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Estimations and Predictors of Non-Compliance in Switchers to Reduced Nicotine Content Cigarettes

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Abstract

Background and Aims—Clinical trials on the impact and safety of reduced nicotine content cigarettes (RNCs) are ongoing, and an important methodological concern is participant compliance with smoking only RNCs. Our aims were to measure non-compliance biochemically with urine cotinine (COT) and total nicotine equivalents (TNEs), compare with self-reported non-compliance, and identify associated covariates.

Design—Secondary analysis of a double-blind, parallel, randomized clinical trial.

Setting—10 research centers from the USA, enrolling participants from June 2013 to July 2014.

Participants—Volunteer sample of 242 participants (55% Caucasian), average age of 41.2 years, smoking at least 5 cigarettes per day (CPD).

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COI: NLB is a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. The other authors have no conflicts to declare.

Intervention—Smoking very low nicotine cigarettes (VLNCs; 0.4mg nicotine/g tobacco) for 6-weeks.

Measurements—The primary outcome was biochemically verified non-compliance, measured as thresholds of COT/CPD and TNE/CPD ratios, considering changes in nicotine content from conventional levels to VLNCs, and as an absolute threshold of Week 6 TNEs. Self-reported non-compliance was measured via daily phone calls. Key predictors included age, sex, race, menthol preference, nicotine metabolite ratio, time to first cigarette, dependence, CPD, TNEs, tar level and cigarette evaluation.

Findings—Estimates of non-compliance with smoking the VLNC cigarettes exclusively include: the biochemical ratios (both 78%), the Week 6 TNE threshold (76%) and self-report (39%). Of the key covariates, age, dependence and cigarette evaluations of satisfaction were significant; for age, younger participants more likely to be non-compliant (p=0.01; OR=0.98, 95% CI: 0.96–0.99). Dependence was significantly associated with self-reported non-compliance (p=0.01; OR=1.28, 95% CI: 1.06–1.55). Cigarette evaluations of satisfaction were significantly associated with non-compliance (p=0.001; OR=0.71, 95% CI: 0.61–0.82).

Conclusions—Biochemical assessments detect many more cases of non-compliance than self-report, and non-compliance with smoking VLNCs is observed in the majority of participants. Despite non-compliance, smokers reduced their intake of nicotine by an average of 60%, supporting the utility of nicotine reduction.

Introduction

The US Food and Drug Administration and regulators in other countries have the authority to establish tobacco product standards[1]. Mandated reductions in the nicotine content of cigarettes to make then less addictive, has been discussed in the US[2–4] and New Zealand[5], and in international meetings[6] as a promising cigarette “end game” approach[7]. If this intervention is successful in one country, it is likely others will try similar approaches. Because nicotine is the primary addictive constituent in cigarettes, a mandated reduction would likely substantially reduce cigarette smoking behavior and improve public health.

Multiple studies have been conducted to evaluate the effect of nicotine reduction in cigarettes [8–12] with follow-up periods of up to 24 months, showing that switching to reduced nicotine content cigarettes (RNCs) resulted in a reduction in cigarettes smoked per day[8–12] and self-reported dependence[8,10,12],, and few adverse events[9–12]. A challenge to the interpretation of these studies is that while the research questions pertain to a regulatory environment in which only RNCs are available, the clinical trials are conducted in an unregulated environment in which participants can use other products, including their usual brand cigarettes. One study did ensure compliance by enrolling participants in an inpatient setting, and this study also observed a decrease in smoking[13].

Because smokers tend to be brand-loyal, and RNCs may not satisfy in the same manner as the usual brand[14], study participants often continue to smoke some conventional cigarettes even when they are asked to only smoke RNC investigational cigarettes. Additionally, participants may not honestly self-report non-compliance. Any level of non-compliance may

influence estimates of the effect of RNCs, and studying the extent of non-compliance in the context of nicotine reduction is important.

