abstinent[a] (N=144) N (% of Total) or Mean (SD)	Total[b] (N=376) N or Mean (SD)	P-Value[c]
Gender				
Male	128 (61.8)	79 (38.2)	207	1.0
Female	104 (61.5)	65 (38.5)	169	
Age (years)	44.6 (11.8)	46.4 (11.1)	45.3 (11.5)	.12
Race				
Caucasian	116 (57.1)	87 (42.9)	203	
African American	96 (65.8)	50 (34.2)	146	.10
Other	20 (74.1)	7 (25.9)	27	
BMI (Body Mass Index; kg/m^2)	28.7 (6.1)	29.7 (6.5)	29.1 (6.3)	.18
Baseline NMR (nicotine metabolite ratio)				
Slow Metabolizers <0.31	135 (67)	67 (33)	202	**.03**
Normal Metabolizer ≥0.31	97 (56)	77 (44)	174	
Week 2 Salivary Varenicline Concentration (ng/ml)	10.0 (13.0)	11.1 (10.2)	10.4 (12.0)	**.01**
Week 1 Nausea[d]				
No incidence/Does not bother at all	155 (60)	102 (40)	257	.83
Mild	61 (62)	38 (38)	99	
Moderate	5 (71)	2 (29)	7	
Severe	-	-	-	
Week 2 Nausea[e]				
No incidence/Does not bother at all	158 (61)	102 (39)	260	.42
Mild	60 (61)	38 (39)	98	
Moderate	11 (73)	4 (27)	15	
Severe	3 (100)	0 (0)	3	

[a] Abstinence based on CO-verified point-prevalence, CO≤8ppm (intent-to-treat);

[b] Limited to N=376 participants who provided a Week 2 saliva sample for varenicline testing;

[c] P-values derived from Mann-Whitney U tests or Chi-Square Test for Independence (comparing smoking against abstinent);

[d] N=363 completed the survey and provided a Week 2 salivary sample;

[e] N=376 completed the survey and provided a Week 2 salivary sample