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Acceptability of SPECTRUM Research Cigarettes among Participants in Trials of Reduced Nicotine Content Cigarettes

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Abstract

Objectives—SPECTRUM research cigarettes (SPECTRUMs) are being used in trials evaluating the effects of switching to reduced nicotine content (RNC) cigarettes. Because smokers have a high brand affinity, we evaluated if they were willing to switch and continue smoking normal nicotine content (NNC) SPECTRUMs.

Methods—We asked smokers (N = 341) to rate their own brand of cigarettes and NNC SPECTRUMs (after 2 weeks of use) using subjective measures including satisfaction, reward, taste, and craving reduction. We measured plasma cotinine, exhaled carbon monoxide (CO), and cigarettes per day (CPD), and recorded reasons for dropping out.

Results—After 2 weeks, 95% of participants chose to continue using SPECTRUMs for an additional 18 weeks. Moreover, 67% said SPECTRUMs were as good as or better than their own

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Conflict of Interest Statement

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brand, and 65% said they would consider purchasing them. Ratings of satisfaction, reward, and craving reduction were 10%-15% lower on SPECTRUMs than on their own brand ($p < .01$). There were no differences in these ratings between menthol and non-menthol smokers.

Conclusions—Menthol and non-menthol SPECTRUMs are acceptable to smokers. Lower SPECTRUM ratings were likely due to brand switching and did not hinder study retention.

Keywords

reduced nicotine content cigarettes; brand switching

In 1994, Benowitz and Henningfield suggested that if the nicotine content of cigarettes were to be reduced significantly (to approximately 0.5 mg/cigarette), this would markedly reduce their ability to produce and sustain addictive smoking.¹ They hypothesized that this reduction could decrease the prevalence of cigarette smoking by making it easier for current tobacco users to quit, and by making it much less likely that youth who try cigarettes will become addicted to them.

This potential regulatory option only became a realistic possibility with the passage of the 2009 Family Smoking Prevention and Tobacco Control Act (FSPTCA).² The FSPTCA gave the Food and Drug Administration (FDA) the authority to regulate the manufacturing of cigarettes and to create product standards that could include reducing the nicotine content of cigarettes to non-addictive levels. To evaluate whether a nicotine reduction policy would be feasible, the National Institutes of Health (NIH) and the FDA began funding studies designed to understand perceptions, product use behaviors, biological effects, and toxicant exposure of smokers using reduced nicotine content (RNC) cigarettes.^{3,4} The studies published to date show that RNC cigarette smokers are not at any additional risk of harm after switching to RNC cigarettes (eg, via increased compensatory smoking, worsened mental health, increased substance use, or severe nicotine withdrawal symptoms).⁵⁻⁹

However, it could be argued that research cigarettes provided to participants in RNC trials are not acceptable or not an adequate model cigarette in which to test the likely effects, regardless of their nicotine content. The root of this argument is that there is an inherent problem in trying to understand the acceptability of RNC cigarettes because brand switching, even to commonly available premium brands with adequate nicotine content, influences both the objective smoking behavior and subjective ratings of cigarettes.¹⁰⁻¹⁴ For instance, Zacny and Stitzer¹² asked smokers to rate their own brand of cigarettes (1.0 mg nicotine yield) on a number of subjective measures and then switched them to Camel brand (1.1 mg yield) and Marlboro Lights (0.7 mg nicotine yield). When participants were switched to either of these new brands, there was a 32% decrease in the subjective rating of “satisfaction” and a 35% decrease in how likely they would be to purchase these brands compared to their usual brand. The authors concluded that these subjective ratings are further evidence of an often observed “behavioral brand loyalty that is common among smokers.”

In addition, it has been demonstrated that a smoker’s brand loyalty is sensitive to the suggestion of a brand change even when they are not actually switched. For instance,

Mercincavage et al¹¹ conducted an evaluation of nicotine content descriptions of cigarettes provided to participants. In the trial, participants were given their own brand of cigarettes but were told that they were receiving either normal nicotine content (NNC), low nicotine content, or very low nicotine content cigarettes, and were then asked to rate the cigarettes that they smoked. Even though they were actually smoking their own brand of cigarettes, participants reported that the cigarettes described as having very low nicotine content provided less craving reduction, were weaker, and were too mild relative to their own brand. The authors concluded that negative responses to RNC cigarettes, at least in part, are related to subjective expectations that lower nicotine content cigarettes will not be as good as their own brand.

