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# Effects of 6-Week Use of Reduced-Nicotine Content Cigarettes in Smokers With and Without Elevated Depressive Symptoms

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## Abstract

**Background:** The FDA recently acquired regulatory authority over tobacco products, leading to renewed interest in whether reducing the nicotine content of cigarettes would reduce tobacco dependence in the United States. Given the association between depressive symptoms and cigarette smoking, it is important to consider whether smokers with elevated depressive symptoms experience unique benefits or negative consequences of nicotine reduction.

**Methods:** In this secondary analysis of a randomized clinical trial that examined the effects of cigarettes varying in nicotine content over a 6-week period in non-treatment-seeking smokers, we used linear regression to examine whether baseline depressive symptom severity (scores on the Center for Epidemiologic Studies Depression Scale [CES-D]) moderated the effects of reduced-nicotine content (RNC) cigarettes, relative to normal-nicotine content (NNC) cigarettes, on smoking rates, depressive symptom severity, and related subjective and physiological measures.

**Results:** Of the 717 participants included in this analysis, 109 (15.2%) had CES-D scores ≥ 16, indicative of possible clinical depression. Relative to NNC cigarettes, RNC cigarettes reduced smoking rates, nicotine dependence, and cigarette craving, and these effects were not significantly moderated by baseline CES-D score. A significant interaction between baseline CES-D score and cigarette condition on week 6 CES-D score was observed ($p < .05$); among those with CES-D scores ≥ 16 at baseline, those assigned to RNC cigarettes had lower week 6 CES-D scores than those assigned to NNC cigarettes. Among those in the lowest nicotine content conditions, biochemically confirmed

compliance with the RNC cigarettes was associated with an increase in CES-D score for those with baseline CES-D scores < 16 and no change in CES-D score for those with baseline CES-D scores ≥ 16.
**Conclusions:** These findings provide initial evidence that a reduced-nicotine standard for cigarettes may reduce smoking, without worsening depressive symptoms, among smokers with elevated depressive symptoms.
**Implications:** This secondary analysis of a recent clinical trial examined whether depressive symptom severity moderated the effects of reduced-nicotine cigarettes on smoking and depressive symptoms. Results indicate that, regardless of baseline depressive symptoms, participants randomized to reduced-nicotine cigarettes had lower smoking rates, nicotine intake, nicotine dependence, and craving at week 6 post-randomization than those assigned to normal-nicotine cigarettes. In participants with higher baseline depressive symptoms, those assigned to reduced-nicotine cigarettes had lower week 6 depressive symptoms than those assigned to normal-nicotine cigarettes. These results suggest that a nicotine reduction policy could have beneficial effects for smokers, regardless of depressive symptom severity.

## Introduction

In the United States, 8% of adults have current depression, and the prevalence of smoking among these adults is significantly higher than that of adults without a current mental health condition (40% vs. 15.5%).[1] The elevated risk of smoking among people with depression is due to both a higher likelihood of becoming tobacco dependent and a lower likelihood of smoking cessation.[1,2] Not surprisingly, depression is associated with elevated risks for tobacco-related disease and death.[3–5]

Moreover, elevated depressive symptoms in general are associated with smoking progression and persistence.[6–12] Barriers to cessation in smokers with elevated depressive symptoms include high levels of cigarette craving and withdrawal-related negative affect, along with beliefs that smoking improves negative affect.[13,14] Although smoking reduces withdrawal-related negative affect, smoking cessation is associated with improvement, rather than worsening, in depressive symptoms over time.[15] Nevertheless, the perception that smoking improves depressive symptoms may contribute to smoking persistence in this population. Finding effective methods of improving smoking cessation rates among smokers with elevated depressive symptoms and others with psychiatric disorders is critical to reducing tobacco-related deaths in the United States.[16]

In 2009, the US Food and Drug Administration (FDA) acquired regulatory authority over tobacco products, including the authority to reduce, although not eliminate, the nicotine content of cigarettes.[17] Reducing the nicotine content of cigarettes to a level below that which sustains dependence may help established smokers quit and prevent new smokers from becoming dependent.[18–20] A large clinical trial[21] recently confirmed the results of previous smaller studies[22–25] by finding that smokers who were switched to reduced-nicotine content (RNC) cigarettes (ie, those containing ≤2.4 mg nicotine per gram tobacco) smoked fewer cigarettes, were less nicotine dependent, and had less abstinence-induced craving after 6 weeks of cigarette use than those randomized to normal-nicotine content (NNC; 15.8 mg/g) cigarettes. Furthermore, although participants were not trying to quit at the time of enrollment, those who had used cigarettes with 0.4 mg/g nicotine during the study made more quit attempts after the active intervention than those who had used NNC cigarettes, suggesting that a nicotine reduction policy might help smokers benefit from other tobacco public health strategies and cessation treatment approaches.