In a previous publication, we estimated non-compliance with exclusive use of very low nicotine content (VLNC) cigarettes by measuring plasma levels of the major nicotine metabolite, cotinine, normalized for cigarette consumption, and comparing within-subject ratios of change in cotinine to the expected change in nicotine exposure based on the product[15]. The cutoff for compliance allowed for up to a 4-fold increase in nicotine exposure compared to baseline to accommodate potential compensation (i.e., smoking cigarettes more intensively) or other sources of variability (e.g., inaccurate reporting of CPD, differences in nicotine content of usual brand from our assumption of 10 mg, biological variability due to differences in renal clearance of nicotine and metabolites, assay variability, etc) without judging the smoker to be non-compliant. It should be noted that 400% compensatory smoking is unlikely to occur, especially given lack of evidence that total puff volume, or the intensity of smoking RNC cigarettes, significantly increases in prior studies[12]. Using this method, 60% of participants were determined to be non-compliant with smoking the VLNC cigarettes exclusively. These objective data were in contrast to 21% of participants self-reporting some level of non-compliance. This analysis demonstrated the necessity of measuring non-compliance biochemically and not relying exclusively on self-report.

A second study was undertaken in which participants smoked VLNC cigarettes exclusively in a controlled environment[16]. Participants were sequestered in a hotel and smoked only VLNCs for 4 days. Pooled urines were collected each day and urine total nicotine equivalents (TNE; the sum of nicotine and six metabolites) were assayed. Total nicotine equivalents are less influenced by changes in metabolism than cotinine, thus more accurately estimate nicotine exposure[17]. Of those smoking only VLNC cigarettes (0.4 mg nicotine/g tobacco), the 95th percentile for TNE was 6.41 nmol/mL. This threshold was proposed as another method by which compliance could be biochemically confirmed.

The current study utilizes data from a large clinical trial[12] to measure and compare three biochemical estimations of non-compliance with VLNC cigarettes. First, it replicates the biochemical estimation of cotinine normalized for cigarette consumption; secondly, it adds an additional analysis of TNE normalized for cigarette consumption; and lastly it measures absolute TNE thresholds for non-compliance. Biochemical methods are compared with self-report, as this measure is typically used to assess compliance. In addition, the study reports 50% and 75% reductions in TNEs to explore the proportion of participants with large reductions in nicotine exposure who were likely partially compliant but supplemented VLNCs with some usual brand cigarettes.

Finally, since none of the preceding studies measured factors associated with VLNC cigarette compliance, the current study assesses variables based on known associations with smoking cessation rates: age, sex, race, menthol preference, nicotine metabolite ratio (NMR), time to first cigarette, dependence, CPD, and TNEs [18–25]. Tar level was also included as a predictor as it varied between the two VLNC groups. Tar influences the sensory impact of cigarette smoke, and cigarette evaluations of satisfaction and reward as sensory effects can influence compliance[25].

Methods

Design

A double-blind, parallel, randomized clinical trial was conducted in which 840 daily smokers were randomized to 7 possible cigarette conditions including their usual brand or 1 of 6 research cigarettes (Spectrum cigarettes, obtained from National Institutes on Drug Abuse)[17]. One participant was determined to be ineligible after randomization and was excluded.

Participants

Participants were healthy volunteers who were required to smoke at least 5 cigarettes per day for the past 12 months, and not have used other nicotine/tobacco products more than 9 times in the past 30 days.

Intervention

Participants were asked to smoke only their assigned research cigarettes for 6 weeks, although, compliance was not incentivized. If participants smoked non-study cigarettes or used other nicotine/tobacco products (i.e. e-cigarettes, smokeless tobacco, cigars and nicotine replacement therapies) they were encouraged to report this to researchers at every study visit.

The study cigarettes contained the following nicotine contents (mg nicotine/g tobacco) averaged across menthol and non-menthol products: 15.8, 5.2, 2.4, 1.3, 0.4, and 0.4-HT (high tar). When assigned to study product, participants were given menthol vs. non-menthol cigarettes based on preference. For purposes of these non-compliance estimations, the focus will be on the lowest level of nicotine (i.e. 0.4 mg/g) which includes 242 participants. Within this group, there were two levels of tar yields (i.e.13 mg and 9 mg). We focused on the VLNC group because the large difference in nicotine levels between conventional and VLNC cigarettes allowed us to be confident in assessing compliance. This is not possible with higher levels of nicotine content, because when nicotine levels are closer to those of conventional cigarettes and there is possible compensatory smoking or other sources of variability as mentioned previously, there can easily be overlap in nicotine intake between compliers and non-compliers[14].

