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Nondaily Smokers' Changes in Cigarette Consumption With Very Low-Nicotine-Content Cigarettes
A Randomized Double-blind Clinical Trial

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Supplemental content

IMPORTANCE The US Food and Drug Administration is considering limiting cigarettes to very low nicotine levels. Cigarette consumption of nondaily intermittent smokers (ITS), who compose one-third of US adult smokers, could feasibly increase or could be unaffected if their smoking is not motivated by nicotine seeking.

OBJECTIVE To compare cigarette consumption in ITS receiving very low-nicotine-content cigarettes (VLNCCs) or identical normal-nicotine-content cigarettes (NNCCs).

DESIGN, SETTING, AND PARTICIPANTS This randomized double-blind clinical trial was conducted from June 2015 to July 2017 at a single US site. Volunteer ITS not planning to quit were recruited via media. Overall, 297 individuals enrolled, and 238 were randomized. Analyses were intent-to-treat.

INTERVENTIONS After a 2-week baseline of smoking their own brand of cigarettes provided gratis, ITS were randomized to VLNCCs or NNCCs for 10 weeks.

MAIN OUTCOMES AND MEASURES The number of cigarettes per day (CPD) was assessed by real-time reporting, timeline follow-back reports, and cigarette butt counts. The primary outcome was change in CPD from baseline to weeks 9 to 10 of intervention, adjusting for baseline CPD.

RESULTS The mean (SD) age of the 238 randomized participants was 37.9 (13.8) years. Of 238 participants, 108 (45%) were men. At baseline, the mean (SD) CPD was 3.1 (2.9). In intent-to-treat analyses using multiple imputation to address missing data, the VLNCC group had a mean decrease of 1.6 CPD (95% CI, 1.1-2.0; 51% of baseline) vs 0.05 decrease with NNCCs (95% CI, −0.5 to 0.4; 2% of baseline). Treatment group differences were not materially moderated by sex, race/ethnicity, or history of daily smoking. Cheating with conventional cigarettes, inferred from cotinine assays, was more common in the VLNCC group (OR, 2.95; 95% CI, 1.54-5.66), but sensitivity analyses showed significant VLNCC effects among the compliant participants as well. In longitudinal analysis of CPD over time with random intercept and slope, the VLNCC and NNCC groups differed significantly in both linear (−0.15; 95% CI, −0.22 to −0.08; $P < .001$) and quadratic (0.0026; 95% CI, 0.0010-0.0042; $P = .002$) trends: CPD dropped by 43.8% in the VLNCC group over 4 weeks, then leveled off thereafter. Abstinence (intent-to-treat, biochemically verified) in weeks 9 to 10 postrandomization did not differ significantly by treatment group (VLNCC, 10.2% vs NNNC, 5.0%; $P = .28$).

CONCLUSIONS AND RELEVANCE Switching to VLNCCs caused substantial smoking reduction among ITS but did not significantly increase abstinence. Response to a VLNCC intervention suggests that nicotine-seeking motivates ITS' smoking.

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Tobacco smoking, the leading cause of preventable mortality,[1] is typically maintained by nicotine dependence.[2,3] This underlies a policy proposal that smoking could be reduced or eliminated if the nicotine levels in tobacco were reduced to a level too low to initiate or maintain dependence.[4,5] The US Food and Drug Administration, which regulates tobacco,[6] announced in 2018 that it is considering mandating such reductions.[7,8]

Consistent with several small studies,[9,10] a large study of daily smokers (≥10 cigarettes per day) by Donny et al[11] reported that very low-nicotine-content cigarettes (VLNCCs) reduced mean consumption by about 5 cigarettes a day, a decrease of 23% to 30%.

However, 25% to 33% of adult US smokers do not smoke daily.[12-14] These intermittent smokers (ITS) nevertheless experience health risks from smoking[15,16] and have low quit rates.[17] It is not clear how ITS might respond to VLNCCs. It is not established whether ITS' smoking is motivated by nicotine-seeking. Intermittent smokers absorb normal amounts of nicotine[18] but do not experience craving or withdrawal when abstaining.[19,20] If ITS smoke for the acute effects of nicotine,[21] smoking VLNCCs might cause them to increase smoking. While heavy daily smokers might find it challenging to substantially increase their cigarette consumption, ITS might find it more feasible, especially on occasions when they particularly seek nicotine.[22] Thus, it is important to evaluate the effect of VLNCCs on ITS' smoking, both to assess the impact of a universal VLNCC policy and to address the role of nicotine in motivating ITS' smoking.