Many of the current RNC trials are providing study participants with SPECTRUM research cigarettes (SPECTRUMs) which are obtained through the National Institute of Drug Abuse's Drug Supply Program.¹⁵ Because one of the difficulties in determining acceptability of RNC SPECTRUMs is untangling the effects of brand loyalty from changes in nicotine content, it is important to evaluate acceptability of the NNC cigarettes first. This includes how ratings change from own brand cigarettes to NNC SPECTRUMs when smokers are switched in an un-blinded manner. This initial assessment of NNC SPECTRUMs also will allow for isolating the impact of decreasing nicotine levels on acceptability when RNC SPECTRUMs are provided in a randomized controlled trial. Therefore, the purpose of this study was 3-fold. First, we evaluated the acceptability of NNC SPECTRUMs by comparing subjective ratings of NNC SPECTRUMs to own brand cigarettes. Second, we assessed participants' ongoing smoking behaviors (including biomarkers) during a one-week baseline period on their own cigarettes and then a 2-week trial period using SPECTRUMs, and the participants' willingness to continue smoking SPECTRUMs for another 18 weeks in a subsequent randomized portion of the trial.^{16,17} Third, we explored if there were any differences in any of these measures among participants who preferred non-menthol versus menthol flavored cigarettes. All evaluations took place during participants' one-week monitoring period on their own brand, followed by a 2-week baseline period, prior to participation in 18-week randomized controlled double-blind trials to evaluate progressive reduction of nicotine in SPECTRUMs.

METHODS

Overall Trial Design and Participants

This report combines data from 2 similarly designed multi-site, randomized, controlled double-blind trials designed to evaluate RNC cigarettes. One trial (Project 1 [P1]) focused on recruiting smokers of low socio-economic status (less than 16 years of education) and the other (Project 2 [P2]) focused on smokers with mood and/or anxiety disorders.^{16,17} P1 recruited participants throughout the greater Harrisburg, PA region and in the greater Washington, DC area. P2 recruited participants throughout the greater Harrisburg, PA region and in the greater Boston, MA area. The full study design and inclusion/exclusion criteria have been reported elsewhere.^{16,17} Briefly, adult smokers (age 18-65) of at least 5 cigarettes per day (CPD) who were not interested in making a quit attempt in the next 6 months were recruited for an 8-month trial and attended an assessment visit (Day -7). After one week of

monitoring smoking on own brand cigarettes, there was a 2-week baseline period where all participants were provided with NNC SPECTRUMs (NRC600, non-menthol flavor and NRC601, menthol flavor) matched to their flavor preference. Each non-menthol SPECTRUM NRC600 cigarette is approximately 84 mm long, just under 0.7g of tobacco, has a filter ventilation of 27.3%, a tar yield of 10.5 mg, and a nicotine yield of 0.8 mg, a nicotine content of 11.6 mg nicotine/cigarette, and a nicotine concentration of 16.5 mg/g of tobacco.^{18,19} Menthol flavored SPECTRUM NRC601 cigarettes have similar characteristics to non-menthols, but they also contain approximately 7540 µg of menthol/g of tobacco.^{18,19}

The baseline period of the trial was partially designed to allow participants to determine whether they found the NNC SPECTRUM brand acceptable prior to the intervention phase where nicotine content was manipulated. It also evaluated whether participants were willing and able to switch from their own brand cigarettes and continue with the trial procedures for another 18 weeks. At the assessment visit (Day -7), participants were consented to the study, were evaluated for study eligibility, and were asked to complete questionnaires including basic demographic information, a medical and tobacco use history, and information about their current cigarette brand. They were then asked to return to the study center in one week after smoking their own brand of cigarettes and while keeping a daily log of how many CPD they smoked. The proposal for these trials anticipated that 30% of those starting on the pre-randomization phase would not start the randomization phase due to dropping out, non-compliance, or simply choosing not to continue. After the baseline period, participants were randomized to either continue to receive NNC cigarettes for the remainder of the trial or to receive progressively lower nicotine doses of RNC SPECTRUMs (double-blind).