Measurements

At baseline, a first morning void urine was collected and participants completed a battery of questionnaires, including the Fagerström Test for Nicotine Dependence (FTND)[27]. Participants were enrolled in an Interactive Voice Response (IVR) system (InterVision Media) two weeks prior to their baseline visit, which called them daily and prompted them to enter the number of study and non-study cigarettes they smoked the previous day. Participants reported any alternative nicotine/tobacco product use during their weekly study visits, and the Cigarette Evaluation Scale (CES)[28] was administered after the first week on study cigarettes. At the end of Week 6, urine was collected again and questionnaires were repeated.

Urine samples, collected at baseline and Week 6, were analyzed for TNEs, the molar sum of nicotine and six metabolites, a measure of daily nicotine intake. Total nicotine, total cotinine, total trans 3′-hydroxycotinine ("total" refers to the sum of the analyte and its respective glucuronide conjugate) and nicotine-N-oxide were quantified in β-glucuronidase treated urine by liquid chromatography tandem mass spectrometry (LC/MS/MS) analysis as previously described[9]. The salivary ratio of 3-hydroxycotinine to cotinine (NMR, nicotine metabolite ratio) was measured as a phenotypic marker of the rate of nicotine metabolism, which has been associated with daily cigarette consumption and the level of tobacco dependence[30, 31].

In measuring non-compliance, we applied the cotinine/CPD ratio method as previously reported[14]. The VLNC group was assigned 0.4 mg/g (nominal mg content), which corresponds to 0.26 mg nicotine/cigarette. While the weight of the tobacco differs slightly across cigarettes [15], 0.26mg was a conservative estimate. As there are no public data on the nicotine content of many brands of conventional cigarettes, we assumed based on literature that their usual brand cigarette contained 10 mg/cigarette of nicotine[32]. We divided the mg/cigarette content by the assumed usual brand content (0.26mg/10mg=0.026) and allowed for up to 4-fold higher ratio to allow for compensatory smoking, use of other nicotine containing substances and/or other sources of variability, (0.026 * 4= 0.10). Thus, any participant with a ratio (baseline COT/CPD divided by Week 6 COT/CPD) greater than 0.10 would be considered non-compliant.

Next, we considered the TNE/CPD ratio, which was defined analogously to the COT/CPD ratio described above. This method was expected to have high concordance with the COT/CPD ratio, however, testing cotinine and TNE separately could provide different estimations of exposure.

The third method measured absolute TNE values. Based on previous data from smokers known to be compliant with VLNC cigarettes, as described in the methods[16], fully compliant subjects are unlikely to have TNEs above 6.41 nmol/mL. Therefore smokers with TNEs above 6.41nmol/mL would be considered non-compliant.

The final method to assess non-compliance was self-report. The primary measure of self-reported non-compliance was any non-study cigarette use reported on daily IVR calls within Week 6, as this assessment corresponded to the timing of the urinary biomarker collection at Week 6. Secondarily, self-reported non-study cigarette use from Weeks 1 through Weeks 6 was determined.

The extent of partial non-compliance was assessed by examining the percent of subjects who reduced their urinary TNEs to 50% or 75% of baseline at Week 6.

Statistical Analysis

Measures of non-compliance were analyzed on the log-scale, except for the reduction in TNEs which was measured with raw values. The association between baseline covariates and continuous measures of non-compliance (COT/CPD ratios, TNE/CPD ratios and

absolute TNEs) was evaluated using linear regression and summarized by the ratio of geometric means (RGM) of the predictor variables.

Covariates included age, race, sex, menthol preference, NMR, time to first cigarette, dependence (FTND scores, with and without CPD), baseline CPD, TNE, tar level and the CES satisfaction and reward subscales. We considered a univariate model for each covariate, as well as a multivariate model that included age, race, sex, NMR, menthol status, time to first cigarette and FTND (without the CPD item). Secondly, we completed a logistic regression analysis, which treated non-compliance as a dichotomous outcome defined by the COT/CPD ratio, TNE/CPD ratio, absolute TNEs and self-reported non-compliance. The model described above was again repeated with dichotomous outcomes.

Results

214 of the 242 VLNC smoker participants had available biomarker data for biochemical analysis of compliance. Baseline characteristics by availability of biomarker data are shown in Table 1, with the only significant difference being in race/ethnicity. There were no significant demographic differences between the combined VLNC groups (N=242) and the rest of the sample (N=598).

