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Short Communication

Cancer Epidemiology, Biomarkers & Prevention

Compensatory Smoking from Gradual and Immediate Reduction in Cigarette Nicotine Content

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Abstract

Reducing the addictiveness of cigarettes by reducing their nicotine content can potentially have a profound impact on public health. Two different approaches to nicotine reduction have been proposed: gradual and immediate. To determine if either of these approaches results in significant compensatory smoking behavior, which might lead to safety concerns, we performed a secondary analysis of data from studies that have utilized these two approaches. The number of cigarettes smoked per day, carbon monoxide exposure, and cotinine levels in plasma or urine were assessed while participants smoked reduced nicotine content cigarettes and compared with when they smoked their usual brand cigarettes. The results showed that in general, these two approaches led to minimal compensatory smoking and reduced levels of cotinine over the course of the experimental period, suggesting that neither of these approaches poses a major safety concern. *Cancer Epidemiol Biomarkers Prev; 24(2); 472–6. ©2014 AACR.*

Introduction

The Family Smoking Prevention and Tobacco Control Act provides the FDA with the authority to regulate tobacco products. Under this act, the FDA can establish standards for constituents in tobacco products, including reducing nicotine in all cigarettes to nonaddictive levels (except to zero). Reducing nicotine content in cigarette tobacco would be unlike prior "light" and "ultralight" cigarettes that achieved reductions in nicotine yield in smoke (not nicotine content), as measured by smoking machines, through the use of ventilated filters and other engineering modifications. The actual nicotine content was in fact similar whether the cigarettes were regular, light, or ultralight, and smokers were easily able to change their smoking behavior to receive higher levels of nicotine. As a tobacco control strategy, reducing nicotine levels in cigarettes has one of the greatest potentials to profoundly impact public health (1). Nicotine reduction could prevent the development of dependence in new smokers and enable those who already smoke to quit, resulting in a dramatic decrease in the prevalence of smoking (2). Therefore, the reduction in harm associated with reducing nicotine in cigarettes is due to decreasing their addictiveness, not toxicity. To date, the scientific evidence supports the feasibility of such a national regulatory measure. Decades of research show that nicotine is the primary agent that is responsible for the addiction to tobacco (1, 3, 4). Recent studies find that when the nicotine content in cigarettes reaches 1 mg or below, reductions in cigarettes smoked per day and exposure to nicotine and some tobacco smoke toxicants (5–8) are observed. Furthermore, some studies show that among smokers motivated to quit, assignment to very low nicotine content (VLNC) cigarettes leads to abstinence rates comparable with medicinal nicotine products (6, 7) or greater when combined with medicinal nicotine (9).

Two different approaches for reducing nicotine content of cigarettes have been proposed and examined. These include either a gradual reduction to nonaddictive levels (5, 8, 10) or an immediate reduction to these levels (6, 7). In determining which approach would be the best for a national policy, one factor to consider is the comparative safety of each of these approaches. One indicator of safety is the extent to which compensatory smoking (increased intensity or rate of smoking) occurs. Compensatory smoking is an important safety issue because if a person smokes more cigarettes or smokes cigarettes more intensively in response to nicotine reduction, they could be exposed to higher levels of tobacco combustion-derived toxicants. To begin addressing this topic, we conducted a secondary analysis of studies that have used these two approaches to determine the extent to which either of these approaches leads to compensatory smoking.

Materials and Methods

This analysis was conducted on five different studies, two focused on gradual reduction in nicotine content of cigarettes (5, 8) and the other three on immediate reduction to VLNC cigarettes (<1 mg nicotine content or <0.1 mg FTC machine-determined nicotine yield; E.C. Donny; unpublished data; refs. 6, 7). The Donny study is based on a predetermined interim analysis of <50% of the targeted sample enrolled in a study examining the dose–response

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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effects of varying nicotine content cigarettes. This project was conducted under the Center for the Evaluation of Nicotine in Cigarettes (CENIC, NCT01681875) and involved 10 institutions and employed a similar design as the Hatsukami and colleagues study (6). Participants were randomized to one of seven different groups with varying levels of nicotine. For this analysis, we examined only those smokers assigned to the lowest dose.

