Increasing Quit Attempts by Transitioning to Very Low Nicotine Content Cigarettes Versus Reducing Number of Cigarettes Per Day: A Secondary Analysis of an Exploratory Randomized Trial

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Abstract

Introduction: The Food and Drug Administration (FDA) has proposed reducing nicotine with very low nicotine content (VLNC) cigarettes. In contrast, reducing nicotine by reducing number of cigarettes per day (CPD) is common. Our prior findings demonstrate that VLNC cigarettes decreased dependence more and were more acceptable than reducing CPD. This secondary analysis explored which reduction strategy increased quit attempts (QA), self-efficacy, or intention to quit more.

Methods: This is a secondary analysis of 68 adult daily smokers not ready to quit randomized to smoke VLNC cigarettes versus reduce CPD over 5 weeks. All participants smoked study cigarettes with nicotine yield similar to most commercial cigarettes ad lib for 1 week (baseline). Participants were then randomized to gradually reduce to 70%, 35%, 15%, and 3% of baseline nicotine over 4 weeks by either (1) transitioning to lower nicotine VLNC cigarettes or (2) reducing the number of full nicotine CPD. All participants received nicotine patches to aid reduction. We assessed (1) QAs using nightly and weekly self-reports, (2) Velicer’s Self-Efficacy to Quit measure weekly, and (3) the Intention-to-Quit Ladder nightly.

Results: More CPD (41%) than VLNC (17%) participants made any QA (odds ratio = 3.4, 95% confidence interval = 1.1, 10.5). There was no difference in QAs ≥24 h. Self-efficacy increased for VLNC but not CPD participants (interaction: \( F = 3.7, p < .01 \)). The condition by time interaction for intention-to-quit was not significant.

Conclusions: Reducing number of CPD increased QAs more than reducing nicotine via switching to VLNC cigarettes. The lack of difference in longer QAs suggests replication tests are needed.

Implications: Reducing the frequency of smoking behavior (ie, CPD) could be a more effective strategy to increase QAs than reducing the magnitude of nicotine in each cigarette (ie, VLNC) per se.
Introduction

The prevalence of smoking in the United States has declined dramatically since the Surgeon General’s report in 1964 but the decline has appeared to slow to less than 1% per year.1-3 This is due, in part, to the fact that most smokers do not plan to make a quit attempt (QA) in the near future.4,5 Making a QA predicts future cessation1,6; thus, increasing QAs among those who are not ready to quit smoking should increase the prevalence of smoking cessation. One way to increase QAs could be to reduce nicotine intake. Presently, reducing cigarettes per day (CPD) is a common strategy to reduce nicotine intake and dependence6,7,8 and has been shown to increase QAs.3,10

The US Food and Drug Administration (FDA) recently proposed regulation to require that all US cigarettes have minimally addictive levels of nicotine; that is, the FDA could force smokers to transition to very low nicotine content (VLNC) cigarettes.11 Switching to VLNC cigarettes has been shown to increase QAs.12 Thus, a policy that reduces nicotine in cigarettes could be another method to decrease nicotine intake and, thereby, increase QAs.

It is unclear whether switching to VLNC cigarettes or reducing CPD increases QAs more. Though both methods aim to reduce nicotine exposure, switching to VLNC cigarettes and reducing CPD may work in different ways. Switching to VLNC cigarettes reduces the magnitude of cigarettes’ primary pharmacological reinforcing (ie, nicotine13), which could disrupt conditioned desires to smoke cigarettes and increase QAs. In contrast, reducing CPD inherently restricts the pattern and frequency of smoking behavior. This could increase QAs by providing smokers with the opportunity to enact control over their smoking and gain practice not smoking in the context of cues that otherwise would have prompted them to smoke.