Several participant characteristics might moderate ITS' responses to VLNCCs. Some ITS have a history of daily smoking,[23] and these converted ITS show greater nicotine dependence[24] and may respond more like daily smokers. Racial differences in ITS have also been demonstrated.[25] Finally, Perkins et al[26] hypothesized that women's smoking is less motivated by nicotine, suggesting sex differences in response to VLNCCs. Accordingly, we evaluated history of daily smoking, race/ethnicity, and sex as potential moderators of VLNCC effects.

Key Points

Question Do nondaily smokers decrease cigarette consumption when switched from their own brand to very low-nicotine-content cigarettes (VLNCC) compared with identical normal-nicotine-content cigarettes (NNCC)?

Findings In this randomized double-blind clinical trial with 238 randomized participants, the mean cigarettes per day was reduced significantly more in the VLNCC group (1.6 cigarettes per day, 51% of baseline) than in the NNCC group (0.05 cigarettes per day, 2% of baseline).

Meaning Like daily smokers, switching to VLNCCs causes nondaily smokers to reduce their cigarette consumption, although it does not necessarily cause them to stop smoking.

Methods

This was a 12-week randomized, controlled, double-blind intervention trial that took place between June 2015 and July 2017. Analyses began August 2017. The trial protocol is available in Supplement 1. After a 2-week baseline period when participants smoked their own brand of cigarettes (provided free to parallel free cigarettes provided subsequently; this increased smoking[27]), participants were randomized (1:1, block size of 10, stratified by own-brand menthol preference) to receive VLNCCs or normal-nicotine-content cigarettes (NNCCs), blinded (identical in appearance), which they were to smoke exclusively for 10 weeks (eFigure 1 in Supplement 2). The study was approved by the University of Pittsburgh institutional review board. Participants provided written informed consent.

Participants

Adult ITS (defined as smoking any amount nondaily, 4-27 days per month) who were not planning to quit in the next 3 months were recruited through media and posters in Pittsburgh, Pennsylvania (see eTable 1 in Supplement 2 for detailed inclusion criteria). The study aimed to recruit 364 participants to achieve 80% power to detect a 20% treatment group difference in change in cigarettes per day (CPD) between baseline and weeks 9 to 10 postrandomization (eAppendix 13.3 in Supplement 1).

Procedures

At research site visits, participants were dispensed cigarettes, returned butts from smoked cigarettes, completed assessments, reported potential adverse events, provided urine specimens, and had carbon monoxide assessed in a breath sample. Participants received financial compensation for attending each visit for a total of $455 (eAppendix 11.0 in Supplement 1).

Cigarettes

Experimental cigarettes had either very low nicotine (VLNCCs: 0.07 mg nicotine delivery; NRC200, NRC201) or normal nicotine (NNCCs: 0.8 mg; NRC600, NRC601)[28] and were identical in appearance; menthol smokers received menthol cigarettes. The tobacco's nicotine content was manipulated genetically so participants could not extract normal amounts of nicotine from the VLNCCs.[28] Cigarettes were provided by the National Institute of Drug Abuse and were approved for use as an Investigational Tobacco Product by the US Food and Drug Administration.

Measures

Cigarette consumption was the primary outcome and was assessed using 3 different methods: (1) timeline follow-back reports of the number of research and conventional cigarettes smoked each day since the prior visit (retrospective reports entered in calendar format)[29-31]; (2) counts of cigarette butts stored in plastic bags issued for each day; and (3) reports from participants each time they smoked via calls to an interactive voice response system; cell phones were provided as needed. Daily, participants received a call to report cigarettes not reported in real time. The 3 methods were highly concordant, yielding a highly reliable composite (mean) measure of daily consumption.[32] Mean CPD was computed during 2-week blocks, relative to time of randomization.

