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# Reasons for Non-compliance in a Trial of Reduced Nicotine Cigarettes

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**Objectives:** In this paper, we examine the rates of, and reasons for self-reported non-compliance in a reduced-nicotine cigarette (RNC) clinical trial. **Methods:** We conducted a secondary analysis of a double-blind, parallel, clinical trial randomizing 839 smokers for 6-weeks to smoke their usual brand or investigational cigarettes ranging from 15.8 mg nicotine/g tobacco (control) to 0.4 mg/g (RNCs). We measured non-compliance, ie, self-reported smoking of non-study cigarettes, on a daily basis. Overall, 252 participants (30%) completed a survey assessing reasons for non-compliance. **Results:** Most participants (68%) reported non-compliance. Smokers receiving RNCs self-reported higher rates of non-compliance ranging from 77% (66%, 86%) to 82% (65%, 93%), than smokers in the control group; 50% (32%, 68%). Self-reported non-compliance decreased with time in the study (52% at Week 1 to 35% at Week 6). The most endorsed situation for non-compliance was the first cigarette of the day (47% of all participants). Older (greater than 44 years) and more nicotine-dependent individuals were more likely to report non-compliance with the first cigarette of the day and after a meal. **Conclusions:** Our results support the importance of nicotine-seeking in non-compliance. Individuals were most likely to be non-compliant in situations when deprived of nicotine.

**Key words:** reduced nicotine; clinical trial; non-compliance; self-report
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The United States (US) Food and Drug Administration, along with select other international regulatory bodies, has the authority to establish tobacco product standards.[1] Nicotine reduction in cigarettes is being considered as a regulatory strategy to reduce or eliminate cigarette smoking[2] in the US,[3-5] and in New Zealand,[6] and has been discussed at international meetings.[7] As nicotine is the primary addictive constituent in cigarettes, mandating a reduction would create an environment in which only reduced-nicotine cigarettes would be available, and potentially aid existing smokers in cessation, prevent experimental smokers from becoming addicted, and benefit public health overall.

Several clinical trials[8-15] utilize either between[8,9,12,13,16] or within-subjects designs[9,11,15] to examine how smokers respond to reduced nicotine cigarettes (RNCs), which have lower nicotine content, but similar tar levels (ie, 8-9 mg per cigarette), compared to cigarettes conventionally sold in stores. In general, clinical trials find that RNCs reduce the

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number of cigarettes smokers per day (CPD),[8-12] dependence,[8-12] and nicotine exposure,[8-12,15] with minimal evidence of compensatory smoking[12] or impact on existing psychiatric symptoms.[16] In smokers seeking treatment to quit, researchers in one study found that RNCs contributed to significantly more quit attempts when combined with nicotine replacement therapy (NRT) and behavioral support, compared to NRT and behavioral support alone.[17] Another found that those smoking RNCs and concurrently using the nicotine patch were more likely to be abstinent from conventional cigarettes, when compared to those smoking RNCs or using the nicotine patch alone.[18]

However, non-compliance to randomized treatment assignment, which occurs when participants smoke conventional cigarettes in place of, or in addition to RNCs, is common; best estimates (using cotinine, a nicotine metabolite) suggest that 60%-78% or higher use normal cigarettes.[19,20] In a secondary analysis by Nardone et al,[19] of the 242 participants in the very low nicotine group, predictors of non-compliance included younger age, higher levels of dependence, and less satisfaction with RNCs. After switching to RNCs, participants' exposure to nicotine still decreased substantially (on average by 60%), so the majority of the cigarettes smoked were RNCs.[19] A causal estimate analysis explored what the effects of Donny et al[12] would have been if participants were compelled to comply and smoke only RNCs.[21] Results were similar to those reported by Nardone et al;[19] however, to extrapolate RNC clinical trial results to a future regulatory environment in which only RNCs would be legally available, encouraging higher rates of compliance is essential.

Non-compliance could be motivated by the pharmacological need for nicotine, such as attenuating nicotine withdrawal or fatigue, and/or by external or contextual factors, such as the desire for taste of the usual brand (UB), or when socially smoking. Additionally, these motivations may be moderated by individual differences in age, sex, and level of dependence. Non-compliance may be more likely to happen during the beginning phases of switching to RNCs, as participants adjust to using RNCs over time.[8,22]

Understanding why and when participants are likely to be non-compliant could help identify challenges that smokers face with implementing a low-nicotine product standard and methods to enhance smoker acceptability of RNC regulations (eg, readily available alternative sources of nicotine). It also could help researchers develop strategies to optimize compliance in RNC clinical trials, by making participants aware of situations and timepoints within the trial in which maintaining compliance may be difficult.