The parent trial is described elsewhere.13 Briefly, we compared a gradual transition to VLNC cigarettes versus reduction in number of CPD and found that transitioning to VLNC cigarettes was more acceptable and resulted in greater reductions in nicotine dependence and cotinine over the study period than reducing CPD. The CPD condition had a greater reduction in total CPD than the VLNC condition over the study period.13 In the present secondary analysis, our a priori aim was to test whether reduction via transitioning to VLNC cigarettes or reducing number of CPD increased QAs of any length more during the reduction period. Our secondary aims were to test which reduction strategy increased self-efficacy and intention to quit more during reduction and which increased QAs and abstinence more during a 1-month follow-up. We had no hypotheses regarding direction of effects.

Methods

Participants

Research personnel recruited 74 participants via Internet advertising, flyers, and word of mouth in the Burlington, VT, area between February 2017 and January 2018. Major inclusion criteria were (1) ≥18 years old, (2) smoke ≥10 CPD 7 days per week, (3) have not used nontobacco nicotine products (eg, electronic cigarettes) or noncigarette tobacco products (eg, smokeless) or smoking cessation medications in the last month, (4) met DSM-5 criteria for Tobacco Use Disorder, and (5) have no plans to stop smoking in the next 30 days. Full inclusion criteria are reported elsewhere.13 All participants smoked ad lib during the baseline week of the study. Only the 68 participants who attended the initial visit and the visit at the end of the baseline week were retained for analysis. The study was approved by the Committee on the Use of Human Subjects in Research at the University of Vermont and registered on www.clinicaltrials.gov (NCT03060083). All participants provided written informed consent.

Design

In this unblinded parallel group randomized trial, participants attended an initial visit and five subsequent weekly visits to answer questionnaires, provide breath samples, and receive study cigarettes and NRT. Participants also answered nightly questionnaires and completed a 1-month follow-up survey online.

We used the same study cigarettes (Spectrum cigarettes, 22nd Century Group, Inc.) as prior studies of VLNC cigarettes.12,14 During the baseline week, we provided participants in both conditions with study cigarettes containing a normal amount of nicotine (17.6 mg/g) and an estimated yield similar to most commercial cigarettes (0.97 mg/cigarette). We instructed participants to smoke only study cigarettes but to smoke as usual during the baseline week.

After the baseline week, we provided participants randomized to use VLNC cigarettes with 100% of their mean number of CPD smoked during the baseline week to use throughout weeks 1 to 4 and instructed them to only smoke cigarettes provided by the study. However, we provided cigarettes with progressively less nicotine at each week: week 1 cigarettes contained 12.3 mg/g nicotine (70% of baseline), week 2 had 6.3 mg/g (35%), week 3 had 2.3 mg/g (15%), and week 4 had 0.6 mg/g nicotine (3%).

We provided participants randomized to reduce CPD with study cigarettes with 100% nicotine content (17.6 mg) throughout weeks 1 to 4 and instructed them to only smoke cigarettes provided by the study. However, we provided progressively fewer numbers of cigarettes at each week: we provided 70% of baseline number of CPD during week 1, 35% during week 2, 15% during week 3, and 3% during week 4.

We provided all participants with 21-mg NRT patches and instructed them to use patches daily during the reduction weeks for two reasons. First, the study required large magnitudes of reduction. In prior studies, large reductions in nicotine without assistance from NRT were very rare.15 Second, many researchers believe that the provision of alternate nicotine sources is essential for a switch to VLNC cigarettes to be successful16 and that many who transition to VLNC cigarettes will supplement with alternative nicotine products.17 A full description of the instructions to use NRT patches is reported elsewhere.13 At the final study visit, we (1) stopped providing study cigarettes, (2) advised smokers to quit, and (3) offered an additional 1-month supply of NRT patches to increase the likelihood of cessation. Participants completed a 1-month online follow-up survey that asked about QAs, self-efficacy, and intention to quit.

Participants were randomized at their initial visit in a 1:1 allocation ratio. The only cigarettes that matched our reduction schedule were mentholated. Thus, we included only current or past menthol cigarette users. We used a computer generated stratified blocked randomization schedule so that the proportion of current and past menthol smokers was similar between groups. In total, 36 participants were randomized to the VLNC condition and 32 to the CPD condition and completed baseline.

