Nicotine & Tobacco Research Volume 9, Number 12 (December 2007) 1309–1323

Pilot study on lower nitrosamine smokeless tobacco products compared with medicinal nicotine

M. Irene Mendoza-Baumgart, Ozlem E. Tulunay, Stephen S. Hecht, Yan Zhang, Sharon Murphy, Chap Le, Joni Jensen, Dorothy K. Hatsukami

Received 29 June 2006; accepted 27 December 2006

Smokeless tobacco (ST) products have the potential to be used as a harm reduction method for cigarette smokers. These products can deliver significantly less toxicants than cigarettes, although they are not toxicant free nor harmless. It is important to examine potential health risks and benefits of these products. These two small pilot studies examined the effects of two different ST products (Exalt and Ariva) compared with medicinal nicotine, another potential harm reduction product. Dependent, healthy adult cigarette smokers, who were motivated to quit smoking, underwent 1 week of baseline smoking measurement. They were then asked to quit smoking and were randomly assigned to use either an ST product or a medicinal nicotine lozenge (MNL, Commit) for 2 weeks, then crossed over to use the other product for 2 weeks. In the last week, following the sampling phase, subjects could choose the product they wished to use. Assessments were made repeatedly during baseline cigarette use and throughout the 5 weeks of treatment. Outcome measures included biomarkers for tobacco exposure and subjective, physiological, and behavioral responses. Tobacco-specific carcinogen uptake was greater from Exalt than from the MNL, and was comparable between the MNL and Ariva. Physiological effects and subjective effects on withdrawal and craving were comparable among Exalt, Ariva, and the MNL. Ariva was preferred over the MNL, which was preferred over Exalt. With the exception of medicinal nicotine products, low-nitrosamine ST products have the greatest potential to result in reduced toxicant exposure compared with other combustible reduced exposure products and have promise for reducing individual risk for disease. However, the population effect of marketing of such products as reduced exposure/reduced risk is unknown. The need for further research in this area and regulation of tobacco products is evident.

Introduction

Although the prevalence of cigarette smoking in the United States and other countries has declined, it remains the leading preventable cause of death. Despite convincing evidence that cigarette smoking poses a serious and dangerous risk to health, some smokers are still unable or unwilling to quit. These so-called inveterate smokers or hard-core smokers are the target of harm reduction strategies that several tobacco control advocates, scientific researchers, and even tobacco companies have been proposing. Although prevention and cessation should remain the primary methods to reduce tobacco-related health burden, the concept of harm reduction has been gaining recognition as a potentially valid component of a tobacco control and public health strategy. For example, the U.S. Institute of Medicine believes that harm reduction is a feasible and justifiable public health policy if implemented with a strong science base (Stratton, Shetty, Wallace, & Bondurant, 2001). In addition, Canada's Federal Tobacco Control Strategy incorporated harm reduction as one of the mutually reinforcing components in its efforts to control tobacco products and their negative effects in society (Health Canada, 2005). Given that the majority of smokers cannot quit, are unwilling to quit, or are not ready to quit, it may be as important to aim interventions at the reduction of

M. Irene Mendoza-Baumgart, M.D., Ozlem E. Tulunay, M.D., Stephen S. Hecht, Ph.D., Yan Zhang, M.S., Sharon Murphy, Ph.D., Chap Le, Ph.D., Joni Jensen, M.P.H., Dorothy K. Hatsukami, Ph.D., Transdisciplinary Tobacco Use Research Center, Cancer Center, University of Minnesota, Minneapolis, MN.

Correspondence: Dorothy K. Hatsukami, Ph.D., Transdisciplinary Tobacco Use Research Center, University of Minnesota, 2701 University Avenue SE, Suite 201, Minneapolis, MN 55414, USA. Tel: + 1 (612) 627-1808; Fax: +1 (612) 627-4899; E-mail: hatsu001@umn.edu

ISSN 1462-2203 print/ISSN 1469-994X online

DOI: 10.1080/14622200701704228

adverse consequences, even with continued use of tobacco or its constituents.

The rationale behind this concept of reducing tobacco toxicant exposure is based on findings from several studies showing that the risk of many tobacco-related diseases and causes of premature mortality are related to the amount of tobacco toxicant exposure. For example, the American Cancer Society Cancer Prevention Studies reported that the risk of smoking-caused mortality is related directly to tobacco smoke intake with the maximum risk reduction achieved by complete cessation (National Cancer Institute, 2001). Parallel results from the Lung Health Study were observed: Reductions in age-related decline in pulmonary function and symptoms were associated with sustained abstinence from cigarette smoking and, to a lesser extent, intermittent abstinence (Anthonisen et al., 1994; Gross, 1994; Kanner, Connett, Williams, & Buist, 1999). Finally, data modeled from the Cancer Prevention Study I of the American Cancer Society to determine years of lives saved from reduced cigarette exposure in smokers of 2 or more packs per day illustrated that sustained significant reduction of exposure to tobacco toxicants can lower risk for premature mortality and that the magnitude of the benefit is related to the amount of reduction in smoking and the age at which reduction occurs (Burns, 1997).

Numerous methods and products have been suggested for achieving tobacco harm reduction in cigarette smokers. These include reduction in the number of cigarettes smoked through use of behavioral, pharmacological, and even environmental methods (e.g., policies on smoking bans), and the much debated use of potential reduced exposure tobacco products (PREPs). PREPs include cigarette-like delivery devices that produce less combustion than traditional cigarettes (e.g., Eclipse, Accord); modified tobacco products that are genetically altered, cured, or sprayed with chemicals to reduce carcinogens (e.g., Quest, Advance, Omni); use of special filters to reduce toxicant levels (e.g., Marlboro UltraSmooth); and smokeless tobacco (ST) products (e.g., Revel, Exalt, Ariva).

Of the various tobacco-containing PREPs, the most likely to lead to significantly reduced toxicant exposure are the ST products. Some public health researchers reported that STs, particularly those with lower nitrosamine contents than conventional U.S. brands (e.g., Ariva and snus), are expected to be less hazardous and harmful than smoking (Bates et al., 2003; Tobacco Advisory Group of the Royal College of Physicians, 2002), and that if smokers switched to ST products, the health burden of tobacco use could be reduced (Ault, Ekelund, Jackson, & Saba, 2004; Levy et al., 2004; McNeill, 2004; Rodu & Cole, 2004). Tobacco companies have marketed some of these products with claims such as ''low-nitrosamine smokeless products'' or ''reduced levels of harmful toxicants'' and have petitioned government regulators to endorse these claims (U.S. Smokeless Tobacco Company, 2003). To date, minimal data have been collected to examine palatability, toxicant exposure, and other effects of these products when smokers switch to ST products.

We conducted two small pilot studies that focused on the effects of STs on toxicant exposure, subjective response, and product preference. The products selected for the present study are the newer ST products that have been marketed by tobacco companies as alternatives to cigarettes when a smoker is unable to smoke in certain situations. In particular, we aimed to determine the effects of these products on toxicant uptake, withdrawal, and self-administration as compared with medicinal nicotine.

Method

Subjects

Smokers were recruited between January and December 2004 from the local Minneapolis–St. Paul metropolitan area via posted flyers, advertisements in local and university newspapers, and advertisements on the radio for a study that was ''comparing new tobacco products and nicotine replacement products.'' Subjects who were interested in quitting smoking were recruited. Potential participants were asked to attend an orientation at which the study was explained in detail. They provided written informed consent and completed questionnaires about tobacco use history, the Fagerström Test for Nicotine Dependence (FTND; Heatherton, Koslowski, Frecker, & Fagerström, 1991), medical history, and demographics. To be eligible to participate in the study, subjects had to be aged 18–65 years, in good physical and mental health as confirmed by medical history, and have smoked at least 15 cigarettes/day for a minimum of 1 year. In addition, they could not currently be using other types of tobacco products on a regular basis, or be using any methods for cutting down on tobacco use. Pregnant and breast-feeding women were excluded from the study.

Study products

Study 1 involved participants using Exalt and the medicinal nicotine lozenge (MNL), 4 mg Commit, in a randomized order. Exalt was chosen because it is a ''low-nitrosamine'' moist snuff product contained in tealike packets that do not require spitting and is marketed in the United States with cigarette smokers

as the target. Exalt is manufactured by Swedish Match using a process known as the Gothia Tek standard, which eliminates or reduces tobacco toxicants. Commit is a nicotine-containing lozenge that comes in either a 2- or 4-mg dose and is manufactured by GlaxoSmithKline. Because the method of administration is similar to that of moist snuff and medicinal nicotine contains only nicotine and no other toxicants, this product was considered the best comparison product. Furthermore, both products result in similar concentrations of nicotine (Kotlyar et al., 2007). Study 2 involved participants using Ariva and the MNL, also in a randomized order. Ariva is manufactured by Star Scientific, and is a mint-flavored, compressed low-nitrosamine tobacco lozenge, about the size of a Tic-Tac breath mint. Ariva dissolves in the mouth without the need to spit. This product was chosen because it is marketed in the United States to cigarette smokers as a product to use when they cannot smoke cigarettes and, of all the tobacco products, it contains the lowest levels of TSNAs (Stepanov, Jensen, Hatsukami, & Hecht, 2006). The level of nicotine in this product is lower than the 4-mg Commit lozenge (Kotlyar et al., 2007).