However, a nicotine reduction policy could also have unintended negative consequences for smokers with elevated depressive symptoms. These smokers might experience transient or longer increases in depressive symptoms, due to elevated withdrawal symptoms and inadequate resources for coping with these experiences. If so, these smokers might increase their cigarette or smoke intake (ie, engage in compensatory smoking) because of expectancies that smoking improves mood.[26] Unlike "light" cigarettes, RNC cigarettes are associated with minimal compensation,[21] but smokers with elevated depressive symptoms may be more likely to attempt to compensate for the reduction in nicotine. Likewise, RNC cigarette studies have shown few effects on mood to date,[27] but no large-scale studies of RNC cigarettes have focused on smokers with elevated depressive symptoms. These smokers might also increase their alcohol or other drug intake in an attempt to cope with negative affect during nicotine withdrawal.[28] This seems unlikely based on the weight of evidence showing that smoking cessation treatment does not increase alcohol use,[29] but effects of extended RNC use on drinking in people with elevated depressive symptoms have not yet been reported. Due to the over-representation of depressive symptoms and related mental health conditions among current smokers, understanding how these smokers respond to RNC cigarettes is essential to consider when determining how to best implement a nicotine reduction policy.[30,31]

The current study is a secondary analysis of the recent large clinical trial of RNC cigarettes[21] and aimed to examine how baseline depressive symptom severity affected responses to RNC cigarettes. Based on the poorer responses of smokers with elevated depressive symptoms to smoking cessation treatments, we hypothesized that participants with elevated depressive symptoms who were assigned to RNC cigarette use during the study would be less likely than those with lower depressive symptoms to experience reductions in cigarettes per day, nicotine exposure, nicotine dependence, and cigarette craving, would be less compliant with RNC cigarettes, and would be less likely to make a quit attempt after the study.

## Methods

### Participants

Participants were recruited at 10 sites across the United States, using community-based advertisements. Participants were required to be at least 18 years of age, to smoke at least 5 cigarettes per day, and to have

breath carbon monoxide (CO) levels of at least 8 ppm or urinary cotinine levels of at least 100 ng/mL. Potential participants were excluded if they were pregnant or breastfeeding, had a positive toxicology screen for illicit drugs other than cannabis, intended to quit smoking within the next 30 days, exclusively used roll-your-own cigarettes, had used tobacco products other than machine-made cigarettes on more than 9 of the past 30 days, reported alcohol binge drinking (>4/5 drinks within 2 hours for women/men) on more than 9 of the past 30 days, or had significant unstable medical or psychiatric conditions. Those with psychiatric disorders other than schizophrenia or schizoaffective disorder were eligible to enroll if they had not experienced a significant change in psychiatric symptoms or psychiatric medication in the past 3 months and had not experienced suicidal ideation in the past month or had made a suicide attempt in the past 10 years.

## Procedure

After a 2-week baseline assessment period during which participants smoked their usual cigarette brand, they were randomized to either their usual brand or to one of 6 investigational cigarette conditions. Research cigarettes, produced for the National Institute on Drug Abuse (NIDA) by 22nd Century Group, Inc, had the following nicotine contents, expressed as mg nicotine per gram tobacco: 15.8, 5.2, 2.4, 1.3, and 0.4 (regular tar) and 0.4 (high tar). Tar yields were 8–10 mg in all conditions except for the 0.4 mg/g (high tar) condition, in which tar yield was 13 ± 2 mg. Participants received menthol or nonmenthol cigarettes according to their preference. Investigators, staff, and participants were blind to condition assignment other than for the usual brand condition. Each week throughout the 6-week intervention period, participants received free study cigarettes, were instructed to smoke only these cigarettes, and received study cigarette compliance monitoring and counseling. Subjective, behavioral, and physiological measures, described below, were collected weekly throughout the baseline and intervention periods. At post-randomization week 6, participants were asked to complete an additional session after abstaining from smoking overnight. Those who reported not having smoked since the previous day and met the abstinence criterion (CO < 50% of the previous day's CO, or < 6 ppm) received additional compensation and completed measures of craving and withdrawal. Participants were recontacted by telephone 30 days after their last session and were asked if they had made a quit attempt since the last visit. The total possible compensation for completing study procedures was $835.