Abstinence for the final 2-week block was also assessed, with biochemical validation via urinary total cotinine (<100 ng/mL; carbon monoxide, <8 ppm).[27,33] (Data from ITS[19] indicated that 14 days of abstinence was rare during ad libitum smoking.) In intent-to-treat (ITT) analyses, smoking was assumed for participants lost to observation.[34,35] On exit from the study, participants were asked to rate their intention to quit smoking (1 indicating not at all and 5 indicating completely) in the succeeding month and in 6 months.

Cotinine concentrations (Total: Free + Glucuronide, ng/mL) in urine were assayed by liquid chromatography–mass spectrometry (Masonic Cancer Center, University of Minnesota)[36,37] in spot urine samples at randomization and 2, 6, and 10 weeks later. We adapted for ITS published algorithms for imputing use of conventional cigarettes (cheating) in participants whose observed cotinine levels were implausible absent such behavior[38,39] (eAppendix 2.4 in Supplement 1).

Participants were instructed not to use other nicotine products (ie, e-cigarettes, nicotine replacement products, smokeless tobacco, pipes, cigars, and hookah) but to report it if they did by timeline follow-back and interactive voice response. The higher reported value was analyzed. Adverse events, coded by the study physician blind to group assignment for seriousness and likely causality, were assessed by spontaneous report and abstracted from the Respiratory Health Questionnaire, as in Donny et al.[11]

Statistical Analysis

The primary analysis assessed change in mean CPD between baseline and the final 2 weeks (9-10) of treatment (selected as a direct, transparent measure of change), controlling for baseline CPD (because change may depend on the starting value). This ITT analysis used multiple imputation (25 iterations) of missing CPD data, using methods for monotone missingness (eAppendix 2.2 in Supplement 1).[40] The imputation used multiple baseline variables to predict composite CPD for those participants with missing CPD values in weeks 9 to 10. Observed data included 3 participants who contributed more than 5 days of interactive voice response in weeks 9 to 10 despite not completing the study. The variables used in imputation were treatment group, age, education, sex, race/ethnicity, daily smoker history, income, number of years smoked, Nicotine Dependence Syndrome Scale score,[41] Wisconsin Inventory of Smoking Dependence Motives Primary Dependence Motives score,[42] exhaled breath carbon monoxide concentration, and prestudy mean and maximum CPD from a retrospective timeline follow-back assessment at enrollment. Sex, race/ethnicity, and history of daily smoking were analyzed as prespecified potential moderators of treatment effects in both ITT and completer-participants analyses.

Secondary analyses of cigarette consumption used linear mixed-effects models with random intercept and slope, with both linear and quadratic terms for 2-week intervals, to assess patterns of change in CPD throughout time.[43] Treatment group differences in abstinence were modeled using logistic regression. Effect coding was used throughout.[44]

Sensitivity analyses addressed cheating with conventional cigarettes, both by self-report (analyses excluding conventional cigarettes or participants reporting ≥10% conventional cigarettes) and by inference from cotinine (eAppendix 2.3 in Supplement 1), as well as use of other nicotine-containing products. Differences in baseline smoking patterns were also examined as moderators, and analyses with log-transformed CPD data were also performed. Sensitivity analyses followed the baseline-to-end comparisons of the primary analysis using observed data.[45] Statistical analyses used 2-sided tests at $P < .05$ (without multiplicity correction), using SAS, version 9.4 (SAS Institute, Inc).

Results

Between June 2015 and May 2017, 297 participants were enrolled, and 238 (80.1%) were randomized. The study did not reach its target sample size during the funding period, but the dropout rate was lower than anticipated. Randomization was successful in balancing the treatment groups, which were similar in demographics and smoking history (**Table**). The mean (SD) age of randomized participants was 37.9 (13.8) years, 120 (55%) were women, 61 (26%) were black, and 118 (50%) were converted ITS. Black race, heavier smoking, and lower education levels were overrepresented in participants who discontinued participation between enrollment and randomization (Table).

Figure 1 and eTable 2 in Supplement 2 show that loss to observation after randomization was similar in the 2 treatment arms. Participants with higher baseline CPD were more likely to be lost (OR, 1.12 per baseline CPD; 95% CI, 1.02-1.24; $P = .02$). Controlling for baseline CPD, sex, and history as a daily smoker were not associated with loss, but black individuals were more likely to be lost (22 [36.1%]) than white individuals (23 [15.1%]) (OR, 1.74; 95% CI, 1.34-5.55; $P = .01$). In a proportional hazards survival analysis controlling for baseline CPD, ongoing CPD during treatment as a time-varying covariate (essentially, response to treatment) did not predict subsequent loss to observation (adjusted hazard ratio for a 1-unit increase in CPD, 1.07; 95% CI, 0.95-1.21; $P = .25$).