The current study utilizes a subset of data from a large RNC clinical trial in which smokers were asked to smoke RNCs with different levels of nicotine or cigarettes with conventional nicotine levels over the course of 6-weeks.[12] This study found that participants smoking RNCs versus conventional nicotine cigarettes were more likely to have smoked at least one non-study cigarette (73%-81% versus 57% in the control group);[12] however, reasons for non-compliance were not reported.

The aims of the current analysis are as follows: (1) to determine rates of self-reported non-compliance and differences by cigarette nicotine level group; (2) to assess whether non-compliance increases or decreases over time, by examining rates of non-compliance by week; and (3) to examine reasons for non-compliance by cigarette group and moderators of these reasons, such as sex, age and dependence.

## METHODS

### Participants and Procedures

In a double-blind, parallel, randomized clinical trial, conducted in the US, 839 daily smokers, were randomized in a 1:1 ratio to their UB or one of 6 research cigarettes with the following nicotine contents (mg nicotine/g tobacco): 15.8 (conventional cigarette nicotine level), 5.2, 2.4, 1.3, 0.4, and 0.4-HT (high tar).[12] Tar levels ranged from approximately 8-10 mg/cigarette, except the HT condition at approximately 13 mg/cigarette.[12] All participants were paid for their time in the study. Methods and participant characteristics are described in detail in the primary paper.[12]

Participants were asked to smoke their study cigarettes for 6-weeks, respond to daily Interactive Voice Response (IVR) system phone calls, and attend study visits weekly. If participants used other nicotine or tobacco products, they were asked to report it at each study visit and to only smoke the study cigarettes given to them. The study design did not penalize participants for being non-complaint.

Smoking only the study cigarettes was encouraged at weekly visits.

**Measures**

Prior to randomization, participants completed the 6-item Fagerström Test for Nicotine Dependence (FTND) as a global measure of cigarette dependence; scores range from 0-10 and higher scores indicate a higher level of dependence.[23] To assess underlying dependence mechanisms, participants completed the 37-item Wisconsin Inventory of Smoking Dependence Motives (WISDM); scores ranged from 11-77 with higher scores indicating higher dependence.[24]

Participants also completed a basic demographic questionnaire.

Self-reported non-compliance was measured via IVR. Participants were called and asked the following questions: *"How many study cigarettes did you smoke yesterday?"* and *"How many other cigarettes (not given to you by the study) did you smoke yesterday?"* Participants responded using their touch-phone keypad. Participants in the UB group were instructed to consider the UB cigarettes provided to them "study cigarettes," and any other cigarettes (other commercial brands; UB purchased on their own) were considered "non-study cigarettes."

At each study visit, participants were asked if they used any other tobacco products including the following: cigars, cigarillos, little cigars, chew/dip, snus, hookah, bidis/clove cigarettes and electronic cigarettes (as electronic cigarettes are regulated in the US as tobacco products). Additionally, they were asked if they used any nicotine replacement products (ie, patch, gum, lozenge, nasal spray and inhaler).

Reasons for non-compliance were examined at the last study visit via an End of Study Survey. All non-UB condition participants were asked: "*When were you most likely to smoke non-study cigarettes*?" and the following list of scenarios were provided: first cigarette of the day, after a meal, when craving a cigarette, when drinking alcohol, with other smokers, when stressed, no particular reason, at regular intervals, when drinking caffeine and other. Participants could endorse up to 3 scenarios. The End of Study survey was added to the trial protocol during the later stages of participant enrollment, and thus, was only available to be administered to the last 252 participants (ie, 30% of the 839 participants).

**Data Analysis**

Demographics and baseline measures of dependence were compared by treatment group using ANOVA or Fisher's exact test, as appropriate. Rates of non-compliance were tallied using a binary indicator of any non-study cigarette use reported on daily IVR calls during a week, and percentages by cigarette group were estimated using the sample proportion. Rates of non-compliance over time were analyzed using a generalized linear mixed model with a linear term for week and a random effect for subject to account for correlation between observations from the same individual. The number of participants endorsing each reason for non-compliance was summarized by the sample proportion. Differences in reasons by cigarette group were tested using Fisher's exact test. Reasons were compared by age (median split), sex, and level of dependence, the latter assessed with the FTND and the WISDM (median split) also using Fisher's exact test.