All products were provided to the subjects in their original packaging. Subjects were informed that we were comparing novel ST products intended for use by smokers versus medicinal nicotine products. They were further informed that the products were being compared on levels of toxicant exposure, product preference, and subjective responses such as withdrawal relief. Subjects were asked to completely substitute these products for smoking. To maximize the use of the products, subjects were asked to use them at least every 2 hr. For all the products, subjects were told to tuck them between their cheek and gum, which in the case of Ariva and the MNL would allow them to dissolve. They were warned against chewing or biting Ariva and the MNL like candy.

Procedure

The crossover design of these two sequential studies is shown in Figure 1. Participants were asked to smoke at their normal rate for a minimum of 1 week prior to randomization. Baseline measurements were assessed at two clinic visits (baselines 1 and 2) during this period of ad lib smoking. At these two baseline assessments, blood samples were collected for white blood cell and hemoglobin counts. First-void urine samples were obtained to assess biochemical markers of nicotine and carcinogen exposure. At the end of the baseline period, participants were randomly assigned to one of the two study products for 2 weeks (period 1) and then crossed over to the other product for 2 weeks (period 2). During this 4-week sampling phase (visits 1–6), participants were required to come for three clinical visits every 2 weeks (e.g., middle of the week for the first and second weeks on the product and at the end of the second week) to assess any adverse effects and to evaluate their compliance with abstinence and use of product. At the end of each 2-week period, blood and urine samples were collected. During the fifth week of study product use (visit 7), participants were given a choice of self-administering whichever product they preferred (Exalt vs. the MNL for Study 1; Ariva vs. the MNL for Study 2). On all visits, participants' carbon monoxide (CO) levels, heart rate, and blood pressure were measured.

During product use, participants were asked to complete subjective questionnaires to assess withdrawal symptoms and to determine whether they disliked or liked the study product that they were currently using. Any possible adverse effects also

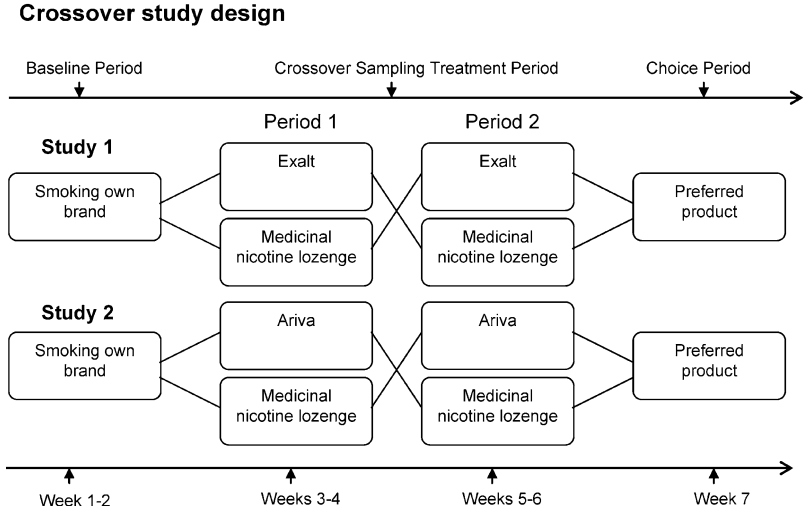

Figure 1. Experimental crossover study design involving a sampling phase consisting of two 2-week periods and a 1-week drug choice phase.

were assessed, and the appropriate course of action or treatment was provided if any were experienced. In addition, brief tobacco cessation counseling was given at each clinic visit, and study products were distributed during these visits. Participants were compensated US$390 for completing the study and received a $110 bonus if they completed all of the sessions and met all of the study requirements (refrained from cigarette use during the 5-week treatment period as verified by CO levels, provided blood and breath samples, and used nicotine lozenge or ST products as prescribed and indicated by self-report). All procedures were approved by the University of Minnesota Institutional Review Board and were in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Outcome measures

At each clinic visit, tobacco and nicotine use status was determined by having participants complete a tobacco use questionnaire that asked about any tobacco use (i.e., ST and cigarette) since the last visit, and by daily records of study product use (i.e., ST and the MNL). Abstinence from cigarette use was verified by breath CO levels of no more than 8 ppm. Other outcome measures were collected at each visit or during product use.

The Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986, 1998) was used to rate nicotine withdrawal symptoms (e.g., cigarette craving, irritability/anger, anxiety/tension, difficulty concentrating, restlessness, impatience, problems with sleep, increased appetite, drowsiness, and depressed mood) as 0=not present, 1=slight, 2=mild, 3=moderate, or 4=severe. The Drug Effects and Liking Visual Analog Scale (Hasenfratz, Baldinger, & Battig, 1993; Jaffe & Glaros, 1986; Kochhar & Warburton, 1990; Pritchard, Robinson, Guy, Davis, & Stiles, 1996), adapted from previous research, was used to allow subjects to describe their liking and desire of the study product; any, good or bad effects from the study product; and effectiveness of the product. Subjects indicated their liking on a 100-mm visual analog scale ranging from not at all to extremely. Physiological measures such as sitting heart rate and blood pressure were obtained using Dinamap (Critikon, Inc., Tampa, Florida).

At the two baseline visits and the visits after which the patients had used the assigned product for 2 weeks (visits 3 and 6), the following additional measures were collected: (a) urine samples to analyze total cotinine, and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), each being the sum of the free and glucuronidated forms (Hecht, 1998) and (b) blood samples to measure white blood cells and hemoglobin levels, which are nonspecific biomarkers related to tobacco use (Eliasson, Lundblad, & Hagg, 1991; Hatsukami et al., 2005; Parry et al., 1997; Sunyer et al., 1996).

Urinary total nicotine and cotinine levels were determined by gas chromatography/mass spectrometry as described previously (Hecht et al., 1999). Analysis for total NNAL, a urinary metabolite of the tobacco-specific lung carcinogen 4-(methylnitrosamino)-l-(3-pyridyl)-l-butanone (NNK), was carried out as described elsewhere (Carmella, Han, Fristad, Yang, & Hecht, 2003). All urinary levels were creatinine adjusted to correct for urine volume.

Data analyses

In each crossover study, we compared baseline characteristics, including demographics, smoking history, and FTND score, between two sequence groups, using the Wilcoxon's rank sum test or Fisher's exact test, for homogeneity related to randomization.

Amount of product use was measured daily through the whole study. Total cotinine, total NNAL, white blood cells, and hemoglobin were measured at baselines 1 and 2 and at visits 3 and 6. Carbon monoxide, blood pressure, and heart rate were measured at all visits, including the two baseline visits and visits 1–7, where visit 7 occurred in the choice week. Drug effect and liking was measured at visits 1–7. For the above-mentioned outcomes, the data during the sampling period (visits 1–6) were analyzed using the general linear mixed models for 2×2 crossover design to evaluate the sequence, visit, and product effects.

Because of the skewness of the distributions and the large variations of the data, general linear mixed models for total cotinine and total NNAL were conducted on their natural log scale. Geometric means and 95% confidence intervals of total cotinine and total NNAL in the original scale were calculated using Cox's method (Zhou & Gao, 1997). In addition, for total cotinine, total NNAL, and CO, baseline data were averaged and compared with those from visits 3 and 6, separately, within each sequence group using the Wilcoxon's signed-rank test. Withdrawal symptoms and craving were measured at all nine time points, but the analyses were focused on period 1. For these outcomes, repeated-measures analyses were conducted to test product, visit (including averaged baseline, visits 1 and 2) and product × visit interaction effects. Product preference during choice week was measured. Summary statistics were calculated for the percentage of the amount of each product used. SAS version 9.1 was used for statistical analyses. All the tests were two sided with a significance level of .05.

For the analyses, participants were required to have a CO level of no more than 8 ppm while they

were assigned to the products. One subject in the Ariva versus MNL study had a CO level of 37 ppm at visit 6 when using the MNL; therefore, the visit 6 CO, total cotinine, and total NNAL values for this subject were excluded from the analyses. Subjects who had a few slips were allowed in the analyses if they had CO levels of greater than 9 ppm but no more than 15 ppm. Three subjects from the Exalt versus MNL study and five subjects from the Ariva versus MNL study had levels in this range among one or two of the six sampling visits. When analyses were conducted on subjects with and without slips for the biomarkers of exposure and symptoms of withdrawal and craving, we observed no differences in the results. Therefore, we included participants with slips in reporting the results.

