

Brief Review

Reduced-nicotine content cigarettes: Is there potential to aid smoking cessation?

Natalie Walker, Chris Bullen, & Hayden McRobbie

Abstract

Introduction: Current smoking cessation treatments largely address pharmacological dependence on nicotine. New approaches are needed that address both nicotine dependence and psychological dependence on cigarettes as the source of nicotine. One such approach is the use of cigarettes with reduced nicotine content.

Methods: We reviewed the available literature on the use of reduced-nicotine content cigarettes as a cessation aid.

Results: One case series study and trial data indicate that reduction in the level of nicotine in cigarette tobacco can reduce the level of nicotine dependence in smokers and do so without adverse effects on cardiovascular biomarkers or significant compensatory smoking. We identified three clinical trials (total $n = 489$) that suggest that smokers can dissociate nicotine delivery from the act of smoking if they use reduced-nicotine content cigarettes in combination with nicotine replacement therapy.

Discussion: The identified studies point to a benefit but involved only a small number of participants and provide only limited data on long-term abstinence. More definitive evidence from larger trials with longer follow-up is needed to clarify the role of reduced nicotine cigarettes as an aid to smoking cessation.

Introduction

Most current smoking cessation strategies involve an abrupt end to smoking followed by the use of pharmacotherapy such as nicotine replacement therapy (NRT) or varenicline to mitigate tobacco withdrawal symptoms. These pharmacotherapies target the problem of biochemical nicotine dependence. However, they fail to address the non-nicotine components of tobacco smoking (Rose, 2006) such as motor and sensory stimuli (e.g.,

the tactile action of puffing on a cigarette, the sensation of smoke in the mouth and throat) and the presence of other psychoactive substances in tobacco smoke beside nicotine (such as acetaldehyde; Belluzzi, Wang, & Leslie, 2005; or monoamine oxidase inhibitors). Such substances may strengthen dependence through mechanisms such as potentiation of nicotine's rewarding effects on the mesolimbic dopaminergic pathway (Anthenelli, 2005).

Cessation strategies that address both aspects of dependence—nicotine and non-nicotine—could potentially enhance quitting success. For example, cigarettes with reduced nicotine content (defined as the amount of nicotine in unburnt tobacco) could theoretically be helpful in the lead up to stopping smoking, by extinguishing the association between the act of smoking cigarettes and receipt of nicotine. Alternatively or in addition to this pathway, such cigarettes might work by making it easier for smokers to cope with nicotine withdrawal by continuing to provide exposure to the non-nicotine addictive components of tobacco smoke and smoking behavior.

Fifteen years ago, Benowitz and Henningfield (1994) hypothesized that progressive reduction in nicotine in cigarettes may reduce nicotine dependence in established smokers. In a recent study testing this hypothesis, Benowitz, Jacob, and Herrera (2006) undertook a semi-blinded cross-over study involving 12 smokers of 10 or more cigarettes/day and asked them on six occasions to smoke 5 cigarettes with progressively decreasing nicotine content (from 10.1 to 0.6 mg per cigarette) and decreasing nicotine yield (the industry's machine-derived measure of nicotine produced by the combustion of a cigarette—from 0.89 to 0.13 mg per cigarette). However, the cigarettes still had a moderate tar yield (the machine-based measure of tar released from the combustion of a cigarette—between 9.6 and 11.5 mg per cigarette). Measures of dependence decreased with decreasing nicotine content and yield, and there was little evidence of compensatory smoking (smoking in such a way as to maintain a desired level of nicotine throughout the day generally achieved by increasing puff frequency and intensity; Russell, 1987) even

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Reduced-nicotine content cigarettes

when the cigarettes with the very lowest nicotine content were smoked.