Cigarette Consumption

In ITT analysis controlling for baseline CPD, the VLNCC group reduced consumption by 1.51 CPD more (95% CI, 0.86-2.17) than the NNCC group throughout 10 weeks ($P < .001$; **Figure 2** and eTable 3 in Supplement 2). Mean change was −1.6 CPD with VLNCCs (95% CI, −1.1 to −2.0; −51% vs baseline) vs −0.05 with NNCCs (95% CI, −0.5 to 0.4; −2% vs baseline). Complete-case analysis showed substantively the same effect (Figure 2). The standardized effect size (Cohen d)[47] was 0.6. Similar treatment effects were seen for log(CPD) (eFigure 2 in Supplement 2) and for both the proportion of days smoked (**Figure 3**) and cigarette consumption on smoking days (eFigure 3 in Supplement 2).

In planned subgroup analyses, VLNCC effects did not vary by sex or race/ethnicity (eFigures 4 and 5 in Supplement 2). Mean decrease among converted ITS was 1.89 CPD (95% CI, 0.80-2.97) more with VLNCC than NNCC, while mean decrease among native ITS without a history of daily smoking was

Table. Participant Characteristics

Characteristic	All Enrolled Participants (n = 297)	Participants Lost Prior to Randomization (n = 59)	All Randomized Participants (n = 238)	P Value[a]	NNCC Group (n = 120)	VLNCC Group (n = 118)	P Value[b]
Demographics							
Age, mean (SD), y	38.2 (13.8)	39.6 (13.8)	37.9 (13.8)	.38	38.4 (14.2)	37.4 (13.5)	.56
Men, No. (%)	135 (45.5)	27 (45.5)	108 (45.4)	.96	49 (40.8)	59 (50.0)	.16
Race/ethnicity, No. (%)							
White	181 (60.9)	29 (49.1)	152 (63.9)		76 (63.3)	76 (64.4)	
Black	88 (29.6)	27 (45.8)	61 (25.6)	.01	34 (28.3)	27 (22.9)	.41
Other	28 (9.4)	3 (5.1)	25 (10.5)		10 (8.3)	15 (12.7)	
Hispanic	16 (5.4)	3 (5.2)	13 (5.5)	.93	6 (5.0)	7 (5.9)	.75
Education, No. (%)							
≤High school	70 (23.6)	23 (37.9)	47 (19.7)		27 (22.5)	20 (17.0)	
Some college	115 (38.7)	22 (37.9)	93 (39.1)	<.01	48 (40.0)	45 (38.1)	.41
≥Bachelor's degree	112 (37.7)	14 (24.2)	98 (41.2)		45 (37.5)	53 (44.9)	
Annual income, mean (SD), $[c]	27 669 (23 180)	24 353 (24 707)	28 481 (22 772)	.22	29 042 (23 715)	27 906 (21 849)	.70
Smoking at enrollment							
Cigarettes per day, mean (SD)[d]	2.0 (1.8)	2.5 (2.1)	1.9 (1.7)	.02	1.9 (1.7)	1.9 (1.6)	.90
Days smoking, mean (SD), wk[d]	3.8 (1.4)	4.1 (1.4)	3.7 (1.4)	.05	3.7 (1.4)	3.7 (1.4)	.91
No. of cigarettes per d, on smoking days, mean (SD)[d]	3.5 (2.7)	4.1 (3.1)	3.4 (2.6)	.09	3.5 (2.9)	3.3 (2.3)	.67
Smoke menthol, No. (%)	158 (53.2)	38 (64.4)	120 (50.4)	.05	62 (51.7)	58 (49.2)	.70
Time smoked, mean (SD), y	16.9 (12.2)	17.5 (11.9)	16.8 (12.3)	.69	17.9 (12.4)	15.7 (12.1)	.16
Past daily smoker, No. (%)	144 (48.7)	26 (44.8)	118 (49.6)	.52	61 (50.8)	57 (48.3)	.70
FTND score of 0, No. (%)[46]	200 (68.0)	23 (39.7)	177 (75.0)	<.001	94 (79.0)	83 (70.9)	.15

Abbreviations: FTND, Fagerstrom Test for Nicotine Dependence; NNCC, normal-nicotine-content cigarettes; VLNCC, very low-nicotine-content cigarettes.