## RESULTS

Table 1 shows sample characteristics by cigarette group. The 2 lowest RNCs groups were combined as there were no differences in non-compliance by tar condition.[19] One statistically significant baseline difference was found between our subset (N = 252) and the trial population (N = 587) in that those in our subset were more likely to be male, $p < .01$. No other statistically significant differences in demographics or dependence at baseline emerged.

Self-reported non-compliance reported via IVR (across all weeks of the study) occurred in 172 (68%) of the 252 participants. Non-compliance was lowest in the UB group (29%), higher in the 15.8 mg/g study cigarette control condition (50%), and highest in the RNC groups (77-82%; Table 1). The self-reported use of other tobacco and/or nicotine products across all weeks of the study was low (ranging from 2%-15% in the RNC groups), and there were no significant differences in use by groups (Table 1).

Reported use of non-study cigarettes significantly decreased over time; 52% of participants reported non-compliance at Week 1 versus 35% of participants at Week 6, $p < .001$.

**Table 1**
**Demographics, Self-reported Non-compliance and Situations for Non-compliance by Cigarette Group**

| Cigarette Group | Usual Brand N = 34 | 15.8 mg/g N = 34 | 5.2 mg/g N = 40 | 2.4 mg/g N = 33 | 1.3 mg/g N = 34 | 0.4 mg/g N = 77 | p value |
|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | |
| Age, mean (SD) | 41(13.6) | 43.9(14.8) | 44.4(12.2) | 41.2(12.2) | 41.6(14.3) | 40.6(12.9) | 0.40 |
| Sex, N (%) male | 27(79%) | 24(71%) | 24(60%) | 24(73%) | 19(56%) | 43(56%) | 0.13 |
| Baseline CPD, mean (SD) | 15.9(8.5) | 16.3(7.1) | 16.2(7.7) | 13.5(4.7) | 15.6(8) | 15.5(7.3) | 0.87 |
| Race white, N (%) | 13(38%) | 15(44%) | 15(38%) | 16(48%) | 16(47%) | 43(56%) | 0.26 |
| Race black, N (%) | 16(47%) | 15(44%) | 20(50%) | 11(33%) | 16(47%) | 23(30%) | 0.23 |
| **Dependence** | | | | | | | |
| FTND, mean (SD) | 5.2(2.4) | 5.1(2.3) | 5.6(1.8) | 4.5(2.2) | 5.4(2.2) | 5(2.1) | 0.43 |
| WISDM, mean (SD) | 41.8(13.2) | 42(13) | 42.1(14.7) | 42.2(9.8) | 40.6(11) | 42.9(12.8) | 0.99 |
| **Self-reported Non-compliance** | | | | | | | |
| Compliant, N (%) | 24(71%) | 17(50%) | 8(20%) | 6(18%) | 7(21%) | 18(23%) | <0.001 |
| Non-compliant, N (%) | 10(29%) | 17(50%) | 32(80%) | 27(82%) | 27(79%) | 59(77%) | |
| **Reasons for Non-compliance** | | | | | | | |
| First cigarette of the day, N (%) | - | 13(38%) | 26(65%) | 18(55%) | 15(44%) | 31(40%) | 0.08 |
| After a meal, N (%) | - | 12(35%) | 23(57%) | 14(42%) | 12(35%) | 24(31%) | 0.09 |
| When craving a cigarette, N (%) | - | 4(12%) | 12(30%) | 8(24%) | 5(15%) | 20(26%) | 0.26 |
| When drinking alcohol, N (%) | - | 7(21%) | 4(10%) | 8(24%) | 9(26%) | 17(22%) | 0.39 |
| With other smokers, N (%) | - | 5(15%) | 6(15%) | 5(15%) | 8(24%) | 10(13%) | 0.74 |
| When stressed, N (%) | - | 1(3%) | 4(10%) | 8(24%) | 5(15%) | 9(12%) | 0.12 |
| No particular reason, N (%) | - | 6(18%) | 2(5%) | 3(9%) | 6(18%) | 7(9%) | 0.29 |
| At regular intervals, N (%) | - | 3(9%) | 2(5%) | 1(3%) | 4(12%) | 11(14%) | 0.34 |
| When drinking caffeine, N (%) | - | 1(3%) | 3(8%) | 2(6%) | 2(6%) | 8(10%) | 0.78 |
| Other, N (%) | - | 2(6%) | 1(2%) | 1(3%) | 3(9%) | 8(10%) | 0.52 |
| **Rates of Other Tobacco and Nicotine Product Use** | | | | | | | |
| | - | 1(3%) | 1(2%) | 5(15%) | 1(3%) | 4(5%) | 0.31 |