Results

Study 1: Exalt versus MNL study

Demographics and smoking history. The visit flowchart is shown in Figure 2A. Biochemical (i.e., total cotinine and total NNAL) and subjective outcome measures were analyzed from participants who were randomized. Data analysis for product preference during choice week was conducted on participants who completed the study.

Baseline measurements showed no significant difference in participant demographics, most measures of tobacco use history, and FTND scores between the two sequence groups (Table 1). The only exception was type of cigarette. Most participants in the MNL–Exalt sequence group smoked light cigarettes, but this was not the case for the Exalt–MNL group ($p=.03$). Dropout rates between sequence groups were not significantly different ($p=.72$).

Amount of product use. We found no significant difference in the amount of product use between the two sequence groups ($p=.41$) and between the two products, Exalt versus the MNL ($p=.94$). However, the amount of product use was significantly greater during period 1 than during period 2 ($p=.0002$). The mean number (*SD*) of products used per day in the Exalt to MNL group was 6.5 (1.1) for period 1 and

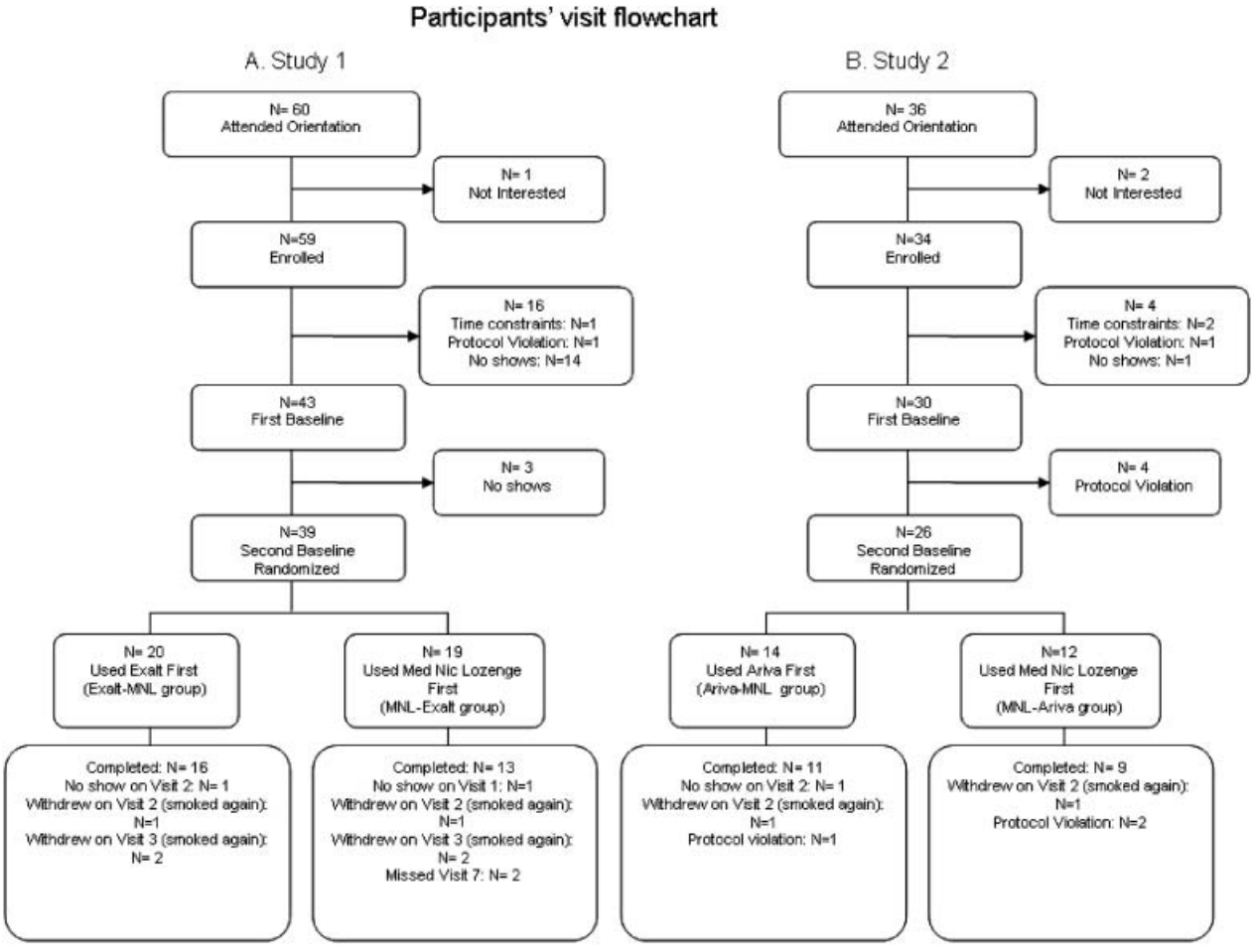

Figure 2. Participant visit flowchart for the Exalt vs. medicinal nicotine lozenge (MNL) study (2A) and the Ariva vs. MNL study (2B).

Table 1. Study 1 baseline characteristics and Fagerström Test for Nicotine Dependence (FTND) scores.

Variable	Overall (*N*=39)	Sequence group	
		MNL-Exalt (*n*=19)	Exalt-MNL (*n*=20)
Demographics			
Age, years; *M* (*SD*)	38.7 (12.0)	37.9 (12.1)	39.5 (12.1)
Mdn	37.0	36.0	43.0
Gender (*n*)			
Male	18	8	10
Female	21	11	10
Ethnicity (*n*)			
Black	3	0	3
Native American	1	0	1
Pacific Islander	0	0	0
Hispanic	1	1	0
White, non-Hispanic	34	18	16
Smoking history			
Cigarettes/day; *M* (*SD*)	21.3 (5.1)	21.8 (6.0)	20.8 (4.3)
Mdn	20.0	20.0	20.0
Years at current rate; *M* (*SD*)	15.4 (12.1)	16.6 (11.9)	14.4 (12.4)
Mdn	12.5	12.0	14.0
Type of cigarettes (*n*)[a]			
Regular	13	3	10
Light	21	14	7
Ultralight	4	1	3
Age at first cigarette; *M* (*SD*)	14.0 (3.3)	13.0 (3.1)	14.9 (3.4)
Mdn	14.0	13.0	16.0
Years as a daily smoker; *M* (*SD*)	22.3 (12.3)	21.4 (12.4)	23.1 (12.5)
Mdn	20.0	18.0	28.0
Number of quit attempts; *M* (*SD*)	7.9 (16.6)	11.9 (23.5)	4.4 (4.4)
Mdn	4.0	5.0	3.0
FTND score; *M* (*SD*)	5.9 (1.7)	5.6 (1.8)	6.1 (1.6)
Mdn	6.0	6.0	6.0

Note. *M*, mean; *Mdn*, median; *SD*, standard deviation. [a]One missing value in the MNL-Exalt sequence group.

5.7 (1.3) for period 2. The mean number (*SD*) of products used per day in the MNL to Exalt group was 6.8 (1.4) for period 1, and 5.9 (1.2) for period 2.

Carbon monoxide, total cotinine, and total NNAL. No significant sequence effects were observed for carbon monoxide, total cotinine, or total NNAL (*p* values≥.15). Visit and product effects are shown in Figure 3. Significant reductions in CO levels were observed from baseline measures during ad lib smoking to the end of periods 1 and 2 of product use within each group (*p* values<.0001). No significant difference in CO levels between Exalt and the MNL was observed ($p=.99$). Significant reductions in total cotinine levels (nmol/mg creatinine) were observed from baseline measures to the end of period 1 of product use ($p=.003$ for the MNL–Exalt group and $p<.0001$ for the Exalt–MNL group) and to the end of period 2 of product use ($p=.008$ for the MNL–Exalt group and $p=.009$ for the Exalt–MNL group). No significant difference in total cotinine levels between Exalt and the MNL was observed ($p=.18$). Similarly significant reductions were observed in total NNAL (pmol/mg creatinine) levels at the end of periods 1 and 2 within each group ($p<.05$). Significant product effects were observed ($p<.0001$), with significantly higher total NNAL levels observed after Exalt use than after MNL use.

Withdrawal symptoms and craving. Analyses of withdrawal and craving scores were focused on period 1 when maximal withdrawal symptoms typically occur. Significant visit effects were observed for total withdrawal symptoms ($p=.0002$) and craving ($p=.01$; Figure 4). For withdrawal symptoms, visits 1 (week 1 postquit) and 2 (week 2 postquit) scores were significantly higher than the averaged baseline ($p=.0001$ and $p=.0007$, respectively), but no differences were found between visits 1 and 2 ($p=.64$). For craving, no significant difference was observed between baseline and visit 1 ($p=.69$); however, craving score was significantly higher at baseline than at visit 2 ($p=.02$), and craving score was significantly higher at visit 1 than at visit 2 ($p=.01$). No significant differences in total withdrawal ($p=.53$) and craving scores ($p=.74$) were found between Exalt and MNL use. No significant visit × product interaction effects were found ($p=.79$ for total withdrawal, and $p=.41$ for craving).