Measures

QA and Abstinence

We measured QAs that lasted ≥24 h as well as any QAs (ie, including QAs that lasted <1 day) by asking participants on nightly surveys “Did you quit or try to quit smoking cigarettes today?” For missed nightly surveys, we assessed QAs using the same question on a timeline follow-back during a weekly visit. We used participants’ self-reported use of study or nonstudy cigarettes during the day immediately following the QA to determine whether the QA lasted ≥24 h. We did not biochemically verify QAs because many were
short and occurred between study visits. Abstinence was a secondary aim given that participants were not planning to quit at baseline. We measured self-reported 7-day point-prevalence abstinence (PPA) weekly and at the online 1-month follow-up by asking “Have you smoked any cigarettes in the past 7 days?” We measured 30-day prolonged abstinence (PA) at the 1-month follow-up by asking “Have you smoked any cigarettes in the past 30 days?” Abstinence during the reduction period was CO verified (<5 ppm) but abstinence at follow-up was not.

Self-efficacy and Intention to Quit
Participants completed Velicer’s Self-efficacy to Quit measure and rated their intention to quit in the next month using the Intention-to-Quit Ladder during weekly visits. Increases in Self-efficacy to Quit and the Intention-to-Quit Ladder have predicted later QAs and cessation in prior studies.

Compliance
Participants self-reported the number of study and nonstudy CPD as well as NRT patch use on their nightly questionnaires and on the 1-month follow-up survey. In order to increase the validity of participants’ self-reports, we (1) informed participants that self-reported noncompliance would not influence their payment or participation and (2) employed a bogus pipeline technique by falsely telling participants we could detect nonstudy cigarettes via breath and urine tests. In fact, biochemical estimation of compliance was not possible because participants used NRT. Participants were debriefed about this deception at the end of the reduction period.

Analyses
Sixty-eight participants attended the visit at the end of baseline and were retained for analysis. We used logistic regression to compare the proportion of VLNC versus CPD participants who made a QA during the reduction period. Next, using Cox proportional hazards regression survival analyses with days as the unit of time, we calculated hazard ratios (HR) to compare time to first QA during the reduction period between the two conditions. To determine if any results were due to differences in compliance between groups, we conducted additional analyses controlling separately for compliance with (1) study cigarettes and (2) NRT patch as fixed variables in the condition by week logistic regressions and as time-varying covariates in the survival analyses during the reduction period. As a fixed covariate, compliance with study cigarettes was calculated as the percent of the mean total CPD during the reduction period that were nonstudy cigarettes. As a time-varying covariate, compliance with study cigarettes was calculated for each day of the reduction period as the percent of the total CPD that were nonstudy cigarettes. As a fixed covariate, compliance with NRT patch was calculated as the percent of days throughout the reduction period when participants reported NRT patch use. As a time-varying covariate, compliance with NRT patch was calculated as a binary variable for whether NRT patch was used for that day. We excluded data from the baseline week (ie, week 0) from our analysis of QAs because participants in both conditions smoked ad lib during baseline (ie, transitioning to VLNC cigarettes or reducing CPD began at week 1). Two participants in the CPD condition and none in the VLNC condition made any QA and none made a ≥24-h QA during baseline. Findings from sensitivity analyses that included QAs made during baseline were similar to findings reported below.

We used logistic regression to compare the proportion of VLNC versus CPD participants who made (1) any QA during the reduction period or 1-month follow-up, (2) ≥24-h QA during the reduction period or 1-month follow-up, (3) 7-day PPA at the 1-month follow-up, and (3) 30-day prolonged abstinence at the 1-month follow-up. In addition, we conducted the same analyses after controlling for patch use during the reduction period and follow-up.