## Measures

### Subjective Measures

Depressive symptoms were measured at baseline using the Center for Epidemiologic Studies Depression Scale (CES-D).[32] The CES-D consists of 20 items scored from 0 to 3, yielding total scores ranging from 0 to 60, with scores ≥16 indicating possible clinical depression.[33] The scale includes four factors: Depressed Affect (eg, sad, lonely), Positive Affect (eg, happy, enjoyed life; negatively scored), Somatic Symptoms (eg, poor appetite), and Interpersonal Problems (eg, people dislike me). Other questionnaires administered at baseline included the Fagerström Test for Nicotine Dependence (FTND),[34] the 37-item Wisconsin Index of Smoking Dependence Motives (WISDM),[35] and the 20-item Positive and Negative Affect Scale (PANAS),[36] a questionnaire that yields two factors, one representing positive affect and the other negative affect. Cigarette craving was measured using the 10-item Questionnaire on Smoking Urges-brief scale (QSU),[37] which has two factors: Factor 1, a measure of craving for positive reinforcing effects, and Factor 2, a measure of craving to reduce negative affect related to abstinence. Nicotine withdrawal symptoms were measured using the Minnesota Nicotine Withdrawal Scale (MNWS).[38] At baseline, the QSU and MNWS were administered under non-abstinence conditions. The QSU and MNWS were re-administered weekly during the intervention period, the FTND and PANAS were re-administered at post-randomization weeks 2 and 6, and the CES-D and WISDM were re-administered at post-randomization week 6. All of the subjective measures had high internal consistency (Cronbach's $\alpha$ = 0.82–0.96), with the exception of the FTND, which had marginal internal consistency (Cronbach's $\alpha$ = 0.66 in the CES-D < 16 group and 0.69 in the CES-D ≥ 16 group).

### Behavioral and Physiological Measures

Throughout the baseline and intervention periods, participants used an interactive voice response (IVR) system to report the number of cigarettes smoked (study-provided and non-study, reported separately) on the previous day. Noncompliance was defined as any self-reported non-study cigarette use. Total cigarette puff volume (ie, sum of the volumes for all puffs smoked in a single cigarette) was collected in the laboratory using Clinical Research Support System (CReSS) Pocket topography measurement instruments (Borgwaldt KC, Richmond, VA). At baseline, participants smoked one of their usual brand cigarettes, and at weeks 2 and 6, participants smoked one of their assigned study cigarettes. Breath CO levels (Bedfont Scientific, Ltd) were collected weekly during the baseline and intervention periods. First-void urine samples were collected at baseline and at post-randomization weeks 2 and 6 for assessment of total nicotine equivalents (TNE), a measure of nicotine exposure. TNE, adjusted for creatinine, was computed as the sum of nicotine, cotinine, trans-3′-hydroxycotinine, and their glucuronides.[39] Nicotine metabolite ratio, an indicator of CYP2A6 enzyme activity,[40] was computed as the ratio of 3′-hydroxycotinine to cotinine from saliva samples collected at baseline. Daily alcohol intake and cannabis use were collected at each visit using timeline followback interviews.[41] Participants were defined as cannabis users at baseline if they reported having used cannabis in the past 30 days or if their baseline urine sample tested positive for tetrahydrocannabinol (THC).

## Statistical Analyses

Group comparisons of measures collected at baseline were conducted using *t* tests for continuous variables and chi-square tests for categorical variables. To maximize statistical power to detect interactions between CES-D score and nicotine content, the two NNC conditions (usual brand, 15.8 mg/g) were combined and compared with the combined four RNC conditions (2.4-0.4 mg/g), as these conditions had similar effects on cigarettes per day and nicotine exposure in the overall sample.[21] The 5.2 mg/g condition was excluded from the analysis because it had mixed effects in the overall sample.[21]

Linear regression was used to examine the effects of cigarette nicotine content (NNC vs. RNC) and baseline CES-D score (CES-D < 16 vs. ≥ 16) on outcome measures collected at post-randomization week 6, first controlling only for baseline levels of each variable (unadjusted), and then after also adjusting for age, race, gender, education, and nicotine metabolite ratio. A similar analytic approach was used to examine interactions between baseline CES-D score and cigarette nicotine content on craving and withdrawal symptoms during the abstinence session. As a secondary approach, CES-D score was entered into the statistical models as a continuous measure. Most outcomes are expressed in the tables as differences between the RNC and NNC conditions, with negative values indicating that those in the RNC condition reported a reduction in this measure relative to

those in the NNC condition. The association between nicotine content and TNE was summarized by the ratio of the geometric mean TNE from the RNC condition relative to the geometric mean TNE from the NNC condition. The association between nicotine content and noncompliance (ie, any non-study cigarette use) was summarized by the odds ratios (ORs) for self-reported noncompliance at post-randomization week 6 for the RNC condition relative to the NNC condition. Similarly, cannabis use was summarized as ORs for self-report of any use at week 6 for the RNC condition relative to the NNC condition. Quit attempts were treated as a binary variable for whether or not the subject made a quit attempt between the post-randomization week 6 visit and the follow-up assessment and were analyzed following the same approach as noncompliance. Daily alcohol intake (drinks per day) was analyzed using quantile regression on the 75th percentile.[42] The 75th percentile was considered because slightly more than half of the respondents reported 0 drinks per day, and the 75th percentile represented the center of the distribution among subjects that reported some drinking, which maximizes our ability to detect an effect of condition on this variable.