[a] Comparison between randomized and nonrandomized groups. χ^2 Test for categorical variables, and *t* test for continuous variables.

[b] Comparison between VLNCC and NNCC groups. χ^2 Test for categorical variables, and *t* test for continuous variables.

[c] Uses midpoints from 12 categories from less than $5000 to more than $80 000.

[d] Timeline follow-back reporting (28 days).

1.07 CPD (95% CI, 0.35-1.79). Converted ITS smoked more at baseline (as previously observed[24]) and accordingly had greater capacity to decrease smoking. When CPD was expressed as a percentage of baseline, converted ITS and native ITS showed very similar two-thirds decrease in CPD (eFigure 6 in Supplement 2). Similarly, heavier baseline smokers showed greater effects but not when expressed as a percentage of baseline, and those who smoked on more days showed a greater percentage of reductions in CPD (eFigures 7 and 8 in Supplement 2).

Analysis throughout 2-week periods also showed that CPD decreased significantly more in the VLNCC group over time (**Figure 4**). In the VLNCC group, cigarette consumption decreased steeply over the first 4 weeks of treatment (by 1.18 CPD [95% CI, 0.76-1.59] or 43.8% of baseline [95% CI, 23.3%-55.4%) and then leveled off (treatment × time interaction, linear $P < .001$, quadratic $P = .002$). A post hoc analysis showed no group differences in CPD change from week 5 on ($\beta = .05$; 95% CI, −0.04 to 0.13; $P = .27$).