Current Study Design

The present study begins at the time point when participants returned with their cigarette logs after smoking their own brand of cigarettes for one week (visit 2, Day 0). Only those who attended this visit and who had a Day 0 plasma cotinine >15ng/mL were included. At the visit, participants completed questionnaires (described below) and provided a blood sample for plasma cotinine analysis. Participants also were provided with a supply of NNC SPECTRUMs matched to their preferred flavor and based on their average past week CPD from the log. Because it was important that participants did not run out of research cigarettes before their next study visit, they were given 150% of the average CPD reported on their cigarette log (at no cost). For P1, participants were given a 2-week supply of research cigarettes, followed up over the phone one week later (Day 7) and asked to return to the study center after one more week (Day 14). For P2, participants were given a one-week supply of research cigarettes, asked to return to the study center one week later (Day 7) to receive a second week's supply, then asked to return to the study center after one more week (Day 14). A second blood sample was obtained at Day 14 in both projects. At each contact, we asked participants to smoke only the research cigarettes they were given, to report any non-research cigarettes or marijuana that they smoked, and to report use of any other tobacco products or nicotine replacement.

Subjective Questionnaires and Cigarette Logs

Demographics, cigarette characteristics, and nicotine dependence—Basic demographic information was self-reported at the assessment visit (Day -7). Years of education attained was recorded on a continuous scale, and for the purposes of this report, it was categorized dichotomously as “high school or less” (ie, 12 years) and “more than high school” (ie, 13+ years). Income was categorized as “low” (\$0-\$19,999), “middle” (\$20,000-\$59,999), and “high” (\$60,000+). We asked participants to describe the type of cigarettes they smoked with regards to cost per pack (in US dollars), length (condensed into 2 categories of 72 mm/85 mm [regular/king] and 100 mm/120 mm [long]), flavor (menthol/non-menthol); we also asked them to indicate if they purchased their cigarettes by the pack, the carton, or if they rolled their own using a machine. The Kessler K6 (K6) was used as an indicator of psychological distress.^{20,21}

Nicotine dependence was assessed using 3 measures: Fagerstrom Test for Nicotine Dependence (FTND),²² Hooked on Nicotine Checklist (HONC),^{23,24} and the Penn State Cigarette Dependence Index (PSCDI).^{25,26} The FTND is the most widely used method for assessing cigarette dependence. It includes 2 items (number of cigarettes smoked and time to first cigarette) that have become known as the Heaviness of Smoking Index (HSI) which are predictive of difficulty in quitting.^{27–30} The HONC was developed to measure loss of autonomy due to nicotine addiction in youth,²³ and subsequently, has been evaluated to measure this construct in adults as well. The PSCDI contains the HSI in addition to questions from the HONC that assess core nicotine dependence symptoms (eg, experience of nicotine withdrawal symptoms) and loss of autonomy. The PSCDI also was designed to allow comparisons of nicotine dependence between various tobacco products.²⁵ The PSCDI was found to be predictive of one-month abstinence in a smoking cessation trial.²⁶

Cigarette rating scales—We asked participants to rate the cigarettes they smoked in the past week (either their own brand or NNC SPECTRUMs) using both the modified Cigarette Evaluation Scale (mCES)³¹ and a modified Cigarette Liking Scale (mCLS).³² The mCES 12-item questionnaire asks participants to rate the cigarettes they smoked in the past week on a 7-point Likert scale with the statement “Please mark the response that best represents how smoking made you feel since your last study visit” (1 = not at all to 7 = extremely). The scale yields 5 subscales including ratings for satisfaction, aversion, psychological reward, enjoyment of respiratory tract sensations, and craving reduction.

The mCLS was modified from a Visual Analog Scale to a 10-point scale (1 = not at all to 10 = extremely), and participants were asked to rate the cigarettes they smoked in the past week on items related to strength, heat, draw, harshness, taste, satisfaction, and tobacco versus just air. An additional question included on Day 14 asked participants to rate the likelihood that they would “buy cigarettes like these” (ie, NNC SPECTRUMs). We categorized responses of 1-4 as “unlikely to purchase,” 5 or 6 as “somewhat likely” to purchase, and scores 7-10 as “very likely to purchase” the SPECTRUMs. Finally, on Day 14, we asked participants: “Compared to your usual cigarettes, how would you rate the cigarettes you smoked in the past week?” on a 5-point scale with anchors of “not really as good” (score of 1-2), “about the same” (score of 3), or “much better” (score of 4-5).