For self-efficacy and intention to quit during the reduction period, we used multilevel modeling with restricted maximum likelihood (REML). We entered time and condition as fixed effects and participant as a random effect. Time was treated as a linear effect. We used week as the time variable in the multilevel models because both outcomes were assessed weekly. We chose covariance structures to minimize Akaike and Bayesian information criteria values. To aid with interpretation of significant time by condition interactions, we also used multilevel modeling to test time as a predictor separately by condition. In addition, we included participants’ compliance with study cigarettes and NRT patch as time-varying covariates for the models testing condition by week interactions. We tested compliance with study cigarettes and NRT patch as covariates in separate models.

Finally, we tested gender and current menthol versus nonmenthol status as moderators of all outcomes (QAs, abstinence, self-efficacy, and intention to quit during the reduction period as well as QAs and abstinence during follow-up). Neither moderated any outcomes and, thus, we did not report findings from these analyses.

Missing data did not significantly differ between conditions: 9% of nightly surveys were missing, 15% missed the final study visit, and 41% missed the 1-month follow-up. In our analyses of QAs and abstinence, missing data were treated as no attempt to quit and no abstinence in the logistic regressions and censored in survival analyses. In our analyses of self-efficacy and intention to quit, missing data were handled as prescribed in multilevel modeling. Specifically, in multilevel modeling, there is no requirement that all observations have the same number of data points. Unbiased estimates were obtained using REML.

Results
Participant Characteristics
Participants were a mean 38.8 (standard deviation [SD] = 13.4) years old and mostly white, non-Hispanic (82%) men (60%) with >12 years of education (72%). Participants smoked a mean 19.4 (SD = 8.4) CPD at baseline and were moderately dependent (mean Fagerstrom Test for Cigarette Dependence = 5.1, SD = 2.0). Characteristics did not significantly differ between conditions.

Quit Attempts
More participants in the CPD condition (41%) than VLNC condition (17%) made any QA during the reduction period (Table 1). The difference between participants in the CPD (13%) and VLNC (8%) conditions who made ≥24-h QAs was not significant. Findings were similar after controlling for NRT patch use and percent nonstudy CPD.

Time to first QA was significantly shorter for the CPD than the VLNC condition during the reduction period (HR = 3.2, 95% CI = 1.2–8.2; Figure 1). This effect remained after controlling for compliance with NRT patch use (HR = 3.1, 95% CI = 1.2–8.1) and use of study cigarettes (HR = 5.1, 95% CI = 1.5–17.7) throughout the reduction period. Time to first ≥24-h QA did not significantly differ between conditions (HR = 0.5, 95% CI = 0.1–2.4) after controlling
for compliance with NRT patch use (HR = 0.6, 95% CI = 0.1–2.5) or percent nonstudy CPD (HR = 2.8, 95% CI = 0.3–27.9).

With regard to QAs throughout the reduction period and follow-up, 44% of VLNC and 44% of CPD participants reported any QA. Similarly, 36% of the VLNC group and 22% of the CPD reported a ≥24-h QA. Differences between conditions were not statistically significant before or after controlling for NRT patch use.

Abstinence

No VLNC participants and one CPD participant (3%) was 7-day point-prevalence abstinent at the end of the reduction period. At the 1-month follow-up, 17% of VLNC participants and 13% of CPD participants reported 7-day PPA. Similarly 14% of VLNC and 13% of CPD reported 30-day prolonged abstinence. Differences between conditions in the above analyses were not significant before or after controlling for NRT patch use.

Self-efficacy and Intention to Quit

For self-efficacy, there were no main effects for condition or time. The condition by time interaction was significant and remained significant after controlling for NRT patch use but not when controlling for percent nonstudy CPD (Table 2). Self-efficacy increased over time in the VLNC (F = 5.3, p < .01) but not in the CPD condition (Figure 2).

For intention to quit, there was no main effect for condition but there was a main effect for time: intention to quit increased during the reduction period. The condition by time interaction was not significant before or after controlling for NRT patch use or percent nonstudy CPD (Table 2).

