Compensatory Smoking from Gradual and Immediate Reduction in Cigarette Nicotine Content

Dorothy K. Hatsukami1, Eric C. Donny2, Joseph S. Koopmeiners3, and Neal L. Benowitz4

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.

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 cigarettes to change their smoking behavior to receive higher levels of nicotine. The Family Smoking Prevention and Tobacco Control Act provides the FDA with the authority to regulate 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 cigarettes to change their smoking behavior to receive higher levels of nicotine.

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...
effects of varying nicotine content cigarettes. This project was conducted under the Center for the Evaluation of Nicotine in Cigarettes (CENIC; NCIIR16181875) 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 assessment 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.

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Benowitz et al. (5)</th>
<th>Benowitz et al. (8)</th>
<th>Donny</th>
<th>Hatzukami et al. (6)</th>
<th>Hatzukami et al. (7)</th>
<th>Benowitz et al. (8)</th>
<th>Donny</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Age</td>
<td>28.7 (8.79)</td>
<td>36.6 (10.97)</td>
<td>41.0 (12.94)</td>
<td>40.7 (13.26)</td>
<td>46.5 (12.25)</td>
<td>37.4 (11.67)</td>
<td>41.5 (12.47)</td>
</tr>
<tr>
<td>Sex: male</td>
<td>11 (55%)</td>
<td>25 (47.2%)</td>
<td>51 (50.5%)</td>
<td>30 (56.6%)</td>
<td>32 (40.5%)</td>
<td>31 (62.0%)</td>
<td>22 (44.9%)</td>
</tr>
<tr>
<td>Sex: female</td>
<td>9 (45.0%)</td>
<td>28 (52.8%)</td>
<td>50 (49.5%)</td>
<td>23 (45.4%)</td>
<td>47 (59.5%)</td>
<td>19 (38.0%)</td>
<td>27 (55.1%)</td>
</tr>
<tr>
<td>Race: white</td>
<td>14 (70.0%)</td>
<td>37 (69.8%)</td>
<td>54 (53.5%)</td>
<td>42 (79.2%)</td>
<td>68 (86.3%)</td>
<td>35 (70.0%)</td>
<td>27 (55.1%)</td>
</tr>
<tr>
<td>Race: black</td>
<td>0 (0.0%)</td>
<td>4 (7.5%)</td>
<td>36 (35.6%)</td>
<td>7 (13.2%)</td>
<td>3 (3.8%)</td>
<td>4 (8.0%)</td>
<td>20 (40.8%)</td>
</tr>
<tr>
<td>Race: other</td>
<td>6 (30.0%)</td>
<td>12 (22.6%)</td>
<td>11 (10.9%)</td>
<td>4 (7.5%)</td>
<td>8 (10.1%)</td>
<td>11 (22.0%)</td>
<td>2 (4.1%)</td>
</tr>
<tr>
<td>CPD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>18.9 (7.4)</td>
<td>23.2 (7.3)</td>
<td>15.6 (7.0)</td>
<td>19.8 (7.1)</td>
<td>19.4 (6.2)</td>
<td>20.2 (7.7)</td>
<td>15.2 (6.6)</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>16.9 (8.1)</td>
<td>25.4 (10.0)</td>
<td>14.8 (7.9)</td>
<td>20.0 (11.4)</td>
<td>23.5 (9.3)</td>
<td>23.3 (10.8)</td>
<td>14.7 (8.6)</td>
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<tr>
<td>FTND&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.2 (2.0)</td>
<td>5.3 (1.9)</td>
<td>5.4 (2.2)</td>
<td>5.1 (2.1)</td>
<td>5.6 (1.7)</td>
<td>5.3 (2.2)</td>
<td>5.1 (1.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Minor variations of some of the variables compared with prior published studies may exist based on the source of the data.

<sup>b</sup>Cigarettes per day.

Safety of Reduced Nicotine Content Cigarettes
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
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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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.K. Hatsukami, E.C. Donny, J.S. Koopmeiners, N.L. Benowitz

Writing, review, and/or revision of the manuscript: D.K. Hatsukami, E.C. Donny, J.S. Koopmeiners, N.L. Benowitz

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.K. Hatsukami, N.L. Benowitz

Study supervision: D.K. Hatsukami, N.L. Benowitz

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

<table>
<thead>
<tr>
<th>Studya</th>
<th>Summary</th>
<th>Time 1</th>
<th>Time 2</th>
<th>Time 3</th>
<th>Time 4</th>
<th>Time 5</th>
<th>Time 6</th>
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<td>0.0</td>
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<tr>
<td></td>
<td>Benowitz et al. (8) Gradual Baseline</td>
<td>0.0</td>
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<tr>
<td></td>
<td>Donny Usual brand Baseline</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td></td>
<td>Hatsukami et al. (6) Baseline</td>
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<tr>
<td></td>
<td>Hatsukami et al. (6) Immediate</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td></td>
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<td></td>
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References to tables and figures are included in the text to guide the reader to the relevant information in the document. The content is structured to provide a comprehensive understanding of the study’s objectives, methodologies, results, and implications.
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