As noncompliance with the RNC cigarettes could lead to an underestimate of their disruptive effects on depressive symptoms, biochemically confirmed compliance with the 0.4 mg/g cigarettes was explored as a moderator of the effect of baseline CES-D score on week 6 CES-D score, adjusting for the same covariates described above. Compliance status was dichotomized according to a preestablished urinary TNE cutoff of 6.41 nmol/mL.[43] Biochemical confirmation of compliance was not conducted in the other cigarette conditions because individual differences in nicotine intake from these cigarettes could result in overlap in the distribution of TNE levels.

Tests were considered significant at $\alpha = 0.05$, two-tailed. Since this research focused on examining the potential unintended negative consequences of nicotine reduction in smokers with elevated depressive symptoms, we considered it more important to avoid Type II error than Type I error. Therefore, we did not correct for the multiple statistical tests. For the same reason, effect sizes (Cohen's *d*) are reported for the effects of cigarette nicotine content in the CES-D < 16 and ≥ 16 groups, with $d = 0.2$ considered a small, 0.5 a medium, and 0.8 a large effect size.[44]

## Results

### Participant Characteristics

Characteristics of the overall sample have been reported.[21] Of the 717 participants included in the current analyses, 109 (15.2%) had CES-D scores ≥ 16 and 608 (84.8%) had CES-D scores < 16. As shown in Table 1, those with CES-D scores < 16 versus ≥ 16 did not differ on age, gender, race, Hispanic ethnicity, education, menthol preference, drinks per day, cannabis use, cigarettes per day, TNE, breath CO level, FTND score, or total cigarette puff volume. By definition, the high CES-D group had significantly higher baseline CES-D scores, and significant between-groups differences were found on all four CES-D factors. In addition, those with CES-D scores ≥ 16 reported higher scores on the WISDM, QSU, and MNWS (all *p*s ≤ .001).

**Table 1.** Baseline Demographic and Smoking Characteristics of Participants With CES-D Scores < 16 vs. ≥ 16

| | CES-D < 16 | CES-D ≥ 16 | |
|---|---|---|---|
| | *n* = 608 (84.8%) | *n* = 109 (15.2%) | *p* |
| Age (mean [*SD*]) | 41.5 (13.3) | 42.1 (13.3) | .67 |
| Gender (% male) | 57.6% | 57.8% | 1 |
| Race | | | |
| White | 51.3% | 53.2% | .59 |
| African American | 38.3% | 33.9% | |
| Other | 10.4% | 12.8% | |
| Hispanic ethnicity | 4.6% | 5.5% | .84 |
| Education (% ≤ 12 y) | 43.4% | 45.0% | .85 |
| Menthol preference | 57.1% | 60.6% | .57 |
| Drinks per day (75th percentile) | 0.71 (0, 4.43) | 0.5 (0, 2.19) | .27 |
| Cannabis past 30 days (%) | 28.6% | 30.3% | .81 |
| Cigarettes per day | 15.5 (7.5) | 15.2 (8.0) | .69 |
| TNE (nmol/mL)[a] | 42.2 (46.3) | 39.9 (37.7) | .52 |
| Breath CO (ppm) | 15.1 (7.9) | 15.1 (8.4) | .99 |
| FTND | 5.1 (2.2) | 5.3 (2.2) | .31 |
| Total cigarette puff volume | 749 (310) | 799 (327) | .16 |
| CES-D score | 6.6 (4.1) | 21.5 (5.4) | **<.001** |
| Depressed Affect | 0.9 (1.4) | 6.3 (2.9) | **<.001** |
| Positive Affect | 9.6 (2.2) | 6.5 (2.4) | **<.001** |
| Somatic Symptoms | 3.0 (2.2) | 8.2 (2.9) | **<.001** |
| Interpersonal Problems | 0.3 (0.7) | 1.5 (1.4) | **<.001** |
| WISDM total | 40.6 (12.4) | 47.1 (12.8) | **<.001** |
| QSU Factor 1 | 19.0 (9.2) | 22.4 (9.3) | **.001** |
| QSU Factor 2 | 10.1 (5.9) | 13.5 (9.1) | **<.001** |
| MNWS | 6.0 (4.5) | 10.7 (5.8) | **<.001** |

Bold values are statistically significant. CES-D = Center for Epidemiologic Studies Depression Scale; CO = carbon monoxide; FTND = Fagerström Test of Nicotine Dependence; MNWS = Minnesota Nicotine Withdrawal Scale; QSU = Questionnaire on Smoking Urges; TNE = total nicotine equivalents; WISDM = Wisconsin Inventory of Smoking Dependence Motives.

[a]Geometric mean (interquartile range) are presented for TNE.