Discussion

This secondary analysis compared transitioning to VLNC cigarettes versus reducing CPD as methods to prompt QAs among participants who were not ready to quit. In comparison to using VLNC cigarettes,
reducing number of CPD resulted in more participants making a QA and a shorter time to first QA lasting any length. However, the two groups did not differ in the incidence of longer quit attempts or abstinence. Transitioning to VLNC cigarettes did but reducing CPD did not increase self-efficacy to quit.

One explanation for the CPD condition’s influence on QAs is that reduction in CPD promotes skills useful for quitting. For example, reducing CPD requires not smoking in the presence of cues that otherwise would have prompted smoking. This promotes learning skills to avoid or resist smoking. In contrast, although transitioning to VLNC cigarettes decreases the magnitude of nicotine reward associated with each cigarette, it does not promote learning from restricting smoking behavior. Another explanation is that simply having fewer study cigarettes in the CPD condition could have prompted smokers to try to quit after they ran out of their supply of cigarettes.

The most likely mechanism for the effects of using VLNC cigarettes on QAs is that repeated smoking in the presence of less and less nicotine disrupts prior smoking/nicotine conditioning. Thus, one possible explanation for the less robust effect of using VLNC cigarettes on QAs is that most of the benefit from transitioning to VLNC cigarettes should come from repeatedly using the lowest nicotine content cigarettes. Our VLNC participants only smoked the lowest dose cigarettes for 1 week. Thus, it is possible that VLNC cigarettes could promote QAs more successfully if participants smoked the lowest level VLNC cigarette for a longer period of time.

Our finding that self-efficacy increased for the VLNC but not CPD condition could be because VLNC participants were more successful in achieving their assigned goals than CPD participants. For example, by the end of the reduction period, VLNC participants were 78.6% compliant, whereas CPD participants were only 27.7% compliant with the study’s ambitious reduction goals. This interpretation is supported by our finding that, when controlling for participants’ noncompliance with study cigarettes (ie, failure to achieve reduction goals), differences between conditions’ self-efficacy to quit were no longer significant.

Prior research on the effects of self-efficacy on making a QA is mixed. One prior study of CPD reduction found that increases in self-efficacy mediated the influence of reduction on making a QA but another did not. It is not clear why, in this trial, switching to VLNC cigarettes increased self-efficacy but not QAs and the opposite was true for reducing CPD. Future research with a larger sample size is needed to adequately test mediators of the influence of VLNC cigarettes versus reducing CPD on QAs.

Limitations and Considerations
Many believe that QAs lasting 24 h or more are more clinically meaningful than short QAs. The fact that our findings were not replicated among ≥24-h QAs may limit the clinical relevance of these findings. We provided NRT to help participants transition to cigarettes with minimal nicotine or make large reductions in CPD and, thus, allow a more sensitive test of VLNC versus CPD strategies. Though

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**Table 2.** *F* values for self-efficacy and intention to quit

|                  | VLNC vs. CPD | Week | Condition × week (adjusted for NRT patch use) | Condition × week (adjusted for % nonstudy CPD) |
|------------------|--------------|------|-----------------------------------------------|-----------------------------------------------|
| Self-efficacy to quit | 1.0          | 1.6  | 3.7**                                        | 4.0**                                        |
| Intention to quit     | 3.2†         | 12.3*** | 1.3                                      | 2.3†                                          |

†*p < 0.1; *p < 0.05; **p < 0.01; ***p < 0.001; CPD = condition that reduced cigarettes per day (*n* = 32); NRT = nicotine replacement therapy patch; VLNC = condition that switched to very low nicotine content cigarettes (*n* = 36).