Cigarette logs, CPD, other tobacco use—At the first study visit, we gave participants a paper log designed to fit on the front of their cigarette pack with a pencil the size of a cigarette and were instructed to log each cigarette (research and non-research) as they smoked it each day.³³ At each visit, participants reported the past 6 days of tobacco use with a timeline follow back procedure aided by their logs. If the participant reported using non-research cigarettes, we recorded the number and included it in the total CPD count. The percentage of non-research cigarettes was calculated by dividing the number of non-research cigarettes smoked by the total cigarettes. If >10% of the participant's total mean CPD was non-research cigarettes, or if the participant reported smoking <50% of their total Day 0 CPD, we considered these to be indicators that the participant did not find the research cigarettes acceptable. Both other tobacco product or marijuana use were collected at each time point and were reported dichotomously (ie, yes, used/no, did not use).

Participant Dropouts and Withdrawals

An additional measure of cigarette acceptability included a willingness to (1) continue with the 18-week randomized portion of the study, and (2) follow the study protocol to smoke only the research cigarettes and not to use other tobacco products or marijuana. Participants were withdrawn and reasons recorded if they reported that they did not want to continue with the study. Those who did not report a reason (eg, non-attenders) were withdrawn as lost to follow up. Participants could also be withdrawn from the study if either of the following criteria were met at both Day 7 and Day 14: (1) >10% of the cigarettes smoked were non-research cigarettes, or (2) other tobacco products or marijuana were used at both time points. Participants were not informed of specific details that would qualify them for withdrawal, but were informed at the time of consent that “frequent use of other tobacco products or marijuana could result in you being withdrawn from the study.”

Biomarkers

Exhaled carbon monoxide (CO, in parts per million [ppm]) was measured using the Bedfont Pico+ Smokerlyzer which uses an electrochemical sensor, has a concentration range of 0-100 ppm, and has an accuracy of +2%.³⁴ Plasma cotinine levels were measured using a commercially available solid-phase, competitive enzyme-linked immunosorbent assay (ELISA) kit from Calbiotech (El Cajon, CA). The assay was carried out as directed by the manufacturers and has a detection limit of 2ng/mL.³⁵ At the time of this report, plasma cotinine was available on a subset of 246 participants.

Data Analysis

Data were analyzed using R version 3.3.2 (<https://www.r-project.org/>). Study participants were described based on demographic and cigarette characteristics overall and by cigarette flavor (menthol and non-menthol). Frequency distributions or means with standard deviations (SD) were calculated. Chi-square tests and 2-tailed t-tests were used where appropriate to determine differences between menthol and non-menthol smokers for variables of interest. The mean scores when smoking own brand cigarettes (Day 0) and NNC SPECTRUMS (Day 14) were computed for each mCES subscale and each individual mCLS question. Within-subject paired t-tests were run to determine the changes in the scores

between the participant's own brand and SPECTRUMs. Two-tailed p-values less than .05 were considered statistically significant. The dependence of the mCES subscales and mCLS questions on demographics, cigarette characteristics and cigarette behaviors in Table 1 was analyzed using linear mixed effect regression models with random slope and random intercepts to take into account the correlated structure among different visits for each individual. A project variable (P1 vs P2) was also included to control for unaccounted for differences between the projects. Using backward elimination method, each subscale in the mCES, the individual questions for the mCLS, CPD, CO, and cotinine were evaluated separately in the regression analysis to evaluate predictors that affected changes from own brand to SPECTRUMs. The predictors screened included all variables from Table 1 and the project variable with the exception of 2 nicotine dependence scales (HONC and FTND). To choose the most appropriate nicotine dependence scale (and avoid multicollinearity), each of the mCES subscale models was run with either the FTND, HONC, or PSCDI as a predictor. The PSCDI was found to have the most consistent predictive power for the response variables, and therefore, was used for all models as the nicotine dependence scale. For example, it was the only one of the 3 dependence measures to predict the craving reduction subscale scores ($p = .014$) and it also predicted Psychological Reward, Smoking Satisfaction and Respiratory Tract subscale scores (all p -values $< .001$).

Study data were collected and managed using Re-search Electronic Data CAPture (REDCap) electronic data capture tools.³⁶

RESULTS

Overall, most participants were female (54.3%), white (68%), smoked menthol flavored cigarettes (58.7%), and had more than a high school education (56.6%). The mean age of participants was 44 years ($SD = 12.1$, range 19-65). At the Day 0 visit, they smoked an average of 19.5 CPD ($SD = 9.9$) of their own brand cigarettes. An overview of baseline study participant demographics, cigarette characteristics, and baseline biomarkers by flavor preference is presented in Table 1. Menthol users differed significantly from non-menthol users in that they had a higher proportion of African Americans, a higher proportion of those who smoked long cigarettes, and they smoked fewer cigarettes per day.