Compliance Analysis

The COT/CPD ratio comparing week 6 to baseline indicated 78% had some level of non-compliance. There were no significant differences in non-compliance between high and regular tar groups (79% non-complaint and 77% non-compliant, respectively, p=0.84). Thus all other results are reported with the groups combined. The distribution of ratios for all VLNC participants is shown in Figure 1.

The TNE/CPD ratio indicated 78% had some level of non-compliance, demonstrating high concordance with the COT/CPD ratio. A 2X2 comparison of both methods is shown in Table 2a, indicating that a vast majority (98%) of participants who were found non-compliant using the COT/CPD ratio criterion were also found non-compliant using the TNE/CPD ratio criterion. Ratios generated by these two methods were strongly correlated with one another (r=0.97, p<0.001).

Absolute TNE values were highly correlated with the COT/CPD ratios (r=0.75, p<0.001), and with the TNE/CPD ratios (r=0.77, p<0.001). A 2X2 comparison of the COT/CPD and absolute TNE methods is shown in Table 2b, indicating that a vast majority (96%) of participants who were found to have some level of non-compliance using the COT/CPD ratio criterion were also found non-compliant using the absolute TNE criterion.

When examining partial non-compliance using the reduction in urinary TNEs, approximately 45% of subjects reduced their daily intake to 50% of baseline and 61% of subjects to 75% of baseline.

Non-compliance was self-reported at Week 6 by 39% of participants in the VLNC group who completed their IVR calls at Week 6 (N=225). Non-compliance was reported by 80% of VLNC participants at any time between Weeks 1 and Weeks 6. Within the control 15.8 mg/g

group, 57% of participants self-reported non-compliance at least one time across all weeks of the study. A small minority of participants in the VLNC groups (*N*=9) reported the use of other nicotine/tobacco products at some time during the study. Of those participants, five had COT/CPD, TNE/CPD ratios and TNE levels consistent with compliance.

Figure 2 demonstrates rates of non-compliance with exclusive use of 0.4 mg/g VLNC cigarettes assessed by all methods.

Predictors of Non-Compliance

Linear regression results examining continuous measures of non-compliance indicated that age was significantly associated with the COT/CPD ratio and TNE/CPD ratio and was marginally associated with TNEs, such that younger subjects on average had higher geometric means. Similar results were observed for age in the multivariate model.

Baseline CPD was significantly associated with TNEs, such that the higher the baseline CPD the higher the geometric mean TNEs. However, baseline CPD was not significantly associated with TNEs in the multivariate model and was not significantly associated with the COT/CPD ratio or the TNE/CPD ratio. Baseline TNEs was not significantly associated with the COT/CPD ratio.

Cigarette evaluations of satisfaction and reward were significantly associated with the COT/CPD ratio, TNE/CPD ratio and TNEs, such that the lower satisfaction and reward were associated with higher geometric mean values. CES-satisfaction was significantly associated with non-compliance in the multivariate model however CES-reward was not. Linear regression results for unadjusted and adjusted models are shown in Table 3.

A logistic regression analysis was conducted with dichotomous biochemical non-compliance outcomes and self-reported non-compliance, with both univariate and multivariate models. Results for both models mirrored those of the linear regression with significant covariates of age, CES-satisfaction and reward predicting biochemical non-compliance. In predicting self-reported non-compliance, dependence (measured as baseline FTND without the CPD variable) was the only significant predictor. Higher dependence was associated with an increased rate of self-reported non-compliance OR=1.28, 95% CI: 1.06–1.55, p=0.01.

Discussion

Our study comparing the effects of reducing the nicotine content of cigarettes on smoking behavior and related symptoms was conducted to help provide a science base for possible future product regulatory action to reduce the addictiveness of cigarettes[12]. We asked subjects to smoke only the research cigarettes so that we could assess their response to RNCs. However, unlike a potential future regulatory scenario in which policy would mandate all available cigarettes and cigarette tobacco be low in nicotine, at present conventional cigarettes are widely available to participants in RNC studies. An important question in generalizing our research findings to a real-world reduced nicotine regulatory situation and possibly informing optimal strategies for nicotine reduction, is how well subjects comply with use of investigational cigarettes and with nicotine reduction. Indeed,

even those in the normal nicotine condition self-reported non-compliance, indicating that there is difficulty with compliance when brand switching. As we observed in a previous study of nicotine reduction with a smaller number of subjects, non-compliance was quite high[15]. In the present study non-compliance was 76–78% using biochemical assessment and 39% by self-report. Despite a high rate of non-compliance, the reduction in TNEs from baseline to Week 6 demonstrates that the experimental endpoint of nicotine reduction was partially met by the majority of subjects.

