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Behavioral and Subjective Effects of Reducing Nicotine in Cigarettes: A Cessation Commentary

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Abstract

This commentary addresses critical questions regarding the impact of the reduction of nicotine on changes in smoking behavior. There appears to be moderate evidence that use of reduced nicotine cigarettes (RNC) increases the likelihood of making a quit attempt among smokers unmotivated to quit and among smokers motivated to quit who also used nicotine replacement therapy (NRT). There was limited evidence that RNC combined with NRT increased smoking abstinence, regardless of motivation to quit. Several plausible mechanisms via which RNC may influence smoking behavior, including reducing dependence, are reviewed. The moderate evidence that abrupt reduction in nicotine reduces self-reported dependence as well as smoking behavior and likelihood of relapse is also reviewed. The data reviewed here suggest that abrupt switching to, and extended use of, RNC can reduce cigarette dependence and several related constructs, including the ability to quit smoking. The data reviewed in this commentary suggest that abrupt reduction in the level of nicotine in combustible cigarettes could reduce smoking behavior, nicotine dependence, and other related constructs and increase quit attempts and eventual smoking cessation.

Does decreasing the nicotine in cigarettes, so that their addictive potential is significantly reduced, help users quit smoking? Using data published before March 2019, we addressed three questions.

1. What data demonstrate changes in quit attempts/success following nicotine reduction?

Ten clinical trials have investigated the impact of reduced nicotine cigarettes (RNC) on quit attempts and smoking abstinence; eight efficacy trials in research settings in the United States or United Kingdom,[1–8] and two effectiveness trials in New Zealand.[9,10]

There is moderate evidence that use of RNC increases the likelihood of making a quit attempt among smokers unmotivated to quit. Two trials investigated whether use of RNC increased the likelihood of making a quit attempt.[7,10] The first trial (N = 33) compared 12 weeks of RNC (0.05 mg nicotine yield) to usual brand.[10] Intervention group participants were more likely to make a quit attempt during the 12-week study period, compared with the control group. There were no group differences in change in motivation to quit. The second trial (N = 840) randomly assigned participants to smoke one of six types of research cigarettes (from 0.76 to 0.03 mg nicotine yield) or their usual brand for 6 weeks.[7] Participants allocated to the lowest nicotine content cigarettes were significantly more likely to have made a quit attempt within 30 days of completing the study, compared with those allocated to the highest nicotine yield cigarettes.

There is moderate evidence that RNC, used in conjunction with nicotine replacement therapy (NRT), increase smoking abstinence in people motivated to quit. Two clinical trials (N = 346 and 1410) have investigated the impact of RNC on smoking abstinence in people motivated to quit.[1,3,9] These trials found a 6-week intervention of progressively RNC (from 0.59 to <0.05 mg nicotine yield) or, when used in combination with NRT and behavioral support, significantly increased short-term quit rates, compared with NRT plus behavioral support,[9] or usual cigarettes.[3] However, only the larger

trial found very low nicotine content (VLNC) cigarettes, when used in combination with NRT and behavioral support, significantly increased medium and long-term quit rates, as well as relapse latency, compared with NRT and behavioral support alone.[9] These results were consistent across a variety of subgroups (eg, sex, age, ethnicity, nicotine dependence).

There is limited evidence that RNC, used in conjunction with NRT, increase smoking abstinence in people unmotivated to quit. Two clinical trials have investigated the impact of RNC on smoking abstinence in people unmotivated to quit.[5,10] The first trial (N = 33) compared 12 weeks of VLNC cigarettes (<0.05 mg nicotine yield) to usual brand.[10] Self-reported continuous abstinence from smoking usual cigarettes at 12 weeks was reported in two participants in the intervention group, compared with one in the control group. The second trial (N = 135) randomized participants to smoke progressively RNC (0.9 to 0.1 mg nicotine yield) for a month or their usual brand.[5] Two people in the reduced nicotine group had quit smoking after 6 months compared with one in the usual brand group.

There is limited evidence that RNC combined with NRT increase smoking abstinence in people (irrespective of motivation to quit). Three trials (N = 98–235) investigated the impact of RNC on smoking abstinence, irrespective of motivation to quit.[3,4,6] Only one trial (N = 165) reported a statistically significant difference in 4-week biochemically verified continuous abstinence rates (weeks 9–12) among the three randomized groups after 6 weeks use of Quest 2 cigarettes (0.30 mg nicotine yield), Quest 3 cigarettes (<0.05 mg nicotine yield) and nicotine lozenges (21%, 43%, and 35%, respectively).[4]