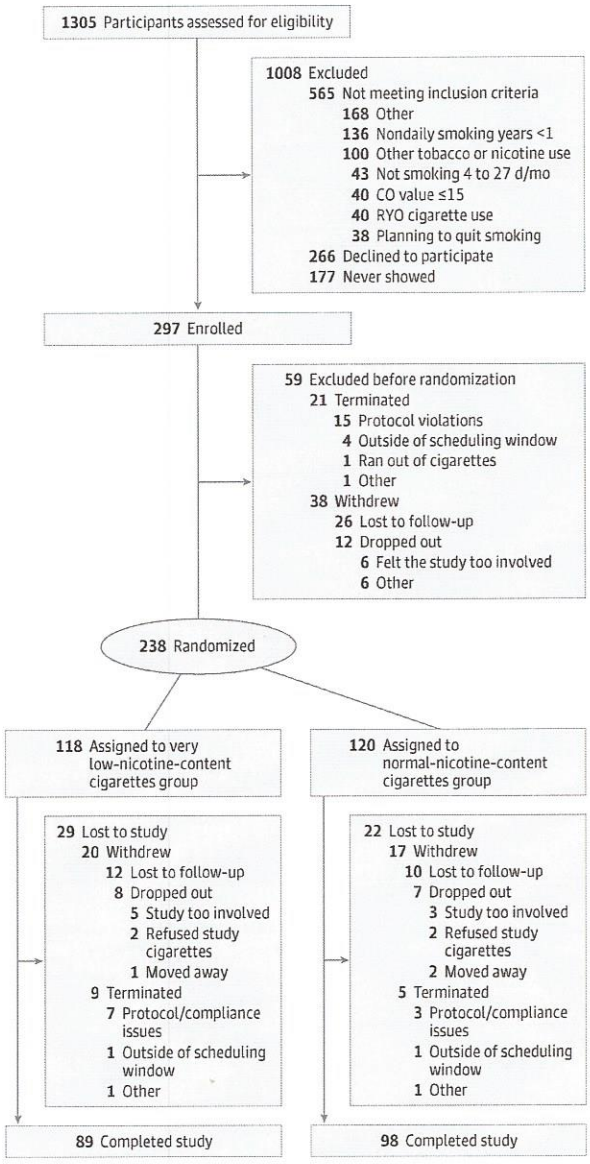
Abstinence and Intention to Quit

Reported abstinence in the last 2 study weeks did not differ by treatment group in logistic regression models controlling for baseline CPD, either in ITT analysis counting lost participants as smoking (VLNCC, 12 of 118 [10.2%] and NNNC, 6 of 120 [5.0%]; OR, 1.78; 95% CI, 0.62-5.12; $P = .28$) or among completers (OR, 1.94; 95% CI, 0.67-5.63; $P = .22$). Intention to quit rating, assessed by *t* tests in 192 participants, mostly study completers, did not vary by treatment group either for the next month (VLNCC, 2.55 [95% CI, 2.27-2.84] and NNCC, 2.39 [95% CI, 2.12-2.66]; $P = .41$) or within 6 months (VLNCC, 2.86 [95% CI, 2.56-3.16] and NNCC, 2.73 [95% CI, 2.44-3.02]; $P = .54$).

Compliance

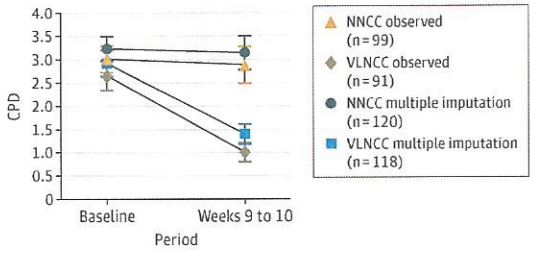
Overall, participants reported that 3.6% (95% CI, 2.4%-4.9%) of the cigarettes they smoked postrandomization were conventional cigarettes. This cheating was concentrated in 27 participants (19 in the VLNCC group and 8 in the NNCC group) who reported 10% or more of their smoking was nonresearch ciga-

Figure 1. Study Flowchart



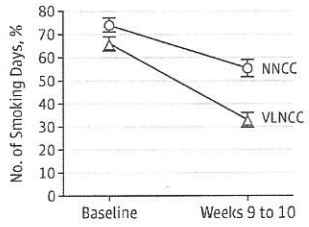
CO indicates carbon monoxide; RYO, roll your own.

Figure 2. Mean Cigarettes per Day (CPD) at Baseline and End of Study



Baseline was 2 weeks before randomization, and weeks 9 to 10 was the end of the study. Observed data are plotted (mean [SE]). Baseline data (own-brand cigarettes provided gratis) are based on observed data, and data for weeks 9 to 10 are based either on observed data (participants not lost to observation) or monotone multiple imputation of missing CPD. Analysis of imputed data indicated that, while controlling for baseline CPD, the very low-nicotine-content cigarettes (VLNCC) group reduced their CPD significantly more than the normal-nicotine-content cigarettes (NNCC) group during the 10-week postrandomization period ($P < .001$). Mean decrease among VLNCC participants was 1.51 CPD (95% CI, 0.86-2.17) more than NNCC participants. Analysis of observed data showed substantively the same effect ($P < .001$). Mean decrease among VLNCC participants was 1.64 CPD (95% CI, 0.93-2.35) more than NNCC participants.

Figure 3. Percentage of Days Smoked at Baseline vs End of Study



Data are mean percentages of days with any smoking during the baseline and weeks 9 to 10 by treatment group. Observed data are plotted (mean [SE]). Analysis indicated that, while controlling for baseline smoking day percentage, the very low-nicotine-content cigarettes (VLNCC) group (n = 91) reduced their days smoking percentage significantly more than the normal-nicotine-content cigarettes (NNCC) group (n = 99) over the 10-week postrandomization period ($P < .001$). Mean decrease among the VLNCC group was 17% (95% CI, 9%-25%) more than the NNCC group.

rettes; they accounted for 69% of all nonresearch cigarettes. The odds of VLNCC participants' being in this group were 2.69 (95% CI, 1.13-6.41) times greater than for NNCC participants ($P = .03$). Primary treatment effects were not substantively changed by excluding these participants or by excluding conventional cigarettes from CPD calculations (eFigures 9 and 10 in Supplement 2).