Cigarette Rating Scales (mCES and mCLS)

The overall mean mCES scores while smoking own brand cigarettes (Day 0) and NNC SPECTRUMs (Day 14) are presented in Figure 1 (menthol and non-menthol combined). In the sample as a whole, ratings for SPECTRUMs were significantly lower than own brand for smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, and craving reduction. In the linear mixed effect models in the whole sample, ratings of SPECTRUMs were lower than ratings of own brand cigarettes for all subscales except aversion after adjusting for other predictors (all p -values $< .01$). In addition, there was a positive relationship between nicotine dependence (PSCDI) and all subscales except for aversion (all p -values $< .02$). When smoking NNC SPECTRUMs at Day 14, there were no statistically significant differences between smokers of menthol and non-menthol on these scales. In the linear mixed effect models, while smoking SPECTRUMs, menthol (vs non-

menthol) cigarettes were associated with higher ratings for Psychological Reward ($p = .011$), Respiratory Tract Sensations ($p = .004$), and Smoking Satisfaction ($p = .005$) Figure 2 presents the overall ratings for the mCLS questions (menthol and non-menthol combined). Ratings were significantly higher for own brand cigarettes than NNC SPECTRUMs for strength, taste, satisfaction, and tobacco versus just air. SPECTRUMs were rated significantly higher on difficulty to draw and harshness as compared to own brand. The only significant difference between the menthol and non-menthol SPECTRUMs rating was for harshness which the menthol smokers rated as less harsh (mean of 3.3) than non-menthol smokers (mean of 3.9, $p = .03$).

These ratings persisted after controlling for other factors in the linear mixed effect models where mCLS ratings of the SPECTRUMs for strength, satisfaction, and tobacco versus just air decreased significantly while draw and harshness increased significantly compared to usual brand. Compared to non-menthol smokers, menthol smokers had significantly higher ratings for taste ($p = .004$), and lower for harshness ($p = .003$), and draw ($p = .039$). Overall at Day 14, 19.8% of participants reported that they would be somewhat likely and 45.2% very likely to purchase “cigarettes like these” (eg, NNC SPECTRUMs), and there was no difference in these proportions between menthol and non-menthol smokers ($p = .44$). Finally, for the overall rating of the NNC SPECTRUMs, 64.6% stated they were about the same as or better than their usual brand, and there was no significant statistical difference in this rating between menthol and non-menthol smokers ($p = .053$).

CPD, CO, and Cotinine

Among those who reported CPD at Day 14, 17/322 (5.3%) reported that their mean daily CPD increased by more than 100% as compared to their baseline CPD. Changes in CPD, CO, cotinine, and cotinine per cigarette from own brand to NNC SPECTRUMs overall and by menthol/non-menthol are presented in Figure 3. CPD increased and cotinine decreased from own brand to NNC SPECTRUMs in these univariate analyses and in the linear mixed effect models even after controlling for other factors ($p < .001$). In addition, greater nicotine dependence (as measured on the PSCDI) was significantly associated with higher CPD, CO, and cotinine in each predictive model (all p -values $< .035$).

Participant Dropouts and Withdrawals

By Day 14, 5.0% (17/341 overall) of participants who attended the Day 0 visit were withdrawn or dropped out of the study. Of these 17, 8 (47%) were lost to follow-up, 4 (23.5%) indicated they did not like the study cigarettes, 2 (11.8%) smoked more than 10% non-research cigarettes (of their total CPD), one (5.9%) reduced total CPD by more than 50% and smoked more than 10% non-research cigarettes, and 2 (11.8%) used other tobacco products or marijuana at both Day 0 and Day 14. Participants who dropped out had similar demographic and cigarette characteristics to the overall study population (data not shown) with the exception that 76.4% (13/17) of those who dropped out smoked long cigarettes, compared with 54% (175/324) of those who did not drop out.

DISCUSSION

The purpose of this study was to determine the acceptability of NNC SPECTRUMs during the baseline period of 2 randomized controlled clinical trials designed to test the effects of progressively reduced nicotine content cigarettes.^{16,17} Our evaluation found that NNC SPECTRUMs are considered acceptable to study participants who smoke both menthol and non-menthol cigarettes and that they are suitable for human clinical trials as demonstrated by both subjective ratings and participant willingness to continue with the trial.