Reduced nicotine cigarettes (RNCs) use tobacco altered by genetic modification technology or selective breeding and are commercially available as the Quest brand, cigarettes marketed by Vector Tobacco Inc. in the United States. Quest 1, 2, and 3 cigarettes have average nicotine contents of 8.9, 5.1, and 1.0 mg per cigarette, respectively, and nicotine yields of 0.6, 0.3, and ≤ 0.05 mg per cigarette, respectively. However, the level of tar is the same in all three strengths (10 mg per cigarette, similar to the level in regular cigarettes), so one would not expect a large degree of compensatory smoking to occur as a person changed from Quest 1 to 2 and 3 cigarettes. However, one small ($n = 50$) randomized trial suggested that compensatory smoking does in fact occur in subjects asked to smoke only one cigarette at each level (with puff volume greatest in those smoking Quest 3; Strasser, Lerman, Sanborn, Pickworth, & Feldman, 2007). A larger trial involving longer term use of Quest found compensatory smoking occurred only “in the early stages of weaning using Quest 1 and Quest 2 cigarettes” (Becker, Rose, & Albino, 2008). The authors of this research concluded that smokers may attempt to compensate for the reduced nicotine content when a certain threshold of nicotine content is crossed but that, when the nicotine content is sufficiently low, compensatory smoking does not occur.

The development of low-nicotine yield cigarettes has been of interest to tobacco companies since the early 1970s, but for marketing rather than health reasons (Dunsby & Bero, 2004). Many brands of low-nicotine yield cigarettes are currently marketed around the world, using descriptors such as “light” and “mild” and claiming to be less addictive than standard cigarettes. However, these products are designed with extra ventilation holes in and above the filter to deliver diluted smoke (and thus less tar) compared with regular cigarettes when smoked by (or as would) a machine (Kozlowski et al., 2006). Furthermore, these cigarettes often contain reconstituted or expanded tobacco and are wrapped in more porous paper, leading to a faster burn rate. By blocking the ventilation holes or altering the puff rate and/or intensity, smokers can readily increase the nicotine intake per cigarette and receive far higher doses of nicotine than the reported machine-derived yields would indicate (Benowitz, 2001; Hammond, Fong, Cummings, & Hyland, 2005; Norton et al., 2008). In contrast, nicotine content is unable to be altered by cigarette design features or manipulated by smoker behavior. Nicotine content may therefore provide a more accurate reflection of true nicotine exposure than nicotine yield.

RNCs deliver a low dose of nicotine in undiluted smoke with the same amounts of tar as in standard cigarettes. This characteristic of RNCs confers an advantage because compensatory smoking may occur if both nicotine and tar are lowered, as in low-nicotine yield cigarettes (Benowitz et al., 2007; Dixon, Kochhar, Prasad, Shepperd, & Warburton, 2003; Hasenfratz, Baldinger, & Battig, 1993; Robinson, Pritchard, & Davis, 1992; Rose & Behm, 2004; Scherer, 1999).

Given the need for new approaches to cessation, the theoretical reasons why RNCs may have potential as a cessation aid, and recent renewed interest in tobacco content regulation, we undertook a literature review to identify studies that investigated the effect of RNCs on quit rates.

Methods

We searched three electronic databases: Medline (1970–December 2008), Embase (1980–December 2008), and the Cochrane Central Register of Controlled Trials (2008); reference lists of all identified papers and tobacco-related conference proceedings were searched for relevant studies using the search terms “reduced nicotine cigarettes,” “nicotine-free cigarettes,” and “denicotinized cigarettes.” Only studies that reported quit rates and involved cigarettes that were low in nicotine content were selected for this review. Both unpublished and published studies were sought, with no restriction on language of publication. Authors were contacted where necessary to clarify understanding of the study design and data.

Results

Five relevant studies were identified: a case series (Benowitz et al., 2007) and four randomized controlled trials (Becker et al., 2008; Hatsukami, 2008; Rezaishiraz, Hyland, Mahoney, O’Connor, & Cummings, 2007; Rose, Behm, Westman, & Kukovich, 2006).