In all studies, daily smokers who were currently stable medically and psychiatrically, not pregnant, and not regularly using other tobacco products were recruited. Assessments were made while smoking usual brand cigarettes (UBC), just before assignment of study cigarettes. All subjects were instructed to abstain from UBC while smoking the assigned study cigarettes. Two of the studies included a control group of UBC smoking (ref. 8; E.C. Donny; unpublished data).

For the gradual reduction studies, smokers not interested in quitting smoking in the next 6 months were asked to smoke progressively lower nicotine content experimental cigarettes (0.8–0.9, 0.6, 0.3–0.4, 0.2, and 0.1 mg FTC machine-determined nicotine yield). Nicotine reduction occurred weekly (5) or monthly (8). In the immediate reduction studies, smokers not interested in quitting (E.C. Donny; unpublished data) or motivated to quit (6, 7) smoked study cigarettes [<0.1 mg machine-determined nicotine yield: 0.05, ref. 6; 0.05–0.09, ref. 7; 0.03, E.C. Donny; unpublished data] over the course of six weeks. All study cigarettes were provided free to participants after randomization, including those participants assigned to the UBC control group.

The primary outcome focused on indices of compensatory smoking and included analysis of number of cigarettes smoked per day (CPD) and expired carbon monoxide (CO) over time across the various studies. In addition, cotinine concentration was measured in plasma in some studies (5, 8) and in urine in others (refs. 6, 7; E.C. Donny; unpublished data) and analyzed to determine the extent of reduction across nicotine doses and not primarily as a measure of compensatory smoking. All cotinine ratios were based on levels in the same biofluid for each subject. Cotinine was measured using chromatographic methods. Compensatory smoking was summarized for an individual by dividing their weekly/monthly value for CPD and CO while smoking reduced nicotine cigarettes (RNC) by the corresponding baseline value while smoking UBC. Within a study, we calculated the mean of these ratios for each time point over the experimental period. An overall summary for each of the strategies was created by calculating a weighted average along with 95% confidence interval (CI) across studies over time with weights inversely proportional to the SEM. We compared the weighted average to 1 at the final time point using a Wald test to test for a significant difference from baseline. This weighting scheme will weight studies based on the precision with which they estimate the mean, with more precise estimates of the mean receiving more weight (i.e., studies with a smaller standard error) and less precise estimates receiving less weight (11). In addition, the groups that continued to smoke UBC over the course of the study were analyzed (ref. 8; E.C. Donny; unpublished data). For these studies, a between-group comparison was completed by dividing the ratio for the RNC group by the ratio for the group smoking UBC over the course of the experimental period (Supplementary Table 1). Finally, to examine the possibility that compensation is occurring in a subset of smokers, we determined the percentages of smokers whose biomarker levels exceeded greater than 150% (50% above baseline; e.g., 15 to 22.5 CPD) and 200% (or 2-fold; e.g., 15 to 30 CPD) of baseline.

Results

Table 1 shows demographic and smoking history data across the various studies and conditions. In general, the Benowitz and colleagues' studies (5, 8) tended to have smokers who were slightly younger compared with the other studies, and the E.C. Donny (unpublished data) study had smokers who smoked fewer mean number of CPD and demonstrated lower expired CO (but no differences in dependence scores), and had a higher prevalence of African Americans.

Table 2 shows the weighted average ratios (experimental week over baseline) for CPD, CO, and cotinine across the two different approaches for nicotine reduction and for the UBC condition. In general, the extent of compensatory smoking for either the gradual or immediate nicotine reduction approach was minimal. The weighted averages indicated a similar, significant decrease in CPD compared with baseline for both the gradual and immediate reduction approaches ($P < 0.003$ and $P < 0.001$, respectively). On the other hand, the weighted average for the UBC condition was associated with a significant increase in CPD ($P < 0.001$). Our data were consistent with at least a 5% reduction in CPD in the gradual group (95% CI, 0.75–0.95) and at least an 11% reduction in the immediate group (95% CI, 0.78–0.89), compared with at least a 12% increase in the UBC group (95% CI, 1.12–1.26). A similar, but nonsignificant, decrease in CO compared with baseline was observed for both nicotine reduction approaches, which suggests a limited risk of compensatory smoking for both strategies. No significant increase in CO was also observed for the UBC