### Moderating Effects of Baseline Depressive Symptoms on Responses to Study Cigarettes

*p* Values for tests of interactions between baseline CES-D score (<16 vs. ≥16) and cigarette nicotine content (RNC vs. NNC) at the week 6 post-randomization visit are shown in Table 2, along with mean differences between the RNC and NNC conditions at this visit. Those assigned to RNC cigarettes had significantly lower week 6 cigarettes per day, TNE levels, FTND scores, and QSU scores, as previously reported,[21] and these effects were not moderated by baseline depressive symptom severity. Effect sizes (*d*) for the effects of cigarette nicotine content on these measures were 0.31–0.84 in the CES-D < 16 group and 0.54–0.77 in the CES-D ≥ 16 group. No effects of RNC cigarettes were observed on week 6 drinks per day, cannabis use, breath CO levels, MNWS scores, or PANAS Positive Affect scores in either group, with effect sizes of 0.08–0.13 in the CES-D < 16 group and 0.03–0.32 in the CES-D ≥ 16 group. Among participants with baseline CES-D scores < 16, those assigned to RNC had lower WISDM scores and made more quit attempts, as was seen in the overall sample[21]; effects of RNC cigarettes on these variables in participants with baseline CES-D scores ≥ 16 were similar but not statistically significant ($d$ = 0.34 for WISDM score and OR = 2.9 for quit attempts). In addition, RNC cigarettes decreased total puff volumes at week 6 in those with baseline CES-D scores < 16 ($p$ < .001, $d$ = 0.49) and did not change total puff volumes in those with baseline CES-D ≥ 16 ($d$ = 0.02), although this interaction was not significant ($p$ = .1).

The only significant interactions between baseline CES-D score and cigarette nicotine content were on week 6 CES-D Total scores, CES-D Depressed Affect scores, and CES-D Somatic Symptoms scores ($p$s < .05). Difference scores indicated that, in participants with CES-D scores ≥ 16 at baseline, week 6 CES-D scores were lower among those assigned to RNC cigarettes than those assigned to NNC cigarettes ($d$ = 0.51–0.62), whereas in participants with CES-D scores < 16 at baseline, week 6 CES-D scores were not affected by cigarette nicotine content ($d$ = 0.01–0.08). A similar trend was observed with week 6 PANAS Negative Affect scores, but this interaction was not significant ($p$ = .06), with effect sizes of $d$ = 0 in the CES-D < 16 group and 0.49 in the CES-D ≥ 16 group.

Participants with baseline CES-D scores < 16 also had significantly increased ORs for self-reported cigarette noncompliance. This increase was driven by higher self-reported noncompliance with NNC cigarettes among those with baseline CES-D scores ≥ 16 (29.0% vs. 17.1%); self-reported noncompliance with RNC cigarettes was not affected by CES-D score (42.1% vs. 39.1%).

When CES-D was entered into the statistical models as a continuous measure, interaction $p$ values were similar, with two exceptions: first, the interactions between baseline CES-D score and cigarette nicotine content on week 6 CES-D Total and Depressed Affect scores were no longer significant ($p$s for the adjusted models = .20 and .21, respectively), and second, the interaction between CES-D score and cigarette nicotine content on cigarette noncompliance became significant ($p$ = .01).

### Impact of Biochemically Verified Compliance in the 0.4 mg/g Nicotine Conditions

The effect of biochemically conformed compliance on week 6 CES-D score was explored in those randomized to the 0.4 mg/g nicotine conditions. Of the 242 participants assigned to one of these conditions, week 6 TNE levels were available from 220 participants. Of these participants, 184 participants had baseline CES-D scores < 16 and 47 of these participants (25.5%) met the TNE compliance criterion, whereas 36 participants had baseline CES-D scores ≥ 16 and nine of these participants (25%) met the compliance criterion (NS). Among those with baseline CES-D scores < 16, participants who were compliant with the 0.4 mg/g cigarettes had 4.8-point higher (95% confidence interval: 1.8, 7.7) CES-D scores at week 6 relative to those who were not compliant ($p$ = .002, $d$ = 0.57). Among participants with baseline CES-D scores ≥ 16, those who were compliant with the 0.4 mg/g cigarettes had 2.3-point lower (−9.6, 5) CES-D scores at week 6 relative to those who were not compliant, but this effect was not significant ($p$ = .546, $d$ = 0.27). The interaction between baseline CES-D score and compliance on week 6 CES-D score was significant when CES-D score was entered as a continuous measure but not when it was entered as a categorical measure ($p$s = .003 and .183, respectively). Similar results were obtained when change in CES-D score was used as the outcome measure rather than week 6 CES-D score, but the interaction between baseline CES-D score and compliance was significant whether baseline CES-D was entered as a continuous or categorical measure ($p$s = .003 and .013, respectively).

### Moderating Effects of Baseline Depressive Symptoms on Abstinence From Study Cigarettes

*p* Values for tests of interactions between baseline CES-D score (<16 vs. ≥16) and cigarette nicotine content on QSU and MNWS scores after overnight abstinence are shown in Table 3, along with mean differences between the RNC and NNC conditions on these scores. Overall, those randomized to RNC cigarettes had less craving and withdrawal after overnight abstinence than those randomized to NNC cigarettes. CES-D score at baseline did not moderate these effects. Interaction test $p$ values were similar when CES-D score was entered in the analyses as a continuous measure.