In their case series, Benowitz et al. (2007) asked 20 smokers to smoke cigarettes *ad libitum* with progressively lower nicotine yield (from 0.8 mg down to 0.1 mg) and content (from 10.1 mg down to 0.6 mg) over a 5-week period, with participants followed up to 10 weeks. Markers of exposure to carbon monoxide, cardiovascular biomarkers, cigarette consumption, and polycyclic aromatic hydrocarbons (PAH) remained stable over time. However, excretion of urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) decreased by about 20% over time. NNAL is a known carcinogen and metabolite of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, a carcinogenic tobacco-specific nitrosamine. Although this study did not aim to study cessation rates, 5 (25%) participants had stopped smoking (biochemically validated) 4 weeks after the end of the reduction period, despite not intending to do so at study entry. The tar yield of the cigarettes remained at a moderate level over the study period (7.8–10.9 mg per cigarette), and no compensatory smoking was detected, as measures of tobacco smoke biomarkers (carbon monoxide and PAH metabolites) and cigarette consumption were stable. Although the study had a number of limitations (small sample size, no control group, and only short-term cessation rates), the findings point to the possibility that gradual reduction in nicotine in cigarettes could increase cessation rates and suggest that nicotine content can be progressively decreased without compensation.

In an unpublished trial (<http://www.clinicaltrials.gov>, website # NCT 00777569) involving 167 participants, Hatsukami (2008) compared the quitting efficacy of Quest 2 cigarettes, Quest 3 cigarettes, and 4-mg nicotine lozenges. Over a 6-week period, there was evidence of reduced NNAL exposure for all three groups, a greater reduction in carbon monoxide exposure in the Quest 3 cigarettes compared with Quest 2 cigarettes, and reduced nicotine dependence in the lozenge and Quest 3 groups (but no change in the Quest 2 group). A significant difference was found in 4 weeks continuous abstinence rates among the different products for Weeks 9–12 (21% in Quest 2, 43% in Quest 3, and 28% in the lozenge group, $p = .04$). This result

needs to be interpreted with caution, however, given the modest sample size. It is also unknown whether the quit rates were validated.

Three small clinical trials suggest that in combination with NRT, RNCs may help smokers to dissociate nicotine delivery from smoking and thus increase their chances of quitting (Table 1). One study reported validated continuous abstinence rates at 4 weeks of 50% in 18 heavy smokers (≥ 20 cigarettes/day) using noncommercially available denicotinized cigarettes donated by Philip Morris (which had a tar content of 9 mg and nicotine yield of 0.08 mg per cigarette) when required, plus a 21-mg NRT patch for 2 weeks prior to quitting compared with 23% in those using denicotinized cigarettes and a placebo NRT patch ($n = 17$; Rose et al., 2006). However, the authors of the study acknowledge that the study had a small number of smokers in each intervention group ($n = 14$ – 18) and a large number of treatment groups (thus more chance of a Type I error); and because mecamylamine was used as a precessation treatment, the study's generalizability is limited.

In the second trial involving heavy smokers (≥ 20 cigarettes/day), 2 weeks of using Quest 3 cigarettes (estimated to be no more than one pack per day, and no standard cigarettes) combined with a 21-mg nicotine patch prior to quitting resulted in less frequent and less intense cravings for cigarettes in the 2-week period before and after the designated quit date, in comparison with the group that received Quest 3 cigarettes alone for 2 weeks prior to quitting (Rezaishiraz et al., 2007). The reported quit rates did not differ significantly between the groups at 3 and 6 months. The study was small ($n = 98$), a third of participants were lost to follow-up, it was unblinded, and biochemical validation of self-reported quit rates was not undertaken.