Physiological effect on vital signs (blood pressure and heart rate), white blood cell count, and hemoglobin level. No significant sequence group, visit, or product effects were found for systolic and diastolic blood pressures, heart rate, white blood cell count, or hemoglobin level (*p* values>.05).

Drug effect and liking. Using a weekly administered visual analog scale to rate drug effects and liking, participants rated the MNL as significantly more likeable ($p<.0001$), desirable ($p=.04$), and effective ($p<.0001$), and as having more good effects ($p=.004$) than Exalt.

Product preference during choice period. Of the 16 participants from the Exalt–MNL group, 6 (37.5%) preferred using Exalt alone, 4 (25%) preferred using the MNL alone, and 6 (37.5%) used both Exalt and the MNL. The median percentage of the amount of Exalt used was 71%. Of the 13 participants from the MNL–Exalt group, 10 (77%) preferred using the MNL alone, none (0%) used Exalt alone, and 3 (23%) used both Exalt and the MNL. The median percentage of the amount of Exalt used was 0%. Overall, among the 29 participants during the choice week, 6 (21%) preferred using Exalt alone, 14 (48%) preferred using the MNL alone, and 9 (31%) used both Exalt and the MNL.

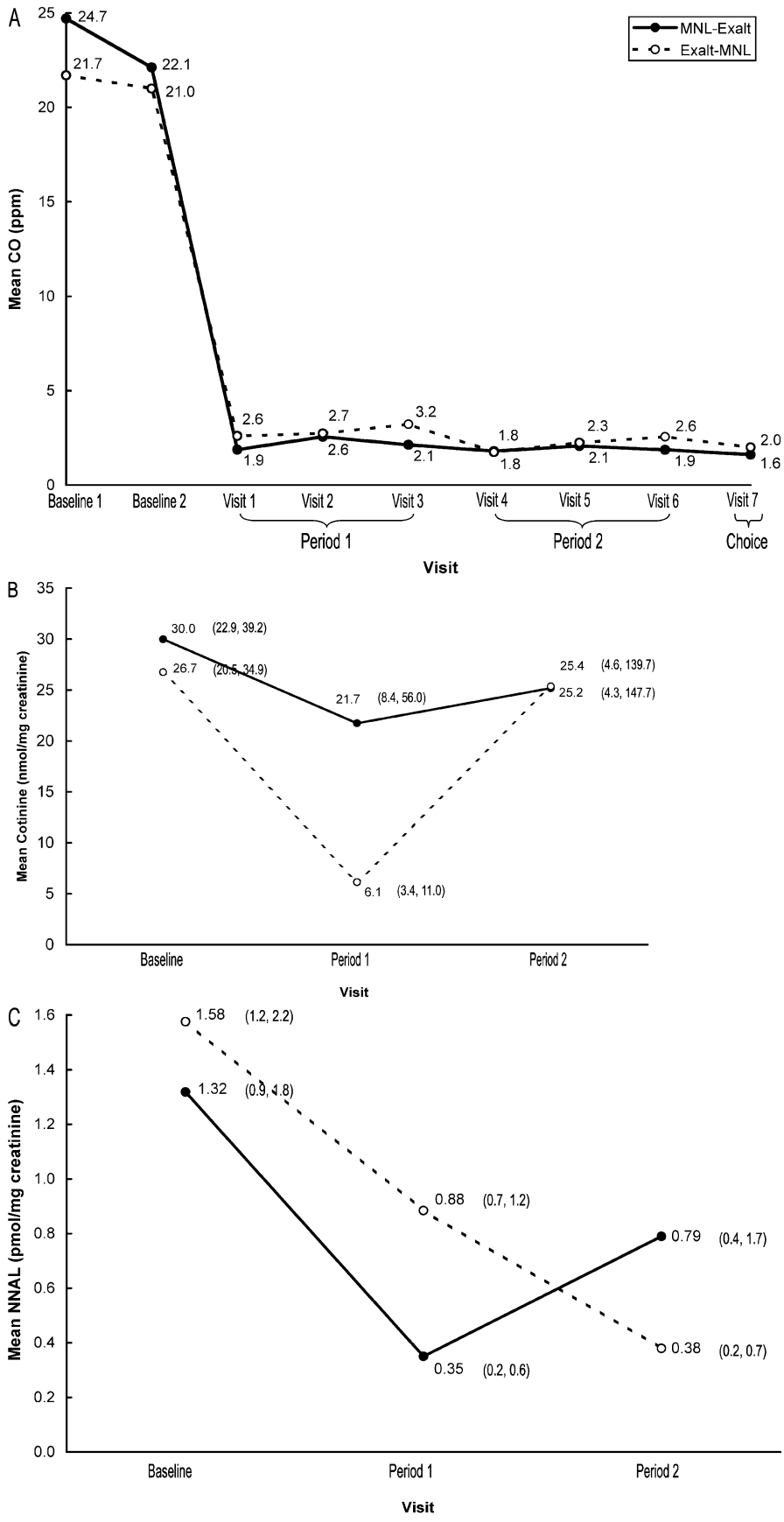

Figure 3. Mean carbon monoxide (CO) and geometric mean (95% confidence interval) total cotinine and total NNAL concentrations over baseline and sampling phases between two sequence groups of Exalt and the medicinal nicotine lozenge (MNL).

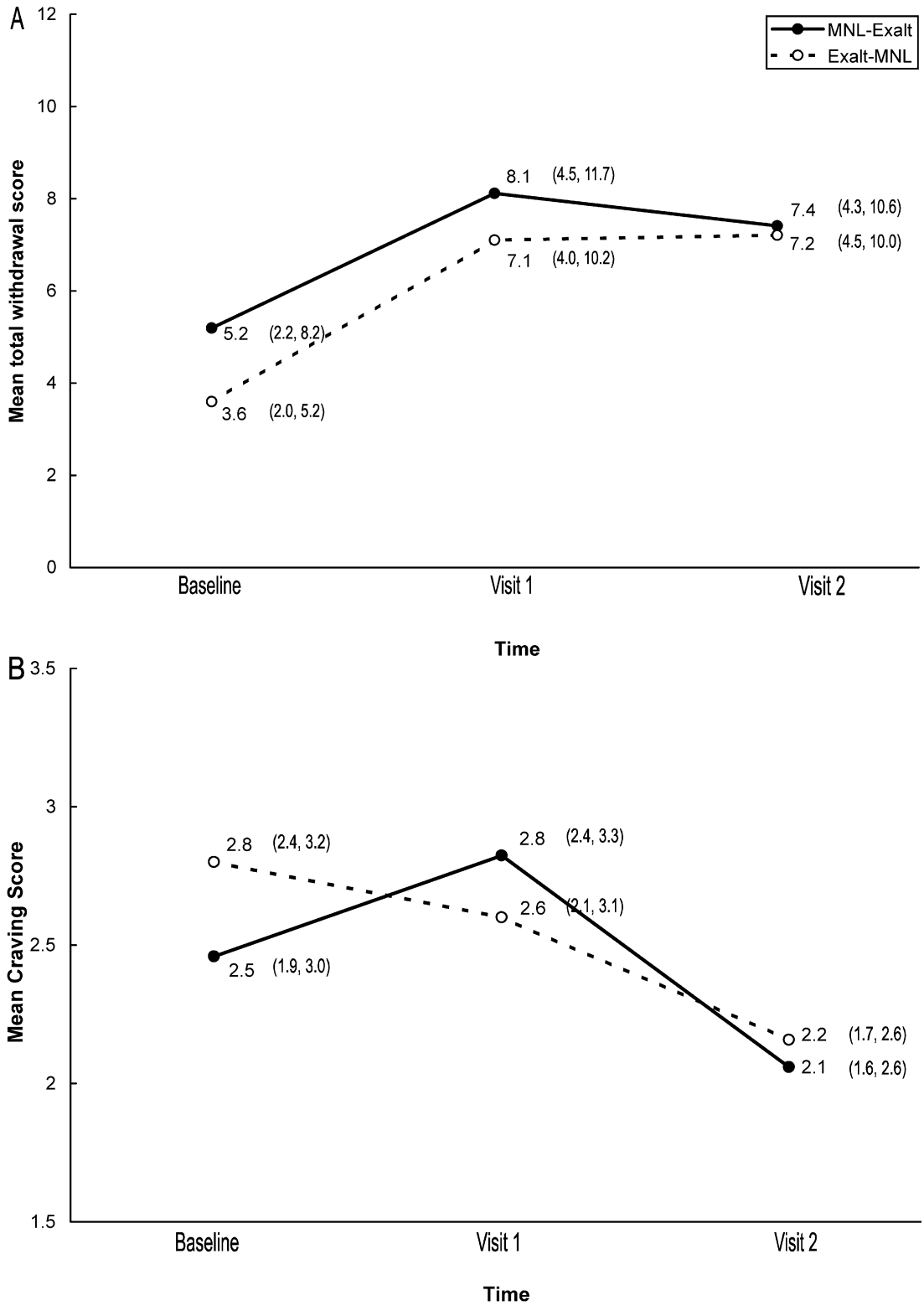

Figure 4. Mean (95% confidence interval) total withdrawal symptoms and craving scores over baseline, visit 1, and visit 2 between two sequence groups of Exalt and the medical nicotine lozenge (MNL).