## Discussion

Reducing the nicotine content of cigarettes to a minimally addictive level has been proposed as a regulatory approach to reducing tobacco dependence and may improve the responses of smokers to other public health and smoking cessation treatment approaches.[19] Results from our recent clinical trial support this hypothesis, by indicating that participants who were switched to RNC cigarettes for a 6-week period had lower smoking rates, nicotine dependence, abstinence-induced craving, and higher post-intervention quit attempts than those who used NNC cigarettes.[21] As smokers with elevated depressive symptoms have relatively poor responses to smoking cessation treatments, concerns have been raised that these smokers could experience unintended negative consequences if the FDA were to institute a nicotine reduction policy.[30,31] Thus, examining the responses of smokers with elevated depressive symptoms to RNC cigarettes is important for informing the FDA about the potential impact of this regulatory policy on public health.

Although this study did not focus on smokers with a diagnosis of depression, the results of the current study indicate that the effects of RNC cigarettes in smokers with elevated depressive symptoms are similar to those with lower depressive symptoms. Specifically, those randomized to the RNC condition experienced reductions in smoking rates, nicotine intake, nicotine dependence, and craving, regardless of CES-D score at baseline. No effects of RNC cigarettes were observed on alcohol or cannabis use in either group. Smoking RNC cigarettes did not lead to deeper smoke inhalation in

**Table 2.** *p* Values for Tests of Interactions Between Baseline CES-D Score and Nicotine Content, and Mean Differences Between the RNC and NNC Conditions at Post-randomization Week 6 in Participants With CES-D Scores < 16 vs. ≥ 16

| | Interaction tests | | CES-D < 16 | | | | CES-D ≥ 16 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted model[a] | Adjusted model[b] | Unadjusted model[a] | | Adjusted model[b] | | Unadjusted model[a] | | Adjusted model[b] | |
| Outcome | *p* | *p* | Mean difference | *p* | Mean difference | *p* | Mean difference | *p* | Mean difference | *p* |
| Drinks per day (75th percentile) | .35 | .30 | 0.1 (−0.3, 0.4) | .48 | 0.01 (−0.22, 0.25) | .96 | 0.6 (−0.4, 1.7) | 1 | 0.5 (−0.2, 1.2) | 1 |
| Cannabis use[c] | .19 | .11 | 1.0 (0.9, 1.0) | .73 | 1.0 (0.9, 1.1) | .81 | 1.1 (0.9, 1.3) | .27 | 1.1 (1.0, 1.3) | .15 |
| CPD | .44 | .47 | −6.4 (−7.7, −5.1) | **<.001** | −6.3 (−7.6, −5) | **<.001** | −5.1 (−8.2, −1.9) | **.002** | −5.5 (−8.7, −2.4) | **.001** |
| TNE[d] | .40 | .41 | 0.5 (0.4, 0.6) | **<.001** | 0.5 (0.41, 0.62) | **<.001** | 0.4 (0.2, 0.6) | **<.001** | 0.4 (0.3, 0.7) | **.001** |
| Breath CO | .52 | .42 | −0.7 (−2, 0.6) | .27 | −0.6 (−1.9, 0.7) | .36 | −2.2 (−5.1, 0.7) | .14 | −2.1 (−5.1, 0.9) | .17 |
| FTND | .99 | .88 | −0.8 (−1.1, −0.6) | **<.001** | −0.8 (−1.1, −0.5) | **<.001** | −0.8 (−1.5, −0.1) | **.03** | −1 (−1.7, −0.2) | **.01** |
| Total puff volume | .06 | .10 | −109 (−151, −67) | **<.001** | −103 (−144, −61) | **<.001** | 1.8 (−108, 111) | .97 | −4.0 (−117, 109) | .95 |
| CES-D Total | **.03** | **.03** | 0.3 (−1.1, 1.7) | .64 | 0.2 (−1.2, 1.6) | .77 | −4.4 (−8.4, −0.4) | **.03** | −4.8 (−8.7, −0.9) | **.02** |
| Depressed | **.03** | **.03** | 0.3 (−0.2, 0.8) | .23 | 0.3 (−0.3, 0.8) | .35 | −1.4 (−3, 0.2) | .10 | −1.8 (−3.3, −0.2) | **.03** |
| Positive | .85 | .99 | 0 (−0.4, 0.5) | .92 | 0 (−0.5, 0.5) | .99 | 0.3 (−1, 1.6) | .69 | 0.2 (−1.2, 1.6) | .77 |
| Somatic | **.01** | **.01** | 0 (−0.5, 0.6) | .90 | 0 (−0.6, 0.5) | .88 | −1.9 (−3.5, −0.3) | **.02** | −2.1 (−3.7, −0.6) | **.01** |
| Interpersonal | .19 | .18 | 0 (−0.1, 0.2) | .75 | 0 (−0.2, 0.2) | .88 | −0.3 (−0.9, 0.3) | .36 | −0.3 (−1, 0.3) | .29 |
| WISDM total | .66 | .66 | −3.2 (−5, −1.5) | **<.001** | −3.6 (−5.3, −1.9) | **<.001** | −1.8 (−5.9, 2.2) | .38 | −2.9 (−6.7, 1) | .15 |
| QSU Factor 1 | .91 | .99 | −4 (−5.3, −2.7) | **<.001** | −4 (−5.3, −2.7) | **<.001** | −4 (−7.6, −0.4) | **.03** | −4.3 (−8, −0.5) | **.03** |
| QSU Factor 2 | .26 | .30 | −1.6 (−2.6, −0.7) | **.001** | −1.6 (−2.6, −0.7) | **.001** | −3.4 (−5.9, −0.9) | **.01** | −3.7 (−6.3, −1.1) | **.01** |
| MNWS | .87 | .67 | −0.5 (−1.2, 0.3) | .22 | −0.5 (−1.3, 0.2) | .14 | −0.7 (−2.8, 1.4) | .52 | −1.3 (−3.4, 0.7) | .20 |
| PANAS positive | .73 | .52 | −0.7 (−1.9, 0.5) | .27 | −0.7 (−1.9, 0.5) | .26 | −0.5 (−3.5, 2.5) | .76 | −0.2 (−3.3, 3) | .91 |
| PANAS negative | .09 | .06 | 0.2 (−0.7, 1.1) | .74 | 0 (−0.9, 0.9) | .96 | −2.2 (−4.9, 0.6) | .13 | −2.7 (−5.3, −0.2) | **.04** |
| Noncompliance[c] | .12 | .15 | 1.3 (1.2, 1.4) | **<.001** | 1.3 (1.2, 1.4) | **<.001** | 1.1 (0.9, 1.4) | .34 | 1.1 (0.9, 1.4) | 0.29 |
| Quit attempt[c] | .96 | .90 | 1.9 (1.2, 2.9) | **.01** | 1.9 (1.2, 2.9) | **.01** | 1.9 (0.7, 5.6) | .23 | 2.9 (0.8, 10.2) | .10 |