A more recent blinded trial involving 346 dependent smokers (who smoked an average of ≥ 15 cigarettes/day) measured quit rates across three groups (Becker et al., 2008). One hundred and sixteen smokers in Group 1 were asked to smoke Quest 1 *ad libitum* for 2 weeks, then Quest 2 *ad libitum* for 2 weeks, then Quest 3 *ad libitum* (plus 21-mg nicotine patch) for 2 weeks, followed by use of decreasing strength NRT patches for 10 weeks (i.e., 21, 14, and 7 mg, placebo). A second group ($n = 116$) followed the same process but used a placebo NRT patch, while a third group ($n = 114$) smoked standard cigarettes in the first 6 weeks (with a placebo patch for the last 2 weeks), followed by use of decreasing strength NRT patches for 10 weeks (i.e., 21, 21, 14, and 7 mg). A significantly higher validated quit rate at 4 weeks was seen in smokers using Quest *ad libitum* plus 21-mg nicotine patch (33%) compared with standard cigarettes plus nicotine patch (22%, $p = .04$). Four-week validated quit rates were not found to differ between the group smoking Quest *ad libitum* plus placebo patch (16%) and the group assigned to standard cigarettes plus a nicotine patch (22%, $p = .89$). There was significant loss to follow-up (30%) in this trial which, when combined with the small sample size, may have resulted in the nonsignificant difference in abstinence rates (actual data not available) reported at 3 and 6 months.

Only two of the five studies provided data on adverse events. The largest trial reported three serious adverse events, of which none were considered to be treatment-related (Becker et al., 2008). The three other trials did not report on adverse events (Hatsukami, 2008; Rezaishiraz et al., 2007; Rose et al., 2006).

The case series study reported no evidence of an increased risk profile in terms of cardiovascular biomarkers over the 10-week study period (Benowitz et al., 2007).

Discussion

Our literature review suggests that progressive reduction in the level of nicotine in cigarette tobacco can reduce the level of nicotine dependence in smokers, with minimal compensatory smoking (when the lowest nicotine content cigarettes are smoked, i.e., Quest 3) and without adverse effects. Furthermore, it appears that if smokers use NRT in combination with RNCs, short-term quit rates are greater than if RNCs are used alone.

The lack of any adverse health effects associated with RNC use in the above trials contrasts with recent *in vivo* research, which postulated that RNCs may increase the risk of harm (Girdhar, Xu, Bluestein, & Jesty, 2008). This research consisted of two studies to investigate whether nicotine modulates platelet activation (with platelet activation state assessed using a standard marker, P-selectin)—one involving 32 smokers and one involving 32 nonsmokers. Subjects in the nonsmoking group were exposed (alternating groups) to secondhand smoke from either medium-nicotine cigarettes (Quest 1, 0.6 mg nicotine yield) or low/zero-nicotine cigarettes (Quest 3, ≤ 0.05 mg nicotine yield) over a 1.5-hr period on each of 2 successive days, with smoke at levels similar to that found in a smoky bar. Exposure to secondhand smoke increased platelet activation state in both groups by 60% ($p < .01$), but there was no significant difference between the groups ($p > .09$). After all subjects in the smoking group had smoked three medium-nicotine cigarettes (Quest 1) over an hour, 16 subjects were randomized to smoke five more of the same cigarettes over a 1- to 2.5-hr period, which led to a 33% increase in platelet activation state ($p < .01$). The other 16 subjects smoked five low/zero-nicotine cigarettes (Quest 3) over a 1- to 2.5-hr period, resulting in a 94% increase in platelet activation state ($p < .01$). The difference between the two groups was also significant ($p < .02$). Based on these findings, the authors concluded that “cigarette nicotine modulates platelet activation *in vivo* in smokers” and therefore may “moderate the risk of cardiovascular disease caused by non-nicotine smoke components,” and thus RNCs may be harmful. The authors of this research do acknowledge that these studies were small, compensation was not measured in the smokers on low/zero-nicotine cigarettes, and the study measured only platelet activation (as a marker for thrombogenesis and cardiovascular disease).