As expected, participants demonstrated some brand loyalty and rated the NNC SPECTRUM brand lower than their own brand on a number of measures. However, the majority of participants indicated that the NNC SPECTRUMs were as good as or better than their own brand (64.6%) and that they would be at least somewhat likely to purchase them (65%). In addition, the differences in ratings from own brand to SPECTRUMs were comparable to those observed in other studies where participants switched to different cigarettes even when the brand being tested was a commercially available premium brand.^{11,12,32}

One could argue that significant decreases in cigarette acceptability could make it harder to detect compensatory smoking in the randomized phase of the trial. However, practically speaking, testing a nicotine reduction standard in a controlled trial requires asking participants to switch brands in some form. As Mercincavage et al¹¹ found, smokers rate that they like cigarettes called “low nicotine content” less than their own brand even when they are actually smoking their own brand. Thus, we believe that switching smokers to a new brand (SPECTRUMs) in an unblinded way prior to reducing nicotine content is the most appropriate way to isolate the effect of nicotine reduction on acceptability while controlling for the brand change. In addition, in the present study, statistically significant differences in ratings between own brand and NNC SPECTRUM brand were less pronounced than previous studies, as we saw decreases of less than 15% for most measures, with the exception of harshness and difficulty to draw (which increased 24% and 14% respectively). This suggests that the differences we observed in ratings between participants’ own brand and the SPECTRUMs were likely a brand switching effect.

The increased ratings on harshness and difficulty to draw bring to the forefront differences in the design features of cigarettes that are less often discussed when evaluating perceptions of cigarettes. Our study used SPECTRUM (NRC600 and NRC601) brand cigarettes that are packaged in a hard pack box, are approximately 84 mm long and are 7.9 mm in diameter, have 23%-27% filter ventilation, and have a machine-smoked nicotine yield of 0.8 mg per cigarette.^{18,19} Though not detailed in this report, the own brand cigarettes that smokers were using when they entered the present study included a variety of commercially available cigarette brands that differed in packaging, length, diameter, nicotine yields, and filter ventilations. Thus, the increased rating in draw between own brand and the SPECTRUMs, for example, is interesting, but not surprising because commercially available cigarettes vary in the amount of filter ventilation ranging anywhere from 0.14% (Newport, regular length, menthol) to 66.6% (TRUE silver, regular length, non-menthol).^{37,38} We did observe some individual differences in ratings between menthol and non-menthol smokers particularly for taste which menthol smokers rated as higher, and for harshness and draw, which were both

lower than those of non-menthol smokers. However, there was no indication that non-menthol smokers dropped out or were withdrawn from the study at a higher rate than menthol smokers.

Despite the variety of possible cigarette design features that participants preferred when they entered the trial, we had a 95% participant retention rate when participants were switched to one of 2 different kinds of NNC SPECTRUMs (either NRC 600 or NRC 601). However, one potential limitation for the interpretation of dropout rates is that the SPECTRUMs were provided to participants at no cost and they were compensated for their participation, which may have contributed to perceived acceptability of the cigarettes and/or retention in the trial. In addition, though participants were not informed of the specific criteria for other tobacco or marijuana use that would trigger their withdrawal from the study, they were informed that this could be the result of “frequent use” of these products. Currently, there is no biochemical way to validate whether participants are smoking NNC SPECTRUMs or their own brand and we did not assess marijuana use biochemically. Thus, this measure is reliant on self-report and it is conceivable that some participants did not report non-research product use accurately out of concern that they would be withdrawn. If participants were not forthcoming about their tobacco or marijuana use, they were permitted to continue with the study when they may have been smoking too many non-research cigarettes, using other products, or smoking marijuana. This creates the possibility that the withdrawal rate reported in the present study, and acceptability in terms of not using other products, is lower than it should be due to undetected participant non-compliance with research cigarettes. However, though possible, we consider it unlikely that participants would agree to attend regular visits over 18 weeks, record their smoking habits, provide blood and urine samples, and continue to report smoking research cigarettes that they actually found unacceptable.