Study 2: Ariva versus MNL study

Demographics and smoking history. The visit flowchart is shown in Figure 2B. Baseline measurements showed no significant difference in participant demographics, tobacco use history, or FTND scores between the two sequence groups (Table 2). Dropout rates between sequence groups were not significantly different ($p=1.00$).

Amount of product use. We found no significant difference in the amount of product use between the two sequence groups ($p=.57$) or between the two periods ($p=.20$). However, the amount of Ariva use was significantly greater than MNL use ($p<.0001$). The mean number (*SD*) for products used per day in the Ariva to MNL group was 7.8 (1.4) for period 1 and 5.0 (0.6) for period 2. The mean number (*SD*) of products used per day in the MNL to Ariva group was 5.3 (0.6) for period 1 and 7.1 (2.1) for period 2.

Carbon monoxide, total cotinine, and total NNAL. We found no significant sequence effects for carbon monoxide, total cotinine, or total NNAL (p values$\geq .56$). Visit and product effects are shown in Figure 5. Significant reductions in CO levels were observed from baseline measures during ad lib smoking to the end of period 1 of product use within each group ($p=.002$ for the MNL–Ariva group and $p=.001$ for the Ariva–MNL group) and to the end of period 2 of product use within each group (both p values$=.002$). We observed no significant difference in CO levels between Ariva and the MNL ($p=0.89$). We observed significant reductions in total cotinine levels (nmol/mg creatinine) from baseline measures to the end of period 1 of product use ($p=.01$ for the MNL–Ariva group and $p=.003$ for the Ariva–MNL group) and significant or near significant reductions at the end of period 2 of product use ($p=.06$ for the MNL–Ariva group, and $p=.01$ for the Ariva–MNL group). We observed similarly significant reductions in total NNAL (pmol/mg creatinine) levels at the end of period 1 (both p values$=.002$) and significant or near significant results at the end of period 2 ($p=.08$ for the MNL–Ariva group, and $p=.004$ for the Ariva–MNL group). No significant product differences were observed for cotinine ($p=0.97$) or total NNAL ($p=.19$).

Table 2. Study 2 baseline characteristics and Fagerström Test for Nicotine Dependence (FTND) scores.

Variable	Overall (*N*=26)	Sequence group: MNL-Ariva (*n*=12)	Sequence group: Ariva-MNL (*n*=14)
Demographics			
Age, years; *M* (*SD*)	35.7 (11.2)	36.4 (10.5)	35.1 (12.1)
Mdn	33.5	33.5	32.5
Gender (*n*)			
Male	10	6	4
Female	16	6	10
Ethnicity (*n*)			
Black	7	4	3
Native American	0	0	0
Pacific Islander	0	0	0
Hispanic	1	0	1
White non-Hispanic	18	8	10
Smoking history			
Cigarettes/day; *M* (*SD*)	20.9 (4.5)	20.0 (3.1)	21.7 (5.5)
Mdn	20.0	20.0	20.0
Years at current rate; *M* (*SD*)	10.3 (9.6)	12.5 (10.4)	8.4 (8.9)
Mdn	8.0	10.0	3.5
Type of cigarettes (*n*)[a]			
Regular	10	7	3
Light	11	4	7
Ultralight	4	1	3
Age at first cigarette; *M* (*SD*)	16.3 (11.6)	13.4 (1.8)	18.9 (15.6)
Mdn	13.5	13.0	14.0
Years as a daily smoker; *M* (*SD*)	17.8 (10.8)	18.9 (10.5)	16.8 (11.4)
Mdn	17.5	18.0	16.5
Number of quit attempts; *M* (*SD*)	3.8 (2.7)	3.3 (2.5)	4.1 (2.9)
Mdn	3.0	3.0	3.0
FTND score; *M* (*SD*)	6.0 (1.5)	6.2 (1.9)	5.8 (1.1)
Mdn	6.0	6.0	6.0

Note. *M*, mean; *Mdn*, median; *SD*, standard deviation. [a]One missing value in the Ariva-MNL sequence group.

Withdrawal symptoms and craving. Significant visit effects were observed for total withdrawal symptoms ($p<.0001$) and craving ($p=.03$; Figure 6). For withdrawal symptoms, visits 1 (week 1 postquit) and 2 (week 2 postquit) scores were significantly higher than the averaged baseline ($p<.0001$, respectively), but only near significant differences were found between visits 1 and 2 ($p=.09$). For craving, no significant differences were observed between baseline and visit 1 ($p=.27$) or between visits 1 and 2 ($p=.11$); however, craving score was significantly higher at baseline than at visit 2 ($p=.01$). We found no significant differences in total withdrawal ($p=.94$) and craving scores ($p=.94$) between Ariva and MNL use, and no significant visit × product interaction effects ($p=.15$ for total withdrawal and $p=.34$ for craving).

Physiological effect on vital signs (blood pressure and heart rate), white blood cell count, and hemoglobin level. No significant sequence group or product effects were found for systolic and diastolic blood pressure, heart rate, white blood cell count, or hemoglobin level (p values$>.05$). No significant visit effects were observed for heart rate, white blood cell count, or hemoglobin level (p values$>.05$). However, the period effects were significant for systolic ($p=.02$) and diastolic blood pressure ($p=.01$), with participants having significantly higher blood pressures during period 1 than during period 2.

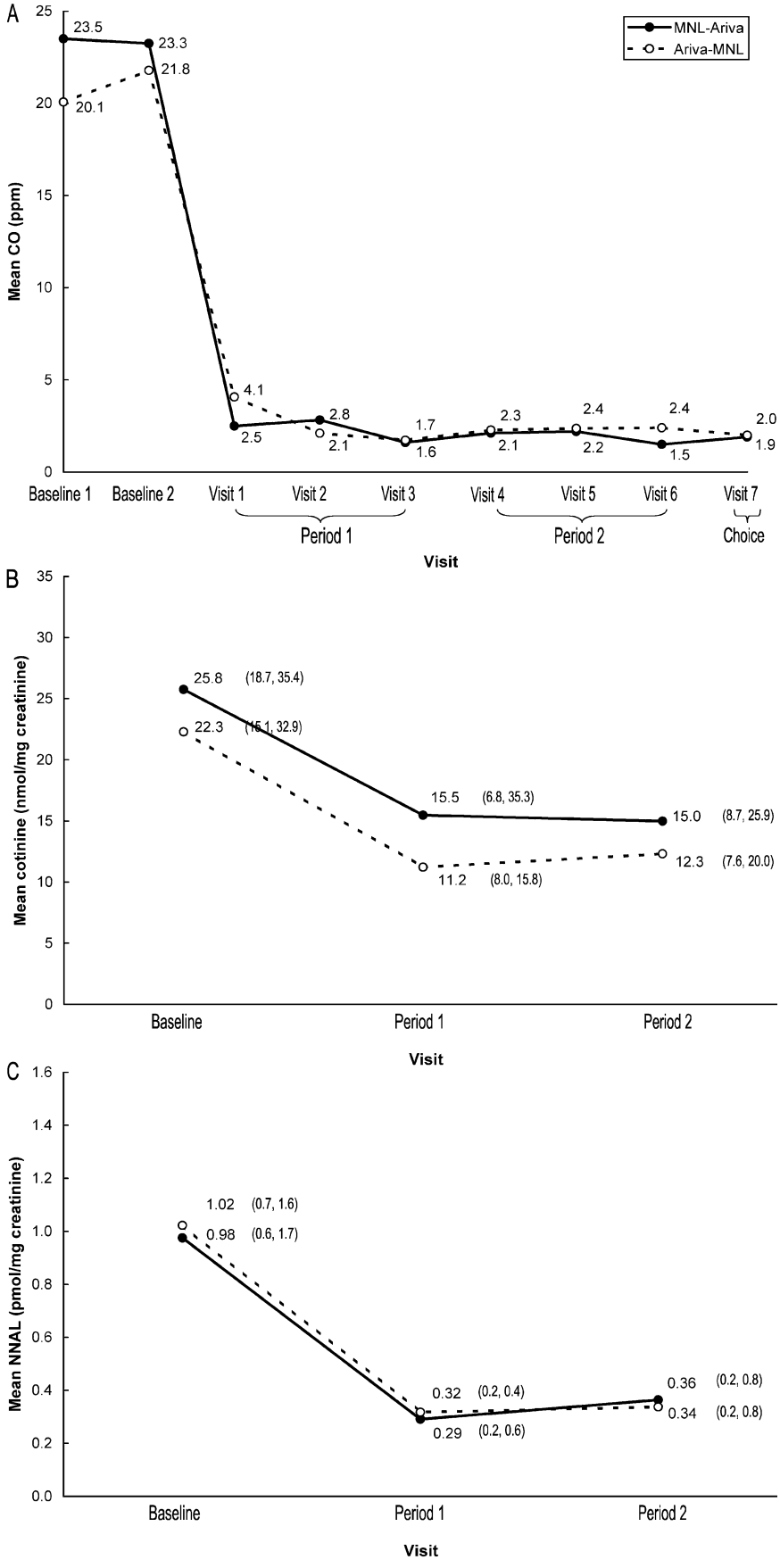

Figure 5. Mean carbon monoxide (CO) and geometric mean (95% confidence interval) total cotinine and total NNAL concentrations over baseline and sampling phases between two sequence groups of Ariva and the medicinal nicotine lozenge (MNL).