Table 1. Baseline and demographic information [mean (SD) or number (percent)] for each study

Variable[a]	Benowitz et al. (5) Gradual	Benowitz et al. (8) Gradual	Donny Immediate	Hatsukami et al. (6) Immediate	Hatsukami et al. (7) Immediate	Benowitz et al. (8) Usual brand	Donny Usual brand
N	20	53	101	53	79	50	49
Age	28.7 (8.79)	36.6 (10.97)	41.0 (12.94)	40.7 (13.26)	46.5 (12.25)	37.4 (11.67)	41.5 (12.47)
Sex: male	11 (55%)	25 (47.2%)	51 (50.5%)	30 (56.6%)	32 (40.5%)	31 (62.0%)	22 (44.9%)
Sex: female	9 (45.0%)	28 (52.8%)	50 (49.5%)	23 (43.4%)	47 (59.5%)	19 (38.0%)	27 (55.1%)
Race: white	14 (70.0%)	37 (69.8%)	54 (53.5%)	42 (79.2%)	68 (86.1%)	35 (70.0%)	27 (55.1%)
Race: black	0 (0.0%)	4 (7.5%)	36 (35.6%)	7 (13.2%)	3 (3.8%)	4 (8.0%)	20 (40.8%)
Race: other	6 (30.0%)	12 (22.6%)	11 (10.9%)	4 (7.5%)	8 (10.1%)	11 (22.0%)	2 (4.1%)
CPD[b]	18.9 (7.4)	23.2 (7.3)	15.6 (7.0)	19.8 (7.1)	19.4 (6.2)	20.2 (7.7)	15.2 (6.6)
Carbon monoxide	16.9 (8.1)	25.4 (10.0)	14.8 (7.9)	20.0 (11.4)	23.5 (9.3)	22.3 (10.8)	14.7 (8.6)
FTND[c]	4.2 (2.0)	5.3 (1.9)	5.4 (2.2)	5.1 (2.1)	5.6 (1.7)	5.3 (2.2)	5.1 (1.9)

[a]Minor variations of some of the variables compared with prior published studies may exist based on the source of the data.
[b]Cigarettes per day.
[c]Fagerstrom Test for Nicotine Dependence.

Table 2. Weighted average (95% CI) of ratio of RNC divided by baseline UBC values for CPD, CO, and cotinine, respectively, for studies associated with gradual[a] and immediate[b] reduction in nicotine and UBCs[c]

Study	Summary	Baseline	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6	*P* value[d]
CPD									
Weighted average (95% CI)	Gradual			1.06 (1.00–1.13)	1.09 (1.02–1.16)	1.05 (0.98–1.13)	0.94 (0.84–1.03)	0.85 (0.75–0.95)	0.003
Weighted average (95% CI)	Immediate		1.09 (1.05–1.13)	1.05 (1.01–1.10)	0.98 (0.93–1.04)	0.95 (0.89–1.00)	0.89 (0.83–0.94)	0.83 (0.78–0.89)	<0.001
Weighted average (95% CI)	Usual brand		1.08 (1.03–1.12)	1.15 (1.1–1.2)	1.13 (1.07–1.19)	1.16 (1.1–1.22)	1.17 (1.11–1.23)	1.19 (1.12–1.26)	<0.001
CO									
Weighted average (95% CI)	Gradual			1.08 (0.98–1.19)	1.04 (0.93–1.15)	1.01 (0.89–1.14)	0.91 (0.8–1.03)	0.97 (0.83–1.11)	0.687
Weighted average (95% CI)	Immediate		1.04 (0.97–1.11)	1.09 (1.01–1.17)	1.02 (0.93–1.10)	0.99 (0.90–1.07)	0.94 (0.86–1.02)	0.94 (0.85–1.02)	0.157
Weighted average (95% CI)	Usual brand		1.08 (0.99–1.18)	1.12 (1.01–1.22)	1.07 (0.96–1.19)	1.06 (0.94–1.17)	1.14 (1.03–1.24)	1.05 (0.94–1.16)	0.353
Cotinine									
Weighted average (95% CI)	Gradual			0.96 (0.86–1.06)	0.63 (0.56–0.70)	0.46 (0.39–0.53)	0.41 (0.33–0.49)	0.38 (0.29–0.47)	<0.001
Weighted average (95% CI)	Immediate			0.36 (0.29–0.43)				0.30 (0.23–0.37)	<0.001
Weighted average (95% CI)	Usual brand			1.07 (0.97–1.16)				0.95 (0.82–1.08)	0.445