One of the aims of our study was to compare different methods of assessing compliance – three biochemical approaches and self-report. Two of the biochemical approaches were similar, examining individual changes in nicotine intake (assessed by urine cotinine or urine TNE) normalized for cigarette consumption, in comparison to predicted changes based on the difference in nicotine content of the RNC and the conventional cigarette. Some smokers might smoke more intensively to compensate for low nicotine availability. The extent of compensation when nicotine availability was limited by restricting the number of cigarettes available to smoke each day has been shown to as high as 300%[33]. While unlikely, we allowed for the possibility of 400% compensation or other sources of variability in the biochemical estimation so as to give subjects the maximal leeway before classifying them as non-compliant. Even with this liberal criterion, nearly 80% were non-complaint. The third biochemical approach used an absolute urine TNE value based on empirical observations of smokers confined to a hotel where they could smoke only research cigarettes[12]. This approach yielded a slightly lower, rate of non-compliance at 75%. Self-report yielded the lowest rate of non-compliance at 39%.

Biochemical measures of non-compliance produced similar rates and are, as expected, much more sensitive than self-report. Given that cotinine is the most straightforward biomarker to measure, we would recommend that the COT/CPD ratio method be used by researchers interested in measuring non-compliance.

We measured demographic and smoking related predictors of non-compliance. We found no significant associations between sex, race, menthol cigarette use, NMR, severity of dependence or time-to-first cigarette and compliance. Age influenced compliance, such that younger smokers were more likely to be non-compliant. Possible explanations for an age effect include that older smokers might be more motivated to quit and viewed the study as a possible method for quitting or that older smokers had more prior quit attempts and were more comfortable with nicotine withdrawal symptoms. Another possibility is that young subjects may have been generally less compliant with study procedures overall, such as attending visits as scheduled and on time. Indeed, younger participants were significantly more likely to drop out of the study both in the total sample ($p<0.001$) and trending in the VLNC groups ($p=0.17$).

While baseline CPD and dependence did not predict non-compliance in general, we did find that CPD predicted non-compliance using the absolute urine TNE approach. This is not surprising since a person smoking a high number of VLNC cigarettes per day would be expected to have levels of TNE closer to the TNE cutoff which was based on the 95 percentile of all VLNC cigarette smokers and could therefore appear non-compliant when

they really were compliant. Conversely, a smoker of few CPD could smoke a few conventional cigarettes and still have TNE below the upper threshold limit, and therefore appear compliant when they were not. Additionally, we found that evaluations of the study cigarettes, especially how satisfying they were, significantly predicted non-compliance. This finding points to the importance of somatosensory aspects in the acceptability of reduced nicotine cigarettes.

The present analysis focused only on the lowest nicotine content group in the clinical trial, where non-compliance would be expected to be most likely. Still, within this group, self-reported dependence and daily nicotine intake were lower at the end of the trial compared to the control condition and on average nicotine intake was reduced by 60%[12], indicating that despite non-compliance, participants were still substantially reducing their exposure and dependence.

We are unable to do the same biochemical estimations with higher nicotine content cigarettes due to overlapping influences of non-compliance and low levels of compensatory smoking. Self-reported non-study cigarette use was more likely to occur with cigarettes of 5.2 mg/g of nicotine or less as compared to the usual brand or 15.8 mg/g control group[12]. However, it is important to note that even in the 15.8 mg/g group, 57% of participants self-reported non-compliance at least once throughout the study, compared to the usual brand at 37%, suggesting that non-compliance is not only driven by nicotine reduction, but also by dissatisfaction with the use of investigational cigarettes.

Our results suggest that the nicotine availability and sensory aspects of the VLNC cigarettes were not sufficient to satisfy individual needs. On the other hand a substantial degree of nicotine reduction was tolerated by most subjects. Thus, while most smokers engaged in some non-compliance, they did not smoke conventional cigarettes to the extent that they achieved a daily nicotine intake similar to their baseline. The extent to which smokers seek additional nicotine to reduce withdrawal symptoms or for positive reinforcement or because they did not like the taste of the research cigarettes is unclear, and remains an important question.