Bold values are statistically significant. CES-D = Center for Epidemiologic Studies Depression Scale; CO = carbon monoxide; CPD = cigarettes per day; FTND = Fagerström Test of Nicotine Dependence; MNWS = Minnesota Nicotine Withdrawal Scale; NNC = normal-nicotine content; PANAS = Positive and Negative Affect Scale; QSU = Questionnaire on Smoking Urges; RNC = reduced-nicotine content; TNE = total nicotine equivalents; WISDM = Wisconsin Inventory of Smoking Dependence Motives.

[a]Adjusted for baseline value only.

[b]Adjusted for age, race (white, African American, other), sex, education (≤12 vs. >12 y), and nicotine metabolite ratio, along with baseline value.

[c]Treatment effect represented by odds ratios.

[d]Treatment effect represented by ratio of geometric means.

**Table 3.** Mean Differences Between the RNC and NNC Conditions at the Abstinence Visit in Patients With CES-D Scores < 16 vs. ≥ 16

| | Interaction tests | | CES-D < 16 | | | | CES-D ≥ 16 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Unadjusted model[a] | Adjusted model[a] | Unadjusted model[a] | | Adjusted model[b] | | Unadjusted Model[a] | | Adjusted Model[b] | |
| Outcome | *p* | *p* | Mean difference | *p* | Mean difference | *p* | Mean difference | *p* | Mean difference | *p* |
| QSU Factor 1 | .52 | .44 | −9.8 (−11.8, −7.9) | **<.001** | −9.9 (−11.9, −8) | **<.001** | −7.4 (−12.9, −1.9) | **.01** | −7.8 (−13.3, −2.3) | **.01** |
| QSU Factor 2 | .83 | .85 | −5.1 (−6.5, −3.7) | **<.001** | −5.2 (−6.6, −3.7) | **<.001** | −5.2 (−9.1, −1.2) | **.01** | −5.9 (−10, −1.9) | **.01** |
| MNWS | .49 | .56 | −2.4 (−3.6, −1.2) | **<.001** | −2.5 (−3.6, −1.3) | **<.001** | −1.3 (−4.7, 2) | .44 | −1.5 (−5.1, 2) | .40 |

Bold values are statistically significant. CES-D = Center for Epidemiologic Studies Depression Scale; MNWS = Minnesota Nicotine Withdrawal Scale; NNC = normal-nicotine content; QSU = Questionnaire on Smoking Urges; RNC = reduced-nicotine content.

[a]Adjusted for baseline value only.