2. How does reducing nicotine exposure increase the chance of cessation?

There are several plausible mechanisms whereby reducing nicotine levels in cigarettes may increase the chance of smoking cessation, with generally larger effects expected among smokers who are motivated to quit and engaged in a cessation attempt. First, use of RNC is associated with decreased levels of dependence and related indices, including abstinence-induced withdrawal symptoms, craving, and smoking amount,[7] all valid predictors of smoking cessation. Second, from a neurobiological perspective, reducing nicotine exposure should downregulate the nicotinic acetylcholine receptors in key brain regions associated with reward, withdrawal, and tolerance. As upregulation of these receptors as a consequence of chronic nicotine exposure is associated with dependence,[11] the decrease in receptor density expected from reduced nicotine exposure should improve the chance of cessation. Third, from a learning-based perspective, smoking RNC may dissociate smoking/nicotine reward from external and internal cues previously paired with smoking.[12] These cues will gradually lose incentive salience through the process of extinction, weakening their tendency to elicit strong urges/cravings, thereby making smoking abstinence more likely. Fourth, several non-nicotine biochemical components of tobacco (eg, minor tobacco alkaloids, monoamine oxidase inhibitors) appear to interact with nicotine to enhance reinforcing effects from smoking.[13,14] Substantial reduction of nicotine levels within cigarettes should reduce these aspects of smoking reinforcement, which could support successful cessation. Finally, smokers may show increased self-efficacy for quitting, and subsequent success,[15] following a period of smoking VLNC cigarettes by achieving a sense of mastery or as a downstream effect of reduced dependence, withdrawal, and craving.

3. Do other changes support assumptions about cessation following nicotine reduction?

We examined studies of smokers motivated and unmotivated to quit to understand how use of RNC influenced both self-reported measures of dependence as well as key dependence criteria, such as cigarettes smoked per day, nicotine exposure, withdrawal symptoms, and likelihood of relapse.

There is moderate evidence that use of RNC for 6 weeks, but not a gradual reduction of nicotine level, reduces self-reported dependence. In a 6-week trial (N = 165),[4] those randomized to RNC (0.05 mg nicotine yield) showed significant reductions in the Fagerström Test for Cigarette Dependence (FTCD) score at 6 weeks, and had lower FTCD scores than participants using cigarettes with 0.3 mg nicotine yield. Another trial (N = 840) found that after 6 weeks, participants who were randomized to smoke lower nicotine cigarettes reported lower dependence than those smoking higher nicotine cigarettes.[7] Finally, a study (N = 1250)[16] found that after 20 weeks of switching, participants in the abrupt reduction to 0.4 mg of nicotine/gram cigarettes group had lower FTCD and Wisconsin Inventory of Smoking Dependence Motives (WISDM)[17] scores than smokers who gradually reduced or those in the control group. However, a study of smokers motivated to quit showed no significant decrease in FTCD scores during the 2 weeks of RNC use before their quit day.[1] It is possible that 2 weeks was not a sufficient duration of use to reduce dependence. Further, there was no reduction in FTCD score when smokers smoked progressively lower nicotine cigarettes over time.[5,18]

There is moderate evidence that use of RNC, but not a gradual reduction of nicotine level, reduces cigarettes smoked per day, nicotine exposure, withdrawal symptoms, and likelihood of relapse.[12] Two studies have shown that 6 weeks of RNC use resulted in fewer cigarettes smoked per day and lower biomarkers of nicotine exposure.[4,7] Participants smoking very low nicotine cigarettes also had significantly reduced craving and withdrawal symptoms[7,19] or an increase in withdrawal symptoms other than craving[4] following abstinence, compared with those smoking usual cigarettes. These effects appear to be specific to abrupt versus gradual reduction in nicotine.[3,5,16] However, gradual reduction has been associated with a significant reduction in cotinine, a nicotine metabolite and measure of nicotine exposure.[5,18]

Among smokers motivated to quit, two trials[4,6] found that smoking very low nicotine cigarettes for six weeks reduced overall biomarkers of nicotine exposure, which, in turn, predicted abstinence 6 weeks after a quit attempt.[20] Another study found that smoking RNC for 2 weeks prequit decreased cotinine levels and reduced craving compared with smoking usual brand.[1] However, participants only reduced the number of cigarettes smoked when participants received nicotine patches; there was no increase in 4-week abstinence rates.

Taken together, these findings suggest that when smokers abruptly switch to VLNC cigarettes for an extended period (ie, 6 weeks), this results in reductions in validated dependence measures, cigarettes smoked, biomarkers of nicotine exposure, and withdrawal symptoms. In other words, when nicotine levels in cigarettes are abruptly decreased, there is a behavioral response among smokers that reduces their cigarette dependence. Gradual nicotine reduction or reduction for a shorter duration (eg, 2 weeks) does not appear to reduce the cigarettes smoked per day or consistently improve subsequent abstinence rates, but it does reduce total nicotine exposure.

Summary

There is credible evidence that RNC increase quit attempts and, when used in conjunction with NRT, increase quit rates (and delay relapse back to smoking) among smokers motivated to quit. There are several plausible mechanisms whereby reducing the level of nicotine in cigarettes may increase the likelihood of smoking cessation. Importantly, there is direct evidence that abruptly switching to RNC is associated with reduced dependence and dependence-related criteria (eg, withdrawal, craving), and ultimately smoking abstinence. In sum, the data reviewed here suggest that abrupt switching to, and extended use of, RNC can reduce cigarette dependence and several related constructs, including the ability to quit smoking.

Declaration of Interests

None declared.

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