**Notes.**
**SD = Standard deviation; CPD = Cigarettes per day; FTND = Fagerstrom test for nicotine dependence; WISDM = Wisconsin Inventory of Smoking Dependence Motives; p values from 2-sample t-test for age, CPD, and baseline measures of dependence and Fisher's exact test for all other endpoints.**

The most frequently reported situation for non-compliance was first cigarette of the day (endorsed by 47% of participants), followed by after a meal (39%), when craving a cigarette (22%), when drinking alcohol (21%), with other smokers (16%), when stressed (12%), no particular reason (11%), at regular intervals (10%), when drinking caffeine (7%), and other reason (7%). The most common explanation for "other reason" was when study cigarettes were unavailable due to forgetting them or to running out of them.

There were no statistically significant differences in reasons for non-compliance by cigarette group (Table 1). Table 2 shows differences in reasons by age, sex, and dependence. Older participants were significantly more likely to endorse non-compliance at the first cigarette of the day ($p < .001$) and after a meal ($p < .01$). Younger participants were

**Table 2**
**Reasons for Non-compliance by Age, Sex and Dependence**

| | Age (Median = 44) | | | Sex | | | FTND (Median = 5) | | | WISDM (Median = 43) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low N = 123 | High N = 129 | p value | Male N = 161 | Female N = 91 | p value | Low N = 94 | High N = 158 | p value | Low N = 126 | High N = 126 | p value |
| **First Cigarette of the Day** | **42(34%)** | **67(52%)** | **0** | 71(44%) | 38(42%) | 0.79 | **32(34%)** | **77(49%)** | **0.03** | 51(40%) | 58(46%) | 0.45 |
| **After a Meal** | **34(28%)** | 55(43%) | 0.002 | 57(35% | 32(35%) | 1 | 20(21%) | 69(44%) | 0 | **36(29%)** | **53(42%)** | **0.03** |
| **When Craving a Cigarette** | 30(24%) | 20(16%) | 0.21 | 27(17%) | 23(25%) | 0.14 | 19(20%) | 31(20%) | 1 | 22(17%) | 28(22%) | 0.43 |
| **When Drinking Alcohol** | 26(21%) | 22(17%) | 0.75 | 29(18%) | 19(21%) | 0.62 | 25(27%) | 23(15%) | 0.02 | 23(18%) | 25(20%) | 0.87 |
| **With Other Smokers** | 23(19%) | 14(11%) | 0.21 | 14(9%) | 23(25%) | 0.001 | 15(16%) | 22(14%) | 0.71 | 15(12%) | 22(17%) | 0.29 |
| **When stressed** | **21(17%)** | **6(5%)** | **0.004** | 14(9%) | 13(14%) | 0.20 | 12(13%) | 15(9%) | 0.41 | 11(9%) | 16(13%) | 0.42 |
| **No Particular Reason** | 10(8%) | 14(11%) | 0.39 | 15(9%) | 9(10%) | 1 | 10(11%) | 14(9%) | 0.66 | 13(10%) | 11(9%) | 0.83 |
| **At Regular Intervals** | 10(8%) | 12(9%) | 0.66 | 13(8%) | 9(10%) | 0.65 | 8(9%) | 14(9%) | 1 | 9(7%) | 13(10%) | 0.5 |
| **When Drinking Caffeine** | 9(7%) | 7(5%) | 0.80 | 12(7%) | 4(4%) | 0.43 | 3(3%) | 13(8%) | 0.18 | 6(5%) | 10(8%) | 0.44 |
| **Other** | 8(7%) | 9(7%) | 0.80 | 9(6%) | 8(9%) | 0.43 | 6(6%) | 11(7%) | 1 | 8(6%) | 9(7%) | 1 |

**Note.**
**FTND = Fagerstrom test for nicotine dependence; WISDM = Wisconsin inventory of smoking dependence motives; p values from Fisher's exact test.**

significantly more likely to endorse non-compliance when stressed ($p < .01$). Female participants were significantly more likely to endorse non-compliance when with other smokers ($p < .01$). Those with higher dependence as measured by FTND ($p < .05$) were significantly more likely to endorse non-compliance at the first cigarette of the day; and those with higher dependence, as measured on both the FTND ($p < .01$) and WISDM ($p < .05$) were significantly more likely to endorse non-compliance after a meal. Those with lower dependence were significantly more likely to endorse non-compliance when drinking alcohol ($p < .05$).