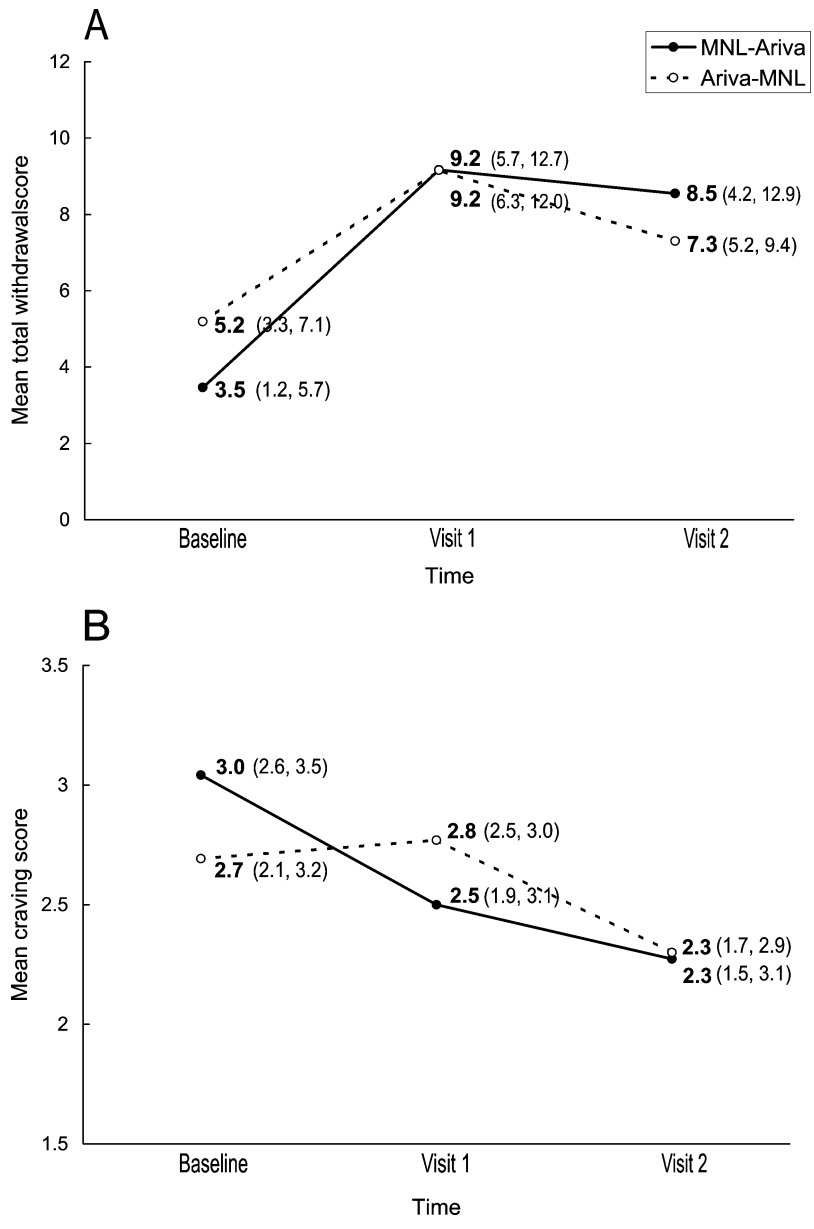

Figure 6. Mean (95% confidence interval) total withdrawal symptoms and craving scores over baseline, visit 1, and visit 2 between two sequence groups of Ariva and the medical nicotine lozenge (MNL).

Drug effect and liking. Participants reported no significant differences between Ariva and the MNL in terms of its likeability (p=.11) and effectiveness (p=.45), although Ariva was rated as significantly more desirable (p=.02). Near significant differences were found in terms of bad effects (p=.07) experienced from Ariva versus MNL use, with higher scores on bad effects with the MNL.

Product preference during choice week. Of the 11 participants from the Ariva–MNL group, 7 (64%) preferred using Ariva alone, 1 (9%) used the MNL alone, and 3 (27%) used both Ariva and the MNL. The median percentage of the amount of Ariva used was 100%. Of the 9 participants from the MNL–Ariva group, 3 (33%) preferred using Ariva alone, 2 (22%) preferred using the MNL alone, and 4 (45%) used both Ariva and the MNL. The median percentage of the amount of Ariva used was 91%. Overall, among the 20 participants during the choice week, 10 (50%) preferred using Ariva alone, 3 (15%) preferred using the MNL alone, and 7 (35%) used both Ariva and the MNL.

Discussion

These pilot studies examined human tobacco toxicant exposure and physiological and subjective responses to two forms of low-nitrosamine ST products compared with medicinal nicotine, as well

as the behavioral preferences for these products. The studies had several limitations, including a small sample size and study participants who might not be entirely representative of the general population of smokers interested in using these products. The small sample size probably accounted for the wide confidence intervals observed for some of the cotinine values in the Exalt versus MNL study and therefore for the differences in cotinine concentrations observed across studies. As observed in Figure 3B, the geometric mean cotinine from the MNL–Exalt group was greater and had a wider 95% confidence interval than that from the Exalt–MNL group at period 1. Also, at period 2, the geometric means for cotinine from both sequence groups were high and had wide 95% confidence intervals. These results were related to large variations in cotinine concentrations. At period 1, two participants from the MNL–Exalt group had urinary cotinine concentrations between 40 and 46 nmol/mg creatinine, whereas only one high concentration (29 nmol/mg creatinine) was observed in the Exalt–MNL group. At period 2, both sequence groups had high cotinine concentrations. In the MNL–Exalt group, one participant had a cotinine level of 117 nmol/mg creatinine, and in the Exalt–MNL group, one participant had a cotinine level of 90 nmol/mg creatinine. These values were not excluded from the analyses because of the randomized study design, but instead we conducted a general linear mixed model analysis of total cotinine and total NNAL on natural log scales to avoid the problems that large variations in raw data may cause for the study results. For purposes of verification, we reanalyzed the data—excluding the outliers—and found no conceptual changes in the results. Notably, none of the individuals who were outliers had CO levels greater than 9 ppm, and total NNAL levels were consistent with values observed for the other subjects.

Other limitations include having examined only two brands of ST and one type of medicinal nicotine. Thus results cannot be generalized to all ST products or medicinal nicotine products. Furthermore, the study design does not reflect how these products may be used in a real-world setting. The ST products targeted toward smokers are currently marketed to be used in situations where smokers cannot smoke or as an alternative to smoking. It is possible that few smokers will completely switch to these ST products. Smokers may instead engage in both smoking and ST use, using ST primarily in places where smoking bans are instituted. The exposure associated with dual use of tobacco products may be greater than that associated with the use of a single product.

With these caveats in mind, we observed four interesting results. First, there was generally a significant decrease in total cotinine levels and carcinogen uptake when smokers switched to Exalt, Ariva, or the MNL. Exalt use produced higher carcinogen uptake compared with MNL use, but Ariva produced no differences compared with the MNL. We found no significant differences in total cotinine levels between Exalt or Ariva when compared with the MNL. Second, neither oral ST product differed from the MNL in changes in cravings or withdrawal symptoms. Third, the physiological effects of the oral ST products on vitals signs (i.e., blood pressure and heart rate), white blood cell count, and hemoglobin level were not significantly different from those associated with the MNL. Fourth, given the choice of which product to use, participants used the MNL more than Exalt but less than Ariva.