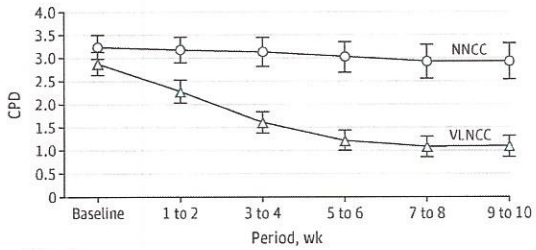
More VLNCC (38 of 107 [35.5%]) than NNCC participants (17 of 108 [15.7%]) were inferred to have cheated based on at least 1 of 3 postrandomization cotinine values (OR, 2.95; 95% CI, 1.54-5.66). As a sensitivity test, we reassessed change in CPD based on the noncheating participants; the effect was still significant (eFigure 11 in Supplement 2) (95% CI, 0.53-2.05; $P < .01$). Urinary cotinine concentrations were also analyzed as continuous variables and showed significantly greater decreases in the VLNCC group (eFigures 12 and 13 in Supplement 2).

The most commonly used nicotine product was e-cigarettes on 0.8% of study days (148 of 17738). Among participants not using e-cigarettes at enrollment or baseline, new use of e-cigarettes was statistically significantly more common in the VLNCC group, particularly among heavier smokers (eFigure 14 in Supplement 2). Excluding participants who increased postrandomization use of other tobacco/nicotine products by 1 or more unit per week did not substantively change treatment effect estimates (eFigure 15 in Supplement 2).

Subjective Discernment of Condition

At exit, participants were asked to guess which cigarettes they had been randomly assigned. Participants in the VLNCC group

Figure 4. Cigarette Consumption by Time and Treatment Group



No. of participants						
NNCC	120	118	109	105	100	99
VLNCC	118	114	105	99	94	91

Mean daily cigarette consumption (observed data are plotted as mean [SE]) in 2-week periods among participants in the very low-nicotine-content cigarettes (VLNCC) and normal-nicotine-content cigarettes (NNCC) groups. Both linear and quadratic trends in cigarettes per day (CPD) varied significantly by group.

were more likely to guess correctly (χ^2 test $P < .01$; 73 [80.2%] vs 39 [39.0%]; OR, 6.34; 95% CI, 3.30-12.20).

Adverse Events

Overall, 83 randomized participants (34.9%) reported an adverse event, of which 34.8% (n = 41) were in the VLNCC group and 35.0% (n = 42) were in the NNCC group (χ^2 test $P = .97$). Three (1 in VLNCC) reported serious adverse events, none related to study treatment.

Discussion

This study demonstrates that switching nondaily smokers to VLNCCs leads to a reduction in cigarette consumption, consistent with the role of nicotine as a primary reinforcer for smoking. Smokers switched to VLNCCs reduced their smoking by 51%, a large effect.[47] Not only did ITS reduce the number of cigarettes they consumed, they also reduced the number of days on which they smoked, suggesting substantial diminution in reinforcement. The VLNCC effect was most prominent in ITS who smoked on more days at baseline and thus were closer to daily smoking. These data extend to nondaily smokers the findings of Donny et al[11] and others[9,10,46] who demonstrated reductions in cigarette consumption (although smaller on a percentage basis) in daily smokers, who may experience withdrawal when nicotine-deprived. This is important because nondaily smokers now constitute 25% to 33% of adult smokers in the United States,[12-14] making it crucial that effects on this fraction of the smoker population be considered in tobacco policy.

Our results suggest that a policy mandating VLNCCs might reduce consumption without leading to quitting in ITS. Reductions in CPD after switching to VLNCCs occurred relatively quickly over 4 weeks, then levelled off, not suggesting a trajectory that would lead to smoking no cigarettes. Despite a trend for more abstinence in the VLNCC group, most VLNCC participants continued to smoke and did not have greater intention to quit than NNCC participants after the 10-week intervention. A similar pattern of reduced consumption without extinction was observed in daily smokers using VLNCCs,[11] suggesting that VLNCCs maintain enough reinforcement to sustain smoking for some individuals for some time or that occasional smoking of conventional cigarettes (which would be difficult if a low-nicotine policy were implemented) maintained smoking. Adverse events were uncommon and did not differ by treatment. Our results mitigate concern that ITS might increase smoking when switched to VLNCCs. That ITS respond to VLNCCs in a manner similar to daily smokers suggests that a universal policy is possible.