The implications of our analysis are as follows. First, studies examining behavioral, subjective and physiological effects of VLNC cigarettes need to be extrapolated cautiously to a real-world nicotine reduction environment in which conventional cigarettes are unavailable, as studies may underestimate certain effects of switching to VLNC cigarettes (e.g., on craving and withdrawal symptoms, number of cigarettes smoked, quitting attempts) due to non-compliant use of usual-brand cigarettes. Second, even when smokers are able to reduce their daily nicotine intake substantially, they may be motivated to supplement with additional nicotine. The exact reasons for this are not yet determined, but could be relief of withdrawal symptoms, the effect of brand switching, need for arousal or mood-altering effects of nicotine and/or conditioned responses. A national nicotine reduction policy might work best if clean alternative sources of nicotine were readily available to deal with nicotine withdrawal symptoms and craving[1].

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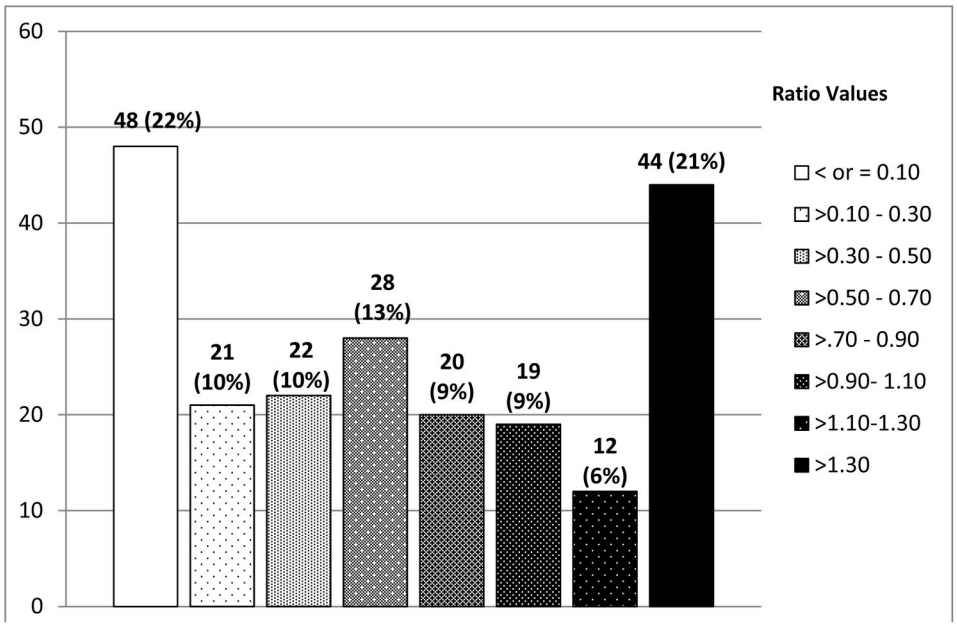