## Conclusions

Most of the sample (68%) self-reported non-compliance with cigarette groups of 5.2 mg/g nicotine and lower having higher rates of non-compliance than UB or conventional nicotine research cigarettes, although non-compliance occurred even in groups receiving conventional levels of nicotine.

For the UB group, reasons for non-compliance are likely due to various non-nicotine factors. Participants could have taken a non-study cigarette from another smoker. If their study supply became depleted, they could have smoked a UB cigarette, but not the ones provided by the study, thus reporting it as "non-study" cigarette use. There is also the possibility that UB participants may have wanted a different tasting cigarette, their UB or another type. In this group, non-compliance likely occurred because participants sought a different sensory experience.

Across RNC groups, non-compliance was much higher, pointing to the importance of lack of nicotine in non-compliance. The first cigarette of the

day, a scenario in which participants would be most nicotine deprived, was the most highly endorsed in RNC groups. However, other situations (eg, after a meal) were also highly endorsed and likely represent a combination of nicotine and non-nicotine (eg, taste, cue-related) factors interacting to motivate non-compliance.

Across all groups, the use of other nicotine and/or tobacco products was low, potentially because these products were not provided as part of the study. Also, during study enrollment (2013-2014) electronic cigarettes may have been on the cusp of gaining market popularity.

Self-reported rates of non-compliance significantly decreased throughout the study. As previously suggested, this could reflect that participants used more conventional cigarettes at the beginning of the study to help adjust to the lower levels of daily nicotine intake.[8] Alternatively, perhaps participants were less likely to self-report non-compliance over time to present that they were adhering to the study protocol. This is an important question and should be explored further.

The most endorsed reason for non-compliance was the first cigarette of the day, and this was not significantly different by cigarette group. For the control condition, it is possible that participants perceived their UB as more effective in reducing their overnight, withdrawal-induced craving, even though the nicotine levels would be similar to the control condition cigarettes. Older and highly dependent individuals were significantly more likely to endorse this reason, along with non-compliance after a meal. Older participants had been smokers for a significantly longer period of time ($p < .001$), and therefore (along with those who were highly dependent), may have had more difficulty with compliance overall. Women were significantly more likely to be non-compliant when with other smokers, corresponding with evidence that women are more social smokers than men.[25]

### Limitations

This analysis included only participants who completed the post-trial survey, which was added during later stages of enrollment, resulting in reduced power compared to the study's primary endpoints. Additionally, the subset of participants in this analysis was significantly more likely to be male than the full-trial population, reducing generalizability. Several cells contained small numbers, which increase variability, and multiple tests of significance can inflate the type I error rate. Although overall attrition rates were low (8%) in the primary clinical trial,[12] a possible bias is not including participants who may have dropped out of the study due to the inability to be compliant. Also, most of the sample had difficulty being compliant the first cigarette of the day, which could limit estimates of any changes in dependence, as it is an item on the FTND.

## IMPLICATIONS FOR TOBACCO REGULATION

Our results can inform future reduced-nicotine policy initiatives in that when smokers are deprived of nicotine, they are likely to seek it from another source. This is most likely to occur early on in the switching process, and if nicotine contents in cigarettes were reduced to 5.2 mg/g or lower. Older and more highly dependent individuals may have greater difficulty with switching. Reduced nicotine cigarettes may be more acceptable to smokers if they retain the taste and flavor of the UB. We can speculate that the acceptability of a nicotine reduction regulatory intervention is likely to be enhanced if smokers are given concurrent access to alternative clean sources of nicotine (eg, nicotine replacement therapy or electronic cigarettes), although we did not test that directly in our study.

### Human Subjects Statement

The Institutional Review Boards at all participating sites approved this study.

### Conflict of Interest Statement

Neal L. Benowitz 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.

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