Although treatment assignment was blinded, ITS smoking VLNCCs were often able to guess they were in the low-nicotine group. This is not surprising, as nicotine's sensory and psychoactive effects are discernable.[41]

Although most participants reported smoking only the experimental cigarettes, some admitted cheating by smoking conventional cigarettes, and others were assumed to have cheated based on their cotinine levels. Importantly, VLNCCs caused reductions in CPD even among those who did not get nicotine elsewhere. Also of interest, cheating was more common in the VLNCC group, as was new use of e-cigarettes, suggesting these behaviors were motivated by nicotine-seeking.

This study contributes to understanding ITS smoking behavior. Studies have documented that ITS inhale, absorb normal amounts of nicotine per cigarette, and metabolize it normally[18] but do not experience withdrawal.[19] We had hypothesized that ITS smoke for the acute reinforcing effects of nicotine,[42] while others have suggested that social or sensory factors might be primary motivators.[48,49] In this study, ITS smoking VLNCCs reduced their smoking and were more likely to seek nicotine elsewhere, suggesting that nicotine-seeking motivates smoking even absent of nicotine dependence. We have previously suggested that ITS might seek immediate reinforcement from acute nicotine administration in particular settings, with this stimulus-driven nicotine-seeking constituting a form of dependence.[50]

Switching to VLNCCs seemingly motivated ITS to seek nicotine elsewhere. Both the original proposal for a low-nicotine cigarette policy[4] and the US Food and Drug Administration's policy announcement[7,8] contemplate an integrated policy of reducing nicotine in cigarettes while making alternative nicotine products available[51,52] to help smokers move away from cigarettes, as smoking carries far greater risk than nicotine itself.[53] Indeed, we saw movement toward e-cigarettes among heavier nondaily smokers who received VLNCCs.

Limitations and Strengths

The study had limitations. Participants were from a single geographic region and were not nationally representative. For example, Hispanic and higher-income ITS were both underrepresented, and black ITS were overrepresented (C. M. Reyes-Guzman, PhD, written communication, March 2018), even after some differential dropout among black participants. Differential dropout of black participants and heavier smokers before randomization underscores that the randomized cohort is not a random sample. Frequent users of other nicotine

products were excluded, also limiting generalizability with regard to how VLNCCs might influence a shift toward use of such products. The enrollment target was not met; however, the sample size was adequate to detect significant treatment effects on CPD. The switch to VLNCCs was not always complete: some participants admitted cheating by smoking conventional cigarettes, and urinary cotinine data suggested additional cheating. However, VLNCC effects were seen even among compliant participants.

A strength of the study was the randomized double-blind design, which allowed the observed changes to be attributed to the cigarettes' nicotine levels. Also, the provision of free cigarettes was kept constant between baseline and treatment phases[11]; thus, the change after randomization could be attributed completely to the experimental manipulation without being complicated by increased consumption when cigarettes were free.[27] Another strength was the inclusion of 3 different measures of cigarette consumption, which demonstrated marked agreement.[32] Greater CPD reductions in the VLNCC group compared with NNCC controls were apparent across key subgroups defined by race/ethnicity, sex, and prior daily smoking history.

Conclusions

This randomized clinical trial was conducted in nondaily smokers, a substantial fraction of the smoking population whose response to VLNCCs had not previously been studied. Switching to VLNCCs resulted in reduced cigarette consumption among these nondaily smokers, much as it does in daily smokers,[11] and there was no evidence of adverse effects such as increased smoking. That daily and nondaily smokers react similarly suggests that reduced nicotine policy need not be concerned about differential response among nondaily smokers. However, while the stated goal of such policy is to increase quitting,[7,8,54] the observed reductions in smoking leveled off after several weeks and switching to VLNCCs did not significantly increase quitting, suggesting that the data do not yet support that expected policy outcome.

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Conflict of Interest Disclosures: Dr Shiffman, through Pinney Associates, consults on tobacco cessation and harm reduction (including nicotine replacement therapy and digital vapor products; by contract, combusted cigarettes are excluded) to Niconovum USA, R. J. Reynolds Vapor Company, and RAI Services Company, all subsidiaries of Reynolds American Inc and British American Tobacco. Previously, Dr Shiffman consulted to NJOY on e-cigarettes and to GlaxoSmithKline Consumer Healthcare on smoking cessation medications and treatments. Dr Shiffman holds patents for a novel nicotine smoking cessation medication that is not under commercial development. No other disclosures are reported.

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