[b]Adjusted for age, race (white, African American, other), sex, education (≤12 vs. >12 y), and nicotine metabolite ratio, along with baseline value.

either group: RNC cigarettes reduced total puff volumes relative to NNC cigarettes in the CES-D < 16 group and did not change total puff volumes relative to NNC cigarettes in the CES-D ≥ 16 group. Furthermore, those with higher depressive symptom severity at baseline who were assigned to RNC cigarettes had lower CES-D scores at week 6 than those assigned to NNC cigarettes. We examined the effect of study cigarette compliance as a moderator of this effect given that noncompliance would be expected to lead to an underestimate of the disruptive effects of nicotine reduction on CES-D score. Those with lower CES-D scores at baseline who were compliant with the 0.4 mg/g nicotine cigarettes had 4.8-point higher week 6 CES-D scores than those who were non-compliant; however, the average week 6 CES-D score among compliant participants were still indicative of low levels of depression. Conversely, those with higher CES-D scores at baseline who were compliant with the 0.4 mg/g nicotine cigarettes had 2.3-point lower week 6 CES-D scores than those who were non-compliant, but this effect was not significant. In light of the small sample sizes in these exploratory analyses, however, these findings are considered preliminary. As reported previously, adverse events related to depression were rare during the study and unrelated to cigarette condition.[21] Thus, the current results suggest that a nicotine reduction policy could have broad beneficial effects for smokers, regardless of depressive symptom severity.

Few studies have investigated the effects of RNC cigarettes in people with elevated depressive symptoms or clinical depression. One study found that RNC cigarettes were less effective than NNC cigarettes at increasing positive affect in response to a positive mood induction procedure among smokers with anhedonia (low positive mood).[45] In a second study, among smokers with current or past depression, RNC cigarettes were less effective than NNC cigarettes at increasing positive mood and reducing negative mood during positive mood induction, but NNC cigarettes also exacerbated the effects of negative mood induction on negative mood.[46] Another study found that smokers with a history of depression smoked more NNC and RNC cigarette puffs during either neutral or negative mood induction, suggesting that they experience stronger acute reinforcing effects of smoking in general, regardless of nicotine content or mood.[47] To our knowledge, the current study is the first to examine the effects of an extended period of RNC cigarette use among people with elevated depressive symptoms, and the first to assess multiple behavioral, subjective, and physiological measures relevant to estimating the potential effects of a nicotine reduction policy in these smokers.

This study has several limitations that must be acknowledged. First, although the CES-D is a reliable and valid measure of depression symptomatology, with CES-D scores ≥ 16 considered indicative of possible clinical depression,[32,33] participants were not clinically diagnosed with depression. Moreover, the average CES-D score in the CES-D ≥ 16 group was in the mild-to-moderate range. Therefore, it is possible that the results of this study may not generalize to people with major depressive disorder. Second, despite the large size of the overall sample, analytic power was limited because only 15% of the sample reported elevated depressive symptoms at baseline (consistent with the national rate of depression among smokers[48]). We attempted to maximize statistical power by combining the four RNC conditions and two NNC conditions that had similar effects on cigarettes per day and nicotine exposure in the overall sample[21] and by conducting secondary analyses with baseline CES-D score entered as a continuous measure. Nevertheless, power was limited to detect significant interactions between depressive symptom severity and cigarette nicotine content. While our negative findings should be interpreted cautiously in view of the power limitation, the pattern of reduction in smoking rates and depressive symptoms among those assigned to RNC cigarettes in the high CES-D group mitigates this concern.

A third limitation is that, although participants were provided with free study cigarettes and were counseled to use only these cigarettes, non-study cigarette use was frequent during the trial. Furthermore, biochemically confirmed rates of compliance with RNC cigarettes are known to be lower than those reported by participants.[49] The application of a strict biochemical abstinence criterion to participants in the 0.4 mg/g nicotine conditions revealed that nicotine reduction had a disruptive effect on week 6 CES-D scores in those with lower baseline CES-D scores, which was not initially evident when compliance was not included as a moderator; likewise, noncompliance with RNC cigarettes could also lead to a minimization of their beneficial effects on smoking rates. Thus, studies that model the effects of a nicotine reduction must attempt to maximize study cigarette compliance and consider the effect of compliance as a moderator. A fourth limitation is that the duration of the trial was only 6 weeks, which may have reduced effects of RNC cigarettes on smoking rates and dependence. Longer trials of RNC cigarettes in smokers with affective disorders are underway (https://clinicaltrials.gov/ct2/show/NCT01928758, https://clinicaltrials.gov/ct2/show/NCT02232737) and will address some of these limitations.

Notwithstanding these limitations, the results of this study provide no indication that a nicotine reduction policy would increase smoking, nicotine or CO exposure, or depressive symptoms among smokers with elevated depressive symptoms. In fact, use of RNC cigarettes significantly decreased smoking rates, dependence, cigarette

craving, negative affect, and CES-D scores among those with elevated baseline CES-D scores. While all smokers should be unambiguously advised to quit smoking completely, smoking cessation rates are exceedingly low among smokers with elevated depressive symptoms.[6] Reducing the nicotine content of cigarettes below an addiction threshold appears to be a potential avenue for reducing cigarette dependence, which may improve responses of these smokers to other public health approaches and smoking cessation treatments.

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## Declaration of Interests

*None declared.*

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