These results lead us to three suggestions. First, tobacco products such as Exalt have nicotine yields that are purportedly comparable with those of the MNL, which can significantly reduce exposure to NNK. In particular, we found that when smokers switched to either Exalt or Ariva, total NNAL levels were decreased by approximately 55% (Exalt) and 70% (Ariva) compared with levels obtained during 1 week of baseline smoking. Interestingly, total NNAL levels in subjects who used Ariva, although higher, were not significantly different from those in subjects who used the MNL, whereas total NNAL levels in subjects who used Exalt were significantly higher, as expected, than those in subjects who used the MNL. These results corroborate data collected by Stepanov et al. (2006) showing the MNL to have nondetectable levels of NNK, the parent compound of NNAL, whereas Exalt and Ariva have 0.24 μg/g product and 0.037 μg/g product, respectively.

These findings make it difficult to ignore the potential of some ST products, specifically Ariva, to reduce exposure to tobacco-specific nitrosamines, particularly NNK, which has been established as a potent lung carcinogen (Hecht et al., 2004; Hurt et al., 2000) and suggested to be a possible contributing factor in the development of oral cancer associated with tobacco use (Hatsukami, Lemmonds, & Tomar, 2004). This important finding requires further investigation so that tobacco users who are unable or unwilling to quit but are looking for methods to reduce exposure to the harmful toxicants in tobacco can receive accurate information about their reduction options. It is already evident that ST use is less hazardous to health than is cigarette smoking (e.g., Hatsukami, Lemmonds, & Tomar, 2004; Rodu & Cole, 2004), and some public health researchers have advocated ST use as a harm reduction approach (e.g., Foulds, Ramstrom, Burke, & Fagerström, 2003; Rodu & Cole, 2004). However, ST use is not without harm and, depending on the product, can result in increased risk of oral and pancreatic cancer

and fetal toxicity (Hatsukami, Lemmonds, & Tomar, 2004; International Agency for Research on Cancer, in press). Furthermore, medicinal nicotine products, which are strictly regulated by the U.S. Food and Drug Administration (FDA), have a known safety and toxicity profile. By contrast, tobacco products are not under the jurisdiction of a regulatory agency and do not need to undergo rigorous safety testing, disclosure of ingredients or toxicants, or human testing. Although Ariva use led to levels of total NNAL and cotinine that were similar to those associated with MNL use, consumers remain unaware of other potential toxicants in the product that have not been carefully monitored by an independent agency. That is, besides NNK, exposures to other tobacco-specific nitrosamines (i.e., NNN), polycyclic aromatic hydrocarbons (e.g., benzo[a]pyrene), and metals have not been assessed (Hecht, 1999).

Our second main conclusion is that a need exists for a regulatory body to oversee tobacco products. The products tested in the two studies have significantly less toxicants than the most popular conventional oral ST products marketed in the United States, such as Skoal and Copenhagen. These popular brands have significant levels of toxicants, even compared with cigarettes. For example, the total tobacco-specific nitrosamine (TSNA) level in Copenhagen long cut is 7.5 μg/g product and in Marlboro full-flavor cigarettes is 6.3 μg/g product (Stepanov et al., 2006). In another study involving ST users, the level of total NNAL achieved by using these popular ST brands was 3.2 pmol/ml creatinine (Hatsukami, Lemmonds, Zhang et al., 2004), compared with 0.98–1.58 pmol/ml creatinine observed in the smokers while smoking. Of even greater concern, some of the ST products used in countries such as India and Sudan have levels that far exceed those found in the popular conventional brands sold in the United States (Idris et al., 1998; Stepanov, Hecht, Ramakrishnan, & Gupta, 2005). For example, toombak, a product sold in Sudan, has TSNA levels that are thousands of micrograms per gram dry weight (Idris et al., 1998). If these products were overseen by a regulatory body, consumers would potentially be informed about the relative levels of toxicant exposure across different products and across brands so that they would not be misled into believing that all ST products have significantly low toxicant levels. The results from the present study further emphasize that ST products are available that have significantly lower total TSNA levels, and consequently lower uptake of total NNAL—compared with conventional U.S. brands and products sold in other countries. This raises the need for performance standards, as proposed in the World Health Organization Framework Convention for Tobacco Control, Article 9 (www.who.int/tobacco/framework/en/), which would include the reduction of toxicant levels of all tobacco products. This reduction would be particularly important in developing countries with products that have extremely high toxicant levels.

Our third main conclusion is based on the product preferences of the study subjects. More palatable medicinal nicotine products, the least toxic of the nicotine-containing products, need to be developed by pharmaceutical companies and considered for approval by the FDA, to compete with the more user-friendly tobacco-containing products. Several authors have discussed the unpalatable taste of medicinal nicotine products as being a major deterrent to compliance with recommended dosing regimens (e.g., Jarvik & Henningfield, 1993; Rose, 1996), resulting in undermedication (Fortmann, Killen, Telch, & Newman, 1988; Henningfield & Stitzer, 1991; Rose, 1996). If existing medicinal nicotine products remain less palatable than the non-FDA-controlled and more palatable tobacco products, consumers will likely prefer using these ST products to reduce their tobacco toxicant exposure, particularly when ST products lead to similar reductions in tobacco withdrawal symptoms and craving.

Palatability is not the only issue. Cost per unit package of ST products is far lower compared with medicinal products. Thus, even with improved palatability of medicinal nicotine products, smokers may tend to use ST products because of cost. Packaging medicinal nicotine products in smaller units at lower price may encourage more smokers to try these products. ''Leveling the playing field'' between tobacco products and medicinal nicotine products through regulation may result in greater availability and access to the safest products for the consumer (Henningfield & Slade, 1998; Slade & Henningfield, 1998). However, it is important to remember that medicinal nicotine is not a safe product and can result in fetal toxicity and increased risk factors for cardiovascular disease (Benowitz, 1999); therefore, the ultimate goal should remain cessation of all nicotine-containing products.

In summary, results from the present study suggest that a low-nitrosamine ST product has strong potential as a harm reduction product and warrants further investigation. Such products led to significantly reduced levels of tobacco-specific nitrosamine uptake compared with cigarettes. Furthermore, this type of product is likely to have far greater potential for harm reduction than some of the other PREPs, such as combustible modified tobacco to reduce toxicants and even perhaps cigarette-like delivery devices (Hatsukami & Hecht, 2005). Among the various brands of ST products sold in the United States and other countries, a product such as Ariva

has the greatest promise for harm reduction because of its low nitrosamine level.

Results from the present study also reinforce the importance of regulation of these tobacco products. Regulation can require identification of toxicants and human testing to determine the extent of toxicant exposure for all tobacco products. Regulation also could require examination of how to market and communicate information about ST products to consumers and the effects of the products on the population as a whole to minimize negative impacts on public health (e.g., greater initiation of tobacco use, less cessation of tobacco use, higher prevalence of dual use of tobacco products). Finally, consideration should be given to how the safest product, medicinal nicotine, can be packaged, labeled, and made more palatable, so that this product will be preferred over tobacco products that contain more than nicotine.

Acknowledgments

This study was funded by NIH grant DA013333.

References

Anthonisen, N. R., Connett, J. E., Kiley, J. P., Altose, M. D., Bailey, W. C., Buist, A. S., Conway, W. A., Jr., Enright, P. L., Kanner, R. E., O'Hara, P., Owens, G. R., Scanlon, P. D., Tashkin, D. P., & Wise, R. A. for the Lung Health Study Research Group. (1994). Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *The Journal of the American Medical Association*, *272*, 1497–1505.

Ault, R. W., Ekelund, R. B., Jackson, J. D., & Saba, R. P. (2004). Smokeless tobacco, smoking cessation and harm reduction: An economic analysis. *Applied Economics*, *36*, 17–29.

Bates, C., Fagerström, K., Jarvis, M. J., Kunze, M., McNeill, A., & Ramstrom, L. (2003). European Union policy on smokeless tobacco: A statement in favour of evidence based regulation for public health. *Tobacco Control*, *12*, 360–367.

Benowitz, N. L. (1999). Snuff, nicotine and cardiovascular disease: Implications for tobacco control. *Journal of the American College of Cardiology*, *34*, 1791–1793.

Burns, D. (1997). *Estimating the benefits of a risk reduction strategy*. Poster presented at the Society for Research on Nicotine and Tobacco 3rd annual scientific conference. Nashville, TN.

Carmella, S. G., Han, S., Fristad, A., Yang, Y., & Hecht, S. S. (2003). Analysis of total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) in human urine. *Cancer Epidemiology, Biomarkers & Prevention*, *12*(11 Pt. 1), 1257–1261.

Eliasson, M., Lundblad, D., & Hagg, E. (1991). Cardiovascular risk factors in young snuff-users and cigarette smokers. *Journal of Internal Medicine*, *230*, 17–22.

Fortmann, S. P., Killen, J. D., Telch, M. J., & Newman, B. (1988). Minimal contact treatment for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: Initial results of the Stanford Stop Smoking Project. *The Journal of the American Medical Association*, *260*, 1575–1580.