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**Figure 2.** Intention to quit and self-efficacy to quit. **p < .01 for post hoc between-condition *t*-test at week 4; CPD = condition that reduced cigarettes per day (*n* = 32); nic = nicotine; VLNC = condition that smoked low nicotine cigarettes (*n* = 36). The presented values are estimated marginal means from the multilevel model.
this may have decreased the generalizability of our findings, if mandated to use VLNC cigarettes, many smokers will likely seek alternative nicotine sources such as NRT.17 Given the increasing prevalence of e-cigarettes,19 smokers will also likely supplement nicotine with e-cigarettes1 and, thus, future research is needed to test reduction with the aid of e-cigarettes. All study cigarettes were mentholated because nonmentholated cigarettes in the doses we wished to test were not available. The use of only mentholated cigarettes limits the generalizability of our findings. However, participants’ current versus past menthol status did not moderate any outcome. Currently, there are no validated methods to biochemically verify compliance with using only VLNC cigarettes when participants are also using NRT.21 We attempted to increase the validity of self-report by informing participants that payment and participation would be unaffected by noncompliance and employing a bogus pipeline technique.21 We instructed participants to make large reductions over a short period of time: it is possible our results might differ if reduction goals were smaller or the duration of reduction was longer. The participants in this exploratory trial were mostly white, heavy smokers who smoked cigarettes daily. Results could differ among a more diverse sample, nondaily smokers, or people who use multiple tobacco products. Finally, the VLNC condition in our study is based on a policy that would result in a gradual transition to VLNC cigarettes. However, it is possible that policy will result in an abrupt switch to VLNC cigarettes.

Conclusions

We compared a proposed strategy (VLNC) versus a common strategy (CPD) with similar goals in nicotine reduction among smokers not ready to quit. Our main finding from this secondary analysis is that reducing CPD resulted in more total QAs but not ≥24-h QAs during the reduction period than transitioning to VLNC cigarettes. However, given the differing results across outcomes, replication tests of our findings are needed. Future research is needed to test (1) different reduction schedules, (2) mediators of the influence of VLNC cigarettes versus reduction in CPD on QAs, and (3) combining using VLNC cigarettes with reducing CPD as a strategy to decrease smoking among those not ready to quit.

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Declaration of Interests

EMK and PWC have nothing to disclose. JRH has received consulting and speaking fees from several companies that develop or market pharmacological and behavioral treatments for smoking cessation or harm reduction and from several nonprofit organizations that promote tobacco control. He also consults for Altria, Philip Morris, and Swedish Match on their harm-reduction products.

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References

1. US Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014:17.

2. Jamal A, Homa DM, O’Connor E, et al. Current cigarette smoking among adults—United States, 2005–2014. MMWR Morb Mortal Wkly Rep. 2015;64(44):1233–1240.

3. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults—United States, 2000–2015. MMWR Morb Mortal Wkly Rep. 2017;65(52):1457–1464.

4. Reid JL, Hammond D, Rynard VL, Madill CL, Burkhalter R. Tobacco Use in Canada: Patterns and Trends. Waterloo, ON: Propel Centre for Population Health Impact, University of Waterloo; 2017.

5. Farkas AJ, Pierce JP, Zhu SH, et al. Addiction versus stages of change models in predicting smoking cessation. Addiction. 1996;91(9):1271–1280; discussion 1281.

6. Hughes JR, Solomon LJ, Naud S, Fingar JR, Helzer JE, Callas PW. Natural history of attempts to stop smoking. Nicotine Tob Res. 2014;16(9):1190–1198.

7. West R, Brown J. Smoking and Smoking Cessation in England 2011: Findings from the Smoking Toolkit Study. London; 2011. http://www.smokingengland.info.

8. Beard E, Fidler J, West R. Is use of nicotine replacement therapy while continuing to smoke associated with increased nicotine intake? Evidence from a population sample. Psychopharmacology (Berl). 2011;218(3):609–610.

9. Klemperer EM, Hughes JR, Naud S. Reduction in cigarettes per day prospectively predicts making a quit attempt: a fine-grained secondary analysis of a natural history study. Nicotine Tob Res. 2019;21(5):648–654.

10. Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. J Consult Clin Psychol. 2004;72(3):371–381.

11. U.S. Food and Drug Administration. Tobacco product standard for nicotine of combusted cigarettes. Fed Regist. 2018;83(52):11818–11843. https://www.federalregister.gov/documents/2018/03/16/2018-05345/tobacco-product-standard-for-nicotine-level-of-combusted-cigarettes.