This review is limited by the possibility that some relevant trials may not have been identified. Furthermore, the studies that were identified involved selected groups of “normal” smokers, and the success of this nicotine reduction strategy may be influenced by individual differences in rates of nicotine metabolism, such as that seen in smokers with psychiatric comorbidities or pregnant women. Despite these issues, further investigation of RNCs as a cessation aid is warranted. Specifically, adequately powered clinical trials with at least 6-month follow-up are needed to clarify the true strength and direction of any association. A small trial ($n = 154$) involving progressive reduction in the nicotine content of cigarettes over 6 months,

Table 1. Summary of randomized trials of reduced nicotine cigarettes in combination with Nicotine Replacement Therapy (NRT) as an aid to smoking cessation

Authors	Design	Sample size	Intervention	Other intervention	Quit rates
Rose, Behm, Westman, & Kukovich (2006)	Randomized double blind to patch but not to cigarettes	35	Three types of cigarettes prequit: usual, low tar and nicotine ^a , or denicotinized for 2 weeks. Two types of patch prequit: 21 mg or placebo for 2 weeks. Three types of patch postquit: 0, 21, or 42 mg for 4 weeks, then 2 weeks of weaning. Two types of nicotinic antagonist mecamylamine postquit: 10 mg/day or placebo for 4 weeks. Quest 3 cigarettes plus 21 mg NRT patch versus Quest 3 cigarettes alone for 2 weeks prior to quitting.	All received brief counseling.	Continuous abstinence at 4 weeks ^b 50% in denicotinized cigarettes + 21 mg NRT patch 23% in denicotinized cigarettes + placebo patch.
Rezaishiraz, Hyland, Mahoney, O'Connor, & Cummings (2007)	Randomized, unblinded	98		All received for 8 weeks postquit NRT patch (4 weeks 21 mg, 2 weeks 14 mg, and 2 weeks 7 mg). All received a behavioral intervention (group sessions and individual counseling).	Self-reported quit rate at 3 months ^c 43% in treatment group 34% in control (not significant) Self-reported quit rate at 6 months ^c 28% in treatment group 21% in control (not significant)
Becker, Rose, & Albino (2008)	Randomized, double blind	346	Quest (1, 2, and 3) plus NRT patch versus Quest (1, 2, and 3) plus placebo patch versus active control (smoking normal cigarettes)	NRT patch of reducing strength used for 10 weeks postquit in Quest plus NRT and active control group. Quest alone group had 10 weeks of placebo patch postquit. All received a behavioral intervention (group sessions and individual counseling).	Continuous abstinence at 4 weeks ^b 33% in Quest + NRT patch group versus 22% in active control ($p = .04$). 16% in Quest + placebo patch group versus 22% in active control ($p = .89$). No statistically significant differences in abstinence rates at 3 or 6 months were noted (data not reported) ^d .

Notes: ^aTar yield = 1 mg per cigarette, nicotine yield = 0.2 mg per cigarette.

^bAbstinence defined as no smoking (not even a puff) from quit date, confirmed by biochemical validation (carbon monoxide testing).

^cPeople who smoked no cigarettes in the 7 days prior to assessment were considered to have quit. No biochemical validation.

^dSix month loss to follow-up = 30%.

followed by 6 months use of cigarettes with the lowest nicotine content is currently under way in the United States (<http://www.clinicaltrials.gov>, website # NCT00264342) with a planned completion date of June 2010. A large, pragmatic community-based trial (involving 1,410 participants) started recruitment in New Zealand in April 2009 and is investigating the use of RNCs (Quest 3) with concomitant NRT-based cessation products (patch, gum, and/or lozenge) on cessation rates at 6 months (www.anzctr.org.au, ACTRN12608000410358). Detailed information on smoking patterns related to the long-term use of the RNCs, smokers attitudes to the RNCs, and adverse event data will also be reported on in this trial. Cost-effectiveness analysis is also planned if the intervention is shown to be superior to standard treatment.

Data from these new trials are particularly relevant in light of the recent move to give the U.S. Food and Drug Administration authority to regulate tobacco products, in particular the enforcement of standards to make cigarettes less harmful, such as by reducing nicotine yields (Curtfman, Morrissey, & Drazen, 2008).

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Declaration of Interests

Drs. Bullen and Walker have no competing interests to declare. Dr. McRobbie has undertaken research and consultancy and received honoraria for speaking at meetings from the manufacturers of smoking cessation medications.

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Reduced-nicotine content cigarettes

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