[a]Benowitz et al. (5) weekly reduction schedule (with Time 1 serving as baseline) and Benowitz et al. (8) monthly reduction schedule (with Times 5 and 6 at the lowest dose); nicotine yields were 0.8–0.9, 0.6, 0.3–0.4, 0.2, and 0.1 mg FTC.
[b]Hatsukami et al. (6), Hatsukami et al. (7), E.C. Donny (unpublished data); study time points are weekly with nicotine yields <0.1 mg. Cotinine was only assessed at baseline, weeks 2, and 6.
[c]Benowitz et al. (8), E.C. Donny (unpublished data).
[d]Significance of mean ratio, assessed at the final time point as compared with 1.

condition. Although the reductions in CO for the RNC cigarette conditions were not significant, our data suggest that any increase in CO would be no more than 2% for the immediate group (95% CI, 0.85–1.02) and no more than 11% in the gradual group (95% CI, 0.83–1.11). Finally, the weighted averages for cotinine suggest a similar, significant ($P < 0.001$) decrease in cotinine compared with baseline for both RNC approaches, with no observed decrease in the UBC condition. A more detailed analysis for each individual study is described in the Supplementary Table 1.

Table 3 shows the percent of individuals whose biomarker levels exceeded 150% and 200% compared with baseline values for CPD and CO. The percentage varied considerably from study to study, but for the two studies that included usual brand controls, the percentage of subjects exceeding 150% or 200% baseline was no different for reduced nicotine versus usual brand smokers.

Discussion

The results from this *post hoc* data analysis suggest minimal if any compensatory smoking for both the gradual and immediate reduction approaches to reducing levels of nicotine content in cigarettes, particularly when compared with UBCs. For example, the percentage of smokers that increased their smoking above a specific threshold in the RNC conditions was similar to the UBC condition. This finding might indicate that smokers who have access to free cigarettes tend to smoke more CPD (regardless of their nicotine content), and our results may in fact reflect an overestimation of the extent of smoking that may occur with RNC if they cost as much as the price of conventional cigarettes.

Our analysis also suggests that there are minimal differences in compensatory smoking across the two approaches to nicotine reduction. Furthermore, the results showed that by the end of the experimental period, similar reductions in cotinine in both approaches were achieved. These substantial reductions in nicotine exposure in both approaches would have implications for the level of nicotine dependence. If these results are replicated and reducing nicotine in cigarettes is found to be a viable national policy approach, the decision for which approach will lead to the greatest public health benefit will rest on factors other than compensatory smoking. For example, on the one hand, gradual reduction would ease the smoker toward nonaddictive cigarettes, potentially leading to less discomfort over the course of time and be associated with greater consumer acceptance. On the other hand, this approach would take longer to achieve public health benefit. That is, a greater number of smokers may be more likely to quit sooner with the immediate reduction to nonaddictive nicotine levels in cigarettes compared with reducing nicotine content levels over time. The gradual reduction approach might also be more difficult to implement and lead to enhanced smoking in some smokers during the initial phases of transition because it is easier to engage in compensatory smoking with cigarettes that are minimally reduced in nicotine content (6, 12). The immediate reduction approach would lead to greater discomfort, but this discomfort may be alleviated with the use of medicinal nicotine (7, 13), other medicinal products, or alternative noncombusted tobacco products that are less toxic than cigarettes. It is also likely that even with an immediate reduction policy, smokers will continue to have access to conventional nicotine content cigarettes until all store supplies have been bought, potentially