A final observation we noted were the changes in CO, CPD, and cotinine between own brand and NNC SPECTRUMs. At first glance, it seems counter-intuitive that CPD and CO would go up while cotinine went down. However, a previous trial also observed an increase in CPD and a decrease in nicotine exposure (measured as Total Nicotine Equivalents) after 2 weeks on NNC SPECTRUMs suggesting that this is not an uncommon effect of brand switching.⁵ It seems plausible that the participants smoked more SPECTRUMs because they were provided at no cost, and subsequently, obtained higher exhaled CO values. In addition, after considering the possible cigarette design features that could differ between cigarettes, participants could have had lower cotinine levels, partly because the SPECTRUMs were shorter and had a slightly lower nicotine yield than many of their own brands. For instance, compared to non-menthol smokers, there was a significantly higher proportion of menthol smokers who also smoked long (100-120 mm) cigarettes (68.5% long menthol vs 36.2% long non-menthol). If we compare, menthol flavored SPECTRUM NRC601s to Newport green long cigarettes, the SPECTRUMs are shorter (–15 mm), contain less tobacco (–67 mg), have more filter ventilation (+2%) and a lower nicotine yield (–0.5 mg).^{18,19,38} All of this suggests the possibility that long cigarette smokers presented to our study with higher baseline cotinine levels, and when they were then switched to regular length cigarettes, they smoked more CPD, resulting in the same exposure to smoke (eg, CO), but lower exposure to nicotine (eg, cotinine). Similar logic, though in the opposite direction, could be used to

explain our findings among non-menthol smokers who had a significantly higher proportion of regular length cigarettes than menthol smokers.

This study was not designed to evaluate the design characteristics of each smoker's individual cigarette brand when they entered the trial or how these features may influence subjective and objective outcomes. However, this type of investigation may be helpful to understand differences in user perceptions when switching to research cigarettes. In particular, given the large proportion of smokers who preferred long cigarettes, a deeper understanding of differences among these smokers would be helpful as the SPECTRUM brand is not available in long lengths.

These observations also have implications for future nicotine reduction trials using the SPECTRUM brand. For instance, those conducting future trials should evaluate biochemical markers with the understanding that commercially available cigarettes have design features that cause variation in biochemical markers of exposure when switching to NNC SPECTRUMs. In addition, commercial cigarette brand details and design features should be recorded when conducting trials of RNC cigarettes so that these features can be studied in the context of switching to RNC cigarettes. Finally, an ongoing challenge of studies using NNC research cigarettes is the difficulty in assessing compliance. Compliance with RNC cigarettes can be assessed biochemically by cross-referencing the possible nicotine exposure a smoker should receive from RNC cigarettes to their actual blood levels. However, when nicotine levels are expected to be comparable, there is no known way to differentiate biochemically between NNC research cigarettes and commercially available cigarettes. Self-reported compliance, as was used in this report, is subject to potential reporting error. These limitations create the need to develop additional compliance measurements that can validate self-reported NNC cigarette use.

A strength of this study is that we report on subjective and objective measures and also examine behavioral data on whether participants were willing to continue with the study. Though subjective measures showed that participants rated the SPECTRUMs lower for satisfaction and taste, the vast majority were willing to continue with the study.

Conclusion

Normal nicotine content (NNC) SPECTRUM research cigarettes are acceptable to both menthol and non-menthol smokers in randomized controlled trials. Although participants rated the SPECTRUMs lower on many subjective measures, this is likely a brand switching effect that did not hinder retention during this phase of the study. In addition, switching smokers from a wide variety of commercially available cigarettes to one of 2 research cigarettes (NRC600 [non-menthol] and NRC601 [menthol]) creates changes in use (eg, CPD) and biochemical markers (eg, CO and cotinine) possibly due to differences in cigarette design features.

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IMPLICATIONS FOR TOBACCO REGULATION

Normal nicotine content (NNC) SPECTRUM research cigarettes are of a quality that is acceptable to the vast majority of research volunteers (95% of our participants were willing to continue for another 18 weeks and 65% would pay for them). When switching to SPECTRUMs in an unblinded manner, overall satisfaction with both menthol and non-menthol flavored SPECTRUMs is slightly lower than with own brand, but this is consistent with what has been found in other studies in which participants believed they were switching to another brand with similar nicotine content (including switching to premium brands and brands that are popular in the marketplace). Menthol and non-menthol SPECTRUMs are an adequate model cigarette in which to test the likely population effects of a reduced nicotine product standard.

Human Subjects Statement

The studies reported here were approved by the Penn State Hershey, George Washington University, and Partners Human Research Committee (Massachusetts General Hospital) Institutional Review Boards.

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Figure 1.

Overall Mean Modified Cigarette Evaluation Subscales (mCES): Own Brand (Day 0) versus Normal Nicotine Content (NNC) SPECTRUM (Day 14)

Note. * Indicates statistical significance at $p < .01$ when comparing Own Brand to NNC SPECTRUM using paired t-test values.

Figure 2.