Figure 1.
Histogram of cotinine/CPD ratios for all VLNC participants

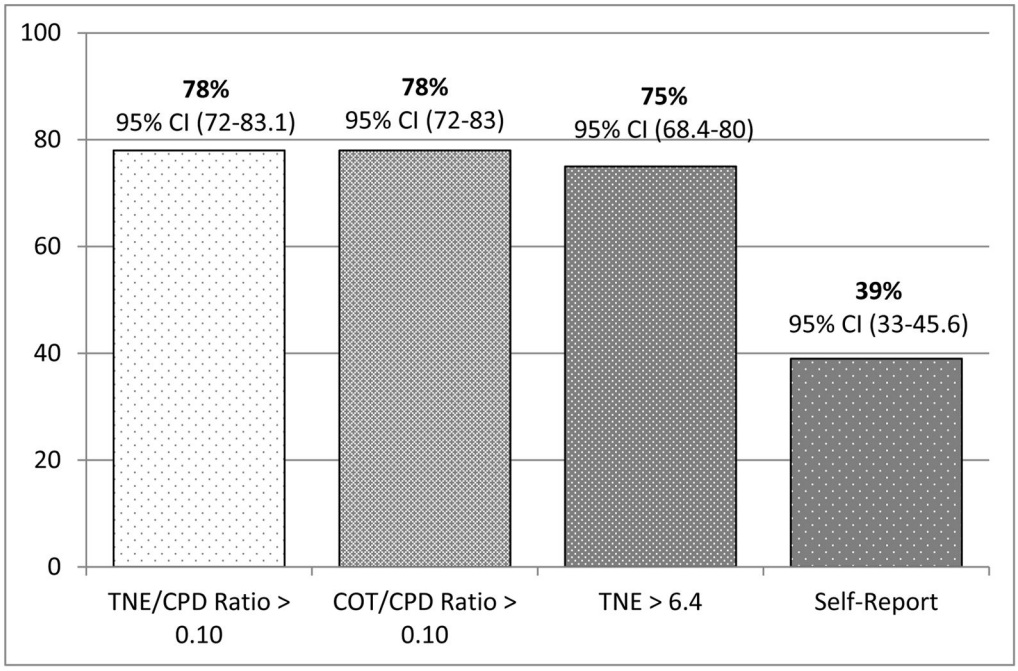

Figure 2.
Percent non-compliance estimated biochemically and by self-report

Table 1

Demographics for low nicotine group subset by availability of biomarker data

Baseline Characteristics (*n*=242)	Low Nicotine Group (*n*=242)	Biomarker Data Available (*n*=214)	Biomarker Data not Available (*n*=28)	*p*-value
Age, yrs	41.2 (13.4)	41.7 (13.4)	37.2 (12.9)	0.09
Sex n(%)				
Male	131 (54.1%)	114 (53.3%)	17 (60.7%)	
Female	111 (45.9%)	100 (46.7%)	11 (39.3%)	0.59
Race/Ethnicity n(%)				
Caucasian	134 (55.4%)	113 (52.8%)	21 (75%)	
Black	81 (33.5%)	77 (36%)	4 (14.3%)	
Other/mixed	27 (11.2%)	24 (11.2%)	3 (10.7%)	0.05
CPD	15.6 (7.5)	15.6 (7.6)	15.3 (7.3)	0.82
Menthol n(%)				
Yes	133 (55%)	95 (44.4%)	14 (50%)	
No	109 (45%)	119 (55.6%)	14 (50%)	0.69
FTND	5.2 (2.2)	5.3 (2.1)	5.1 (2.4)	0.74
TFC				
<30 min	194 (80.2%)	174 (81.3%)	20 (71.4%)	
>30 min	48 (19.8%)	40 (18.7%)	8 (28.6%)	0.22
Expired CO ppm	14.7 (7.4)	14.8 (7.4)	13.5 (7.3)	0.39
NMR	0.22 (0.17)	0.22 (0.17)	0.22 (0.21)	0.99
TNE nmol/mL	40.5 (42.1)	41.5 (42.1)	33.2 (33.5)	0.43
COT nmol/mL	11.4 (11.7)	12 (11.8)	7.7 (10.2)	0.13
CC-COT nmol/mg	9.9 (11.2)	10.5 (11.9)	6.1 (8.7)	0.09

*CPD: cigarettes per day; FTND: Fagerstrom Test for Nicotine Dependence; TFC: time to first cigarette; NMR: nicotine metabolite ratio; TNE: total nicotine equivalents; COT: cotinine; CC-COT: creatinine corrected cotinine

Table 2a, 2b and 2c

2X2 Comparison Tables of Ratio Methods and Self-Report

		COT/CPD Ratio ≤ 0.10	
		Yes	**No**
TNE/CPD Ratio ≤ 0.10	No	4 (8%)	163 (98%)
	Yes	44 (92%)	3 (2%)

		COT/CPD Ratio ≤ 0.10	
		Yes	**No**
Absolute TNE ≤ 6.41	No	6 (13%)	159 (96%)
	Yes	42 (87%)	7 (4%)

		COT/CPD Ratio ≤ 0.10	
		Yes	**No**
Self-Report	No	5 (10%)	77 (46%)
	Yes	43 (90%)	89 (54%)

*Denominators represent number of COT/CPD ratio compliant or non-compliant.