12. Donny EC, Denlinger RL, Tider JW, et al. Randomized trial of reduced-nicotine standards for cigarettes. N Engl J Med. 2015;373(14):1340–1349.

13. Klemperer EM, Hughes JR, Callas PW, Benner JA, Morley NE. Effectiveness of switching to very low nicotine content cigarettes plus nicotine patch versus reducing daily cigarette consumption plus nicotine patch to decrease dependence: an exploratory randomized trial. Addiction. 2019;114(9):1639–1650.

14. Richter P, Steven PR, Bravo R, et al. Characterization of SPECTRUM variable nicotine research cigarettes. Tob Regul Sci. 2016;2(2):94–103.

15. Hughes JR, Carpenter MJ. The feasibility of smoking reduction: an update. Addiction. 2005;100(8):1074–1089.

16. Hartsukami DK, Donny EC. The debate about nicotine addiction and the role of medicinal products: commentary on Zeller. Nicotine Tob Res. 2018;21(3):338–339.

17. Hartsukami DK, Luo X, Dick L, et al. Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. Addiction. 2017;112(1):156–167.

18. Velicer WF, Diclemente CC, Rossi JS, Prochaska JO. Relapse situations and self-efficacy: an integrative model. Addict Behav. 1990;15(3):271–283.

19. Hughes JR, Keely JP, Fagerstrom KO, Callas PW. Intentions to quit smoking change over short periods of time. Addict Behav. 2005;30(4):653–662.

20. Klemperer EM, Hughes JR, Callas PW, Solomon LJ. A mediation analysis of motivational, reduction, and usual care interventions for smokers who are not ready to quit. Nicotine Tob Res. 2017;19(8):916–921.

21. Aguinis H, Pierce CA, Quigley BM. Conditions under which a bogus pipeline procedure enhances the validity of self-reported cigarette smoking: a meta-analytic review. J Appl Soc Psychol. 1993;23(5):352–373.
22. Field A. Discovering Statistics Using IBM SPSS Statistics. London: Sage; 2013.
23. Fagerstrom KO. Determinants of tobacco use and renaming the FTND to the Fagerstrom test for cigarette dependence. Nicotine Tob Res. 2012;14(1):75–78.
24. Donny EC, Jones M. Prolonged exposure to denicotinized cigarettes with or without transdermal nicotine. Drug Alcohol Depend. 2009;104(1–2):23–33.
25. Donny EC, Houtsmuller E, Stitzer ML. Smoking in the absence of nicotine: Behavioral, subjective and physiological effects over 11 days. Addiction. 2007;102(2):324–334.
26. Hatsukami DK, Kotlyar M, Hertsgaard LA, et al. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. Addiction. 2010;105(2):343–355.
27. Dermody SS, Donny EC, Hertsgaard LA, Hatsukami DK. Greater reductions in nicotine exposure while smoking very low nicotine content cigarettes predict smoking cessation. Tob Control. 2015;24(6):536–539.
28. Vangeli E, Stapleton J, Smit ES, Borland R, West R. Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. Addiction. 2011;106(12):2110–2121.
29. Beard E, Aveyard P, McNeill A, et al. Mediation analysis of the association between use of NRT for smoking reduction and attempts to stop smoking. Psychol Health. 2012;27(9):1118–1133.
30. Starr G, Rogers T, Schooley M, Porter S, Wiesen E, Jamison N. Key Outcome Indicators for Evaluating Comprehensive Tobacco Control Programs. Atlanta, GA: Centers for Disease Control and Prevention; 2005.
31. Bao W, Xu G, Lu J, Snetselaar LG, Wallace RB. Changes in electronic cigarette use among adults in the United States, 2014-2016. JAMA. 2018;319(19):2039–2041.
32. Benowitz N. Biochemical verification for compliance with very low nicotine content cigarettes. Personal communication. 2015.