Table 3. Percentage of subjects exceeding 150% and 200% CPD and CO

Study[a]	Summary	Time 1	Time 2	Time 3	Time 4	Time 5	Time 6
Percentage of subjects exceeding 200% (or 2-fold) of baseline CPD and CO							
CPD							
Benowitz et al. (5)	Gradual	Baseline	0.0	0.0	0.0	0.0	5.0
Benowitz et al. (8)	Gradual	0.0	1.9	0.0	0.0	0.0	0.0
Donny	Immediate	0.0	1.0	2.1	1.0	2.1	0.0
Hatsukami et al. (6)	Immediate	0.0	0.0	0.0	0.0	0.0	0.0
Hatsukami et al. (7)	Immediate	0.0	3.2	3.2	3.5	3.6	3.6
Benowitz et al. (8)	Usual brand	0.0	0.0	0.0	0.0	0.0	2.0
Donny	Usual brand	0.0	2.0	10.2	10.2	10.2	6.1
CO							
Benowitz et al. (5)	Gradual	Baseline	0.0	0.0	0.0	0.0	0.0
Benowitz et al. (8)	Gradual	1.9	5.7	8.0	5.9	3.9	7.5
Donny	Immediate	3.3	6.5	5.6	2.2	5.6	7.6
Hatsukami et al. (6)	Immediate	6.7	10.5	11.4	9.4	6.2	6.1
Hatsukami et al. (7)	Immediate	2.8	1.6	5.0	3.5	3.6	1.8
Benowitz et al. (8)	Usual brand	4.1	4.0	6.0	8.0	4.0	2.0
Donny	Usual brand	6.2	6.5	0.0	2.1	4.3	10.4
Percentage of subjects exceeding 150% of baseline CPD and CO							
CPD							
Benowitz et al. (5)	Gradual	Baseline	0.0	0.0	0.0	0.0	5.0
Benowitz et al. (8)	Gradual	0.0	1.9	0.0	0.0	0.0	0.0
Donny	Immediate	0.0	1.0	2.1	1.0	2.1	0.0
Hatsukami et al. (6)	Immediate	0.0	0.0	0.0	0.0	0.0	0.0
Hatsukami et al. (7)	Immediate	0.0	3.2	3.2	3.5	3.6	3.6
Benowitz et al. (8)	Usual brand	0.0	0.0	0.0	0.0	0.0	2.0
Donny	Usual brand	0.0	2.0	10.2	10.2	10.2	6.1
CO							
Benowitz et al. (5)	Gradual	Baseline	0.0	0.0	0.0	0.0	0.0
Benowitz et al. (8)	Gradual	1.9	5.7	8.0	5.9	3.9	7.5
Donny	Immediate	3.3	6.5	5.6	2.2	5.6	7.6
Hatsukami et al. (6)	Immediate	6.7	10.5	11.4	9.4	6.2	6.1
Hatsukami et al. (7)	Immediate	2.8	1.6	5.0	3.5	3.6	1.8
Benowitz et al. (8)	Usual brand	4.1	4.0	6.0	8.0	4.0	2.0
Donny	Usual brand	6.2	6.5	0.0	2.1	4.3	10.4

[a]Benowitz et al. (5) weekly reduction schedule (with Time 1 serving as baseline) and Benowitz et al. (8) monthly reduction schedule (with Times 5 and 6 at the lowest dose); nicotine yields were 0.8–0.9, 0.6, 0.3–0.4, 0.2, and 0.1 mg FTC; all other study time points are weekly with nicotine yields <0.1 mg. Cotinine was only assessed at baseline, weeks 2, and 6 for the immediate reduction studies.

resulting in a more gradual introduction of nonaddictive cigarettes with less associated discomfort.

This study is not without limitations including: the small number of trials and the relatively small number of participants enrolled in these trials; two of the studies involved participants motivated to quit; and lack of representativeness of the samples to the general U.S. population of smokers. Some participants were not fully compliant with smoking reduced nicotine content cigarettes and smoked some conventional cigarettes, which might lead to an underestimation of the occurrence of compensatory smoking.

Although additional research is currently being conducted to determine whether our results can be replicated and to support the feasibility of establishing nicotine standard, our analysis suggests that neither approach results in significant safety concerns related to compensatory smoking.

Disclosure of Potential Conflicts of Interest

N.L. Benowitz is a consultant/advisory board member for Pfizer, GlaxoSmithKline, and McNeil. He has provided expert testimony for tobacco litigation. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH or the FDA.

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