Table 3

Linear Regression results for continuous predictors of non-compliance

Covariates Unadjusted	**COT/CPD ratio**		**TNE/CPD ratio**		**TNE**	
	RGM (95% CI)	***p*-value**	**RMG (95% CI)**	***p*-value**	**RGM (95% CI)**	***p*-value**
Age	0.98 (0.96–0.99)	0.01	0.98 (0.97–1.0)	0.01	0.99 (0.97–1.0)	0.07
Sex	0.98 (0.63–1.51)	0.91	0.91 (0.6–1.36)	0.64	0.78 (0.51–1.21)	0.27
Race	1.37 (0.85–2.18)	0.20	1.38 (0.89–2.14)	0.15	1.03 (0.64–1.64)	0.92
Menthol	1.35 (0.87–2.08)	0.19	1.35 (0.9–2.03)	0.15	1.04 (0.67–1.61)	0.86
NMR	0.84 (0.6–1.17)	0.30	0.88 (0.64–1.21)	0.45	0.98 (0.7–1.38)	0.92
TFC	1.3 (0.83–2.53)	0.20	1.3 (0.78–2.19)	0.32	0.84 (0.48–1.45)	0.53
FTND	0.98 (0.87–1.07)	0.51	0.98 (0.89–1.08)	0.69	1.09 (0.99–1.21)	0.09
FTND-CPD	0.95 (0.83–1.06)	0.30	0.95 (0.85–1.06)	0.37	1.06 (0.94–1.19)	0.36
Baseline CPD	1.0 (0.97–1.03)	0.82	1.01 (0.98–1.03)	0.65	1.05 (1.02–1.08)	0.003
TNE	0.81 (0.62–1.07)	0.15	0.8 (0.62–1.03)	0.09	1.99 (1.52–2.6)	0.001
Tar level	1.04 (0.67–1.6)	0.87	1.06 (0.7–1.59)	0.79	0.95 (0.61–1.46)	0.81
CES-Satisfaction	0.71 (0.61–0.82)	0.001	0.72 (0.63–0.83)	0.001	0.78 (0.67–0.9)	0.001
CES-Reward	0.8 (0.67–0.94)	0.01	0.8 (0.69–0.94)	0.01	0.81 (0.68–0.96)	0.02
Covariates Adjusted						
Age	0.98 (0.96–0.99)	0.01	0.98 (0.96–0.99)	0.01	0.97 (0.95–0.99)	0.01
Sex	1.26 (0.8–1.99)	0.32	1.17 (0.76–1.79)	0.47	0.77 (0.5–1.2)	0.25
Race	1.74 (0.93–3.24)	0.08	1.73 (0.97–3.08)	0.07	1.84 (1.01–3.34)	0.05
Menthol	1.27 (0.75–2.17)	0.38	1.26 (0.77–2.07)	0.36	1.24 (0.74–2.07)	0.42
NMR	0.97 (0.7–1.36)	0.87	1.04 (0.76–1.43)	0.79	1.12 (0.81–1.55)	0.49
TFC	1.23 (0.57–2.64)	0.56	1.07 (0.53–2.18)	0.85	1.09 (0.53–2.27)	0.82
FTND-CPD	1.01 (0.86–1.2)	0.90	1.0 (0.86–1.17)	0.99	1.05 (0.89, 1.23)	0.58
Baseline CPD	1.02 (0.99–1.05)	0.17	1.02 (0.99–1.05)	0.12	1.02 (0.99–1.05)	0.14
TNE	0.9 (0.66–1.22)	0.49	0.87 (0.66–1.15)	0.33	0.99 (0.65–1.5)	0.95
Tar level	1.01 (0.66–1.56)	0.95	1.02 (0.68–1.52)	0.93	0.99 (0.65–1.5)	0.95
CES-Satisfaction	0.7 (0.58–0.85)	0.001	0.72 (0.6–0.85)	0.001	0.8 (0.66–0.96)	0.02
CES-Reward	1.0 (0.8–1.24)	0.98	0.99 (0.81–1.21)	0.92	0.93 (0.75–1.16)	0.53

RGM; ratio of geometric means of univariate predictors, NMR; nicotine metabolite ratio, TFC; time to first cigarette, FTND; Fagerstrom Test for Nicotine Dependence, CPD; cigarettes per day, TNE; total nicotine equivalents, CES; Cigarette Evaluation Scale