Foulds, J., Ramstrom, L., Burke, M., & Fagerström, K. (2003). Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco Control*, *12*, 349–359.

Gross, N. (1994). The Lung Health Study: Disappointment and triumph. *The Journal of the American Medical Association*, *272*, 1539–1541.

Hasenfratz, M., Baldinger, B., & Battig, K. (1993). Nicotine or tar titration in cigarette smoking behavior? *Psychopharmacology*, *112*, 253–258.

Hatsukami, D., & Hecht, S. S. (2005). *Hope or hazard: What research tells us about "potentially reduced-exposure" tobacco products*. Minneapolis, MN: University of Minnesota Transdisciplinary Tobacco Use Research Center, Retrieved from www.tturc.umn.edu/documents/hope_or_hazard-3.pdf

Hatsukami, D., Kotlyar, M., Allen, S., Jensen, J., Li, S., Le, C., & Murphy, S. (2005). Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest*, *128*, 2528–2537.

Hatsukami, D., Lemmonds, C., & Tomar, S. L. (2004). Smokeless tobacco use: Harm reduction or induction approach? *Preventive Medicine*, *38*, 309–317.

Hatsukami, D., Lemmonds, C. A., Zhang, Y., Murphy, S. E., Le, C., Carmella, S. G., & Hecht, S. S. (2004). Evaluation of carcinogen exposure in people who used "reduced exposure" tobacco products. *Journal of the National Cancer Institute*, *96*, 844–852.

Health Canada. (2005). Federal tobacco control strategy. A framework for action. Part 2. Key strategy areas. Retrieved from www.hc-sc.gc.ca/hl-vs/pubs/tobac-tabac/ffa-ca/strateg_e.html

Heatherton, T. F., Koslowski, L. T., Frecker, R. C., & Fagerström, K.-O. (1991). The Fagerström Test for Nicotine Dependence: A revision of the Fagerström Tolerance Questionnaire. *British Journal of Addiction*, *86*, 1119–1127.

Hecht, S. S. (1998). Biochemistry, biology, and carcinogenicity of tobacco-specific N-nitrosamines. *Chemical Research in Toxicology*, *11*, 559–603.

Hecht, S. S. (1999). Tobacco smoke carcinogens and lung cancer. *Journal of the National Cancer Institute*, *91*, 1194–1210.

Hecht, S. S., Carmella, S. G., Chen, M., Dor Koch, J. F., Miller, A. T., Murphy, S. E., Jensen, J. A., Zimmerman, C. L., & Hatsukami, D. K. (1999). Quantitation of urinary metabolites of a tobacco-specific lung carcinogen after smoking cessation. *Cancer Research*, *59*, 590–596.

Hecht, S. S., Murphy, S. E., Carmella, S. G., Zimmerman, C. L., Losey, L., Kramarczuk, I., Roe, M. R., Puumala, S. S., Li, Y. S., Le, C., Jensen, J., & Hatsukami, D. K. (2004). Effects of reduced cigarette smoking on the uptake of a tobacco-specific lung carcinogen. *Journal of the National Cancer Institute*, *96*, 107–115.

Henningfield, J. E., & Slade, J. (1998). Tobacco-dependence medications: Public health and regulatory issues. *Food and Drug Law Journal*, *53*(Suppl.), 75–114.

Henningfield, J. E., & Stitzer, M. L. (1991). *New developments in nicotine delivery systems*. New York: The Cortlandt Group.

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*, *43*, 289–294.

Hughes, J. R., & Hatsukami, D. (1998). Errors in using tobacco withdrawal scale. *Tobacco Control*, *7*, 92–93.

Hurt, R. D., Croghan, G. A., Wolter, T. D., Croghan, I. T., Offord, K. P., Williams, G. M., Djordjevic, M. V., Richie, J. P., Jr., & Jeffrey, A. M. (2000). Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine & Tobacco Research*, *2*, 327–336.

Idris, A. M., Ibrahim, S. O., Vasstrand, E. N., Johannessen, A. C., Lillehaug, J. R., Magnusson, B., Wallstrom, M., Hirsch, J. M., & Nilsen, R. (1998). The Swedish snus and the Sudanese toombak: Are they different? *Oral Oncology*, *34*, 558–566.

International Agency for Research on Cancer. (in press). Smokeless tobacco and tobacco-specific nitrosamines. In, *IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans* (Vol. 89). Lyon, France.

Jaffe, A. J., & Glaros, A. G. (1986). Taste dimensions in cigarette discrimination: A multidimensional scaling approach. *Addictive Behaviors*, *11*, 407–413.

Jarvik, M. E., & Henningfield, J. E. (1993). Pharmacological adjuncts for the treatment of tobacco dependence. In: C. T. Orleans, & J. Slade (Eds.), *Nicotine addiction: Principles and management* (pp. 245–261). New York: Oxford University Press.

Kanner, R. E., Connett, J. E., Williams, D. E., & Buist, A. S. (1999). Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: The Lung Health Study. *American Journal of Medicine*, *106*, 410–416.

Kochhar, N., & Warburton, D. M. (1990). Puff-by-puff sensory evaluation of a low to middle tar medium nicotine cigarette designed

to maintain nicotine delivery to the smoker. *Psychopharmacology*, *102*, 343–349.

Kotlyar, M., Mendoza-Baumgart, M. I., Li, Z. Z., Pentel, P. R., Barnett, B. C., Feuer, R. M., Smith, E. A., & Hatsukami, D. K. (2007). Nicotine pharmacokinetics and subjective effects of five smokeless tobacco products. *Tobacco Control*, *16*, 138–142.

Levy, D. T., Mumford, E. A., Cummings, K. M., Gilpin, E. A., Giovino, G., Hyland, A., Sweanor, D., & Warner, K. E. (2004). The relative risks of a low-nitrosamine smokeless tobacco product compared with smoking cigarettes: Estimates of a panel of experts. *Cancer Epidemiology, Biomarkers, & Prevention*, *13*, 2035–2042.

McNeill, A. (2004). Harm reduction. *British Medical Journal*, *328*, 885–887.

National Cancer Institute. (2001). *Risks associated with smoking cigarettes with low machine-measured yields of tar and nicotine* (Smoking and Tobacco Control Monograph No. 13; NIH Publication No. 02-5074). Bethesda, MD: U.S. Department of Health and Human Services, National Institutes of Health, Author.

Parry, E. M., Ballantine, J. A., Ellard, S., Evans, W. E., Jones, C., Kilic, N., & Lewis, R. I. (1997). Biomonitoring study of a group of workers potentially exposed to traffic fumes. *Environmental and Molecular Mutagenesis*, *30*, 119–130.

Pritchard, W. S., Robinson, J. H., Guy, T. D., Davis, R. A., & Stiles, M. E. (1996). Assessing the sensory role of nicotine in cigarette smoking. *Psychopharmacology*, *127*, 55–62.

Rodu, B., & Cole, P. (2004). The burden of mortality from smoking: Comparing Sweden with other countries in the European Union. *European Journal of Epidemiology*, *19*, 129–131.

Rose, J. E. (1996). Nicotine addiction and treatment. *Annual Review of Medicine*, *47*, 493–507.

Slade, J., & Henningfield, J. E. (1998). Tobacco product regulation: Context and issues. *Food and Drug Law Journal*, *53*(Suppl.), 43–74.

Stepanov, I., Hecht, S. S., Ramakrishnan, S., & Gupta, P. C. (2005). Tobacco-specific nitrosamines in smokeless tobacco products marketed in India. *International Journal of Cancer*, *116*, 16–19.

Stepanov, I., Jensen, J., Hatsukami, D., & Hecht, S. S. (2006). Tobacco-specific nitrosamines in new tobacco products. *Nicotine & Tobacco Research*, *8*, 309–313.

Stratton, K., Shetty, P., Wallace, R., & Bondurant, S. (Eds.). (2001). *Clearing the smoke: Assessing the science base for tobacco harm reduction*. Institute of Medicine. Washington, DC: National Academies Press.

Sunyer, J., Munoz, A., Peng, Y., Margolick, J., Chmiel, J. S., Oishi, J., Kingsley, L., & Samet, J. M. (1996). Longitudinal relation between smoking and white blood cells. *American Journal of Epidemiology*, *144*, 734–741.

Tobacco Advisory Group of the Royal College of Physicians. (2002). *Protecting smokers, saving lives. The case for a tobacco and nicotine regulatory authority*. London: Royal College of Physicians of London.

U.S. Smokeless Tobacco Company. (2003). Recent developments: The role of smokeless tobacco as a reduced risk alternative to cigarette smoking, *Federal Trade Commission petition*. Greenwich, CT: Author.

Zhou, X.-H., & Gao, S. (1997). Confidence intervals for the log-normal mean. *Statistics in Medicine*, *16*, 783–790.