Overall Mean Modified Cigarette Liking Scales (mCLS): Own Brand (Day 0) versus Normal Nicotine Content (NNC) SPECTRUM (Day 14)

Note. * Indicates statistical significance at $p < .05$ when comparing Own Brand to NNC SPECTRUM using paired t-test values.

Figure 3.

a-d: Mean Changes in Exhaled Carbon Monoxide (CO), Plasma Cotinine, Cigarettes per Day (CPD), and Plasma Cotinine per Cigarette While Smoking Own Brand (Day 0) vs. Normal Nicotine Content (NNC) SPECTRUM (Day 14): Overall and by Menthol/Non-menthol Smokers

Note. * Indicates statistical significance at $p < 0.001$ when comparing own brand to NNC SPECTRUM using paired t-test values.

Figure a.) $N = 324$: 189 menthol, 135 non-menthol; Figure b.) $N = 246$: 138 menthol, 108 non-menthol; Figure c.) $N = 321$: 187 menthol, 134 non-menthol; Figure d.) $N = 243$: 136 menthol, 107 non-menthol.

Table 1

Study Participant Demographic and Smoking Characteristics at Baseline (Day 0) While Smoking Own Brand Cigarettes by Menthol and Non-menthol Smokers

	Menthol (N = 200)	Non-Menthol (N = 141)	p-value
Female, % (n)	54.0 (108)	54.6 (77)	1.00
Race, % (n)			<0.001
African American	37.5 (75)	5.7 (8)	
White	55.0 (110)	86.5 (122)	
Other	7.5 (15)	7.8 (11)	
Hispanic Ethnicity, % (n)	4.5 (9)	2.8 (4)	0.62
Mean Age (SD, range)	44.1 (11.8, 19 - 65)	43.8 (12.6, 19 - 65)	0.81
Education, % (n)			0.13
12 Years	47.0 (94)	38.3 (54)	
13+ Years	53.0 (106)	61.7 (87)	
Income Level, % (n)			0.12
Low (\$0-\$19,999)	44.1 (67/152)	30.2 (35/116)	
Middle (\$20,000-\$59,999)	32.9 (50/152)	38.8 (45/116)	
High (\$60,000+)	23.0 (35/152)	31.0 (36/116)	
Cigarette Type, % (n)			0.58
Purchase by Pack/Carton	87.5 (175)	80.9 (114)	
Roll-Your-Own (Machine-Rolled with Tubes and Filters)	12.5 (25)	19.1 (27)	
Cigarette Size, % (n)			<0.001
Regular/King (72mm and 85mm)	31.5 (63)	63.8 (90)	
Long (100mm and 120mm)	68.5 (137)	36.2 (51)	
Mean Cigarette Cost, (SD, range), in USD	6.49 (2.35, 0.55 -11.00)	5.64 (2.73, 0.24 -11.00)	0.003
Mean Cigarettes per Day (CPD), (SD, range)	17.7 (8.8, 2.2 - 56.6) ^a	22.0 (10.8, 1.3 - 60)	<0.001
Mean Exhaled Carbon Monoxide (CO), (SD, range), in ppm	27.5 (15.0, 4 - 85)	30.6 (15.2, 4 - 100)	0.06
Mean Cotinine, (SD, range), in ng/mL (N = 246: 138 menthol, 108 non-menthol)	279.2 (146.3, 18.1 - 705.1)	305.8 (151.0, 32.6 - 918.0)	0.15
Median Cotinine, in ng/mL	260.1	284.5	0.14
Mean Cotinine per Cigarette, (SD, range), in ng/mL	17.6 (11.0, 2.3 - 84.1)	15.7 (8.9, 3.5 - 68.9)	0.13
Mean Kessler K6 Score, (SD, range)	5.1 (5.0, 0 - 21)	5.1 (4.7, 0 - 21)	0.96
Mean Fagerstrom Test for Nicotine Dependence (FTND) Score, (SD, range)	6.1 (2.1, 0 - 10)	6.6 (2.2, 1 - 10)	0.03
Mean Penn State Cigarette Dependence Index (PSCDI) Score, (SD, range)	13.2 (3.4, 3 - 20)	13.7 (3.4, 5 - 20)	0.16
Mean Hooked on Nicotine Checklist (HONC) score, (SD, range)	7.7 (2.3, 0 - 10)	7.8 (2.0, 2 - 10)	0.52

^aAll participants met inclusion criteria for CPD at the assessment visit (Day -7). CPD reported here is based on the Day 0 cigarette log after 1 week of smoking own brand cigarettes.