CLINICAL TRIALS

Smoking reduction treatment with 4-mg nicotine gum: A double-blind, randomized, placebo-controlled study

Background: **Smoking reduction may provide a harm-reduction alternative treatment for smokers who are not ready to quit smoking. This study evaluated the efficacy of nicotine gum in helping smokers reduce or quit smoking.**

Methods: **This randomized, double-blind, placebo-controlled trial involved 364 smokers who were not ready to quit but were willing to reduce their smoking intensity. Participants received either 4-mg nicotine gum (n = 184) or placebo gum (n = 180) as desired for up to 12 months. The primary outcome was sustained smoking reduction, which was defined as a decrease in daily cigarette consumption of at least 50% compared with baseline. Secondary measures included point-prevalence abstinence, intention to quit, and cardiovascular risk markers.**

Results: **At 4 months, the sustained smoking reduction rate in the nicotine gum group was twice that of the placebo group (15.8% versus 6.7%, $P = .008$). Point-prevalence abstinence was 6.6% for the nicotine gum group and 2.2% for the placebo group ($P = .07$). At 13 months, there was a significant difference in the smoking reduction rate for the nicotine (8.2%) and placebo (2.8%) groups ($P = .036$). At month 13, the abstinence rates were 12% and 4.5% for the nicotine and placebo groups, respectively ($P = .012$). Concomitant use of nicotine gum and cigarette smoking was well tolerated. Carbon monoxide levels decreased significantly ($P = .01$).**

Conclusion: **Nicotine gum may be an efficacious harm-reduction alternative for smokers who are not ready to quit and may promote smoking cessation, the ultimate goal in the treatment of tobacco dependence. (Clin Pharmacol Ther 2005;78:689-96.)**

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Abrupt cessation for the treatment of nicotine dependence currently motivates only a small proportion of smokers to quit and is not attractive for smokers who are not currently ready to quit. It is,therefore, important to develop interventions appropriate for smokers who are not willing or able to quit.[1-6] Harm reduction, achieved by smoking fewer cigarettes per day, may offer an alternative treatment strategy for smokers who are unable or unwilling to quit smoking.[6-8]

Smokers who try to reduce their cigarette consumption unaided generally compensate by smoking fewer cigarettes more intensely or gradually reverting to their original cigarette consumption. Partial nicotine substitution, or using nicotine medications to supplement

cigarettes, allows smokers to reduce their cigarette consumption without withdrawal symptoms,[9] as demonstrated in recent smoking reduction studies that used either the nicotine inhaler[1] or nicotine gum.[4,10]

The goal of this study was to explore the efficacy and safety of nicotine gum treatment for smoking reduction. Our study included smokers with a smoking intensity of at least 20 cigarettes per day, instead of 15 cigarettes per day as used in earlier smoking reduction studies with gum.[4] Because only a sufficiently high nicotine dose has been found to decrease tobacco consumption among heavy smokers,[11] 4-mg nicotine gum was used in this study. Earlier trials indicated that most participants interested in smoking reduction have a relatively high daily cigarette consumption, and this population of smokers represents the likely target group for the smoking reduction approach.

The primary objective of this study was to investigate the efficacy of 4-mg nicotine gum in reducing cigarette consumption among smokers not ready to quit. Secondary objectives included investigating the effect of smoking reduction on biomarkers and expired carbon monoxide levels, examining the effect of smoking reduction on intention to quit, and establishing whether smoking reduction would increase smoking cessation rates.

METHODS

Study design. This double-blind, randomized, parallel-group study, performed at 2 medical centers (University of Tübingen Medical Center, Tübingen, Germany, and Klinik Hirslanden, Zürich, Switzerland), compared the efficacy and safety of 4-mg nicotine gum versus placebo in reducing smoking over a 12-month study period. All participants provided informed consent, and the study was approved by the ethics committees of the University Hospital of Tübingen, Tübingen, Germany, Klinik Hirslanden, Zürich, Switzerland, and Swissmedic, Swiss Federal Agency for Therapeutic Products, Bern, Switzerland, and was performed in accordance with the Declaration of Helsinki.

Participants. Participants were recruited via newspaper advertisements, which invited smokers willing to change their smoking behavior but unwilling to quit to participate in a smoking reduction study. Participants were offered treatment free of charge and travel expense vouchers but did not receive any monetary compensation for their participation in the study.

Participants who qualified for the study were aged at least 18 years, consumed at least 20 cigarettes per day, smoked regularly for at least 3 years, had an expired-air CO level of at least 15 ppm, and had made at least 1 failed quit attempt within 2 years before the study but not within the previous 6 months. The last inclusion criterion ensured that participants included had had difficulties achieving abstinence on their own. Smokers who had not made a serious quit attempt were encouraged to try abrupt cessation.

Exclusion criteria included intent to quit smoking within the next month, current use of nicotine replacement therapy, and current involvement in other smoking cessation or smoking reduction programs. Certain health conditions also precluded participation, including unstable angina pectoris, myocardial infarction within the preceding 3 months, receiving psychiatric treatment or medication, and co-occurring alcohol or drug problems.

Study conditions. Eligible participants were randomized to receive either 4-mg nicotine gum (Nicorette; Pfizer Consumer Healthcare, Helsingborg, Sweden) or placebo gum. The placebo gum was similar in appearance and taste to the nicotine gum but contained no nicotine. The gum was used as desired for up to 12 months. Participants were instructed to use the gum whenever they had an urge to smoke and to chew between 6 and 24 pieces daily. They were told that the goal was to reduce smoking as much as possible by substituting the nicotine in cigarettes with the nicotine gum. Although participants were informed that smoking reduction was the goal, they were not informed that a 50% reduction was the study objective. Treatment was supplied at each visit as required and between appointments via telephone counseling or additional visits if necessary.

Measurement of treatment compliance was based on participants' self-reported gum use (number of pieces consumed) throughout the trial. Participants were asked the following questions: Have you stopped smoking? If the answer to the first question is "no," are you smoking on a daily basis? If the answer to the second question is "yes," on average, how many cigarettes do you smoke per day? If the answer to the second question is "no," on average, how many cigarettes do you smoke per week? Self-reported abstinence was validated by exhaled-air CO values. In addition, plasma cotinine levels were measured and compared over the course of the study. Records of dispensed medication were also used to verify compliance. Concomitant medications were recorded and were allowed, with the exception of treatments for tobacco dependence or smoking cessation delivered outside of this study.

Assessments. Nine clinic visits were scheduled, and data collection occurred at baseline, 6 weeks, 4 months, and 12 months. Full medical and smoking histories

were assessed at baseline. Smoking status (ie, whether the participant had quit or, if still smoking, average number of cigarettes smoked per day) was assessed at all visits and was biologically confirmed by use of expired-air CO measurements. Treatment compliance and experience of adverse events were assessed at all visits after baseline.

Blood samples were collected at baseline, 4 months, and 12 months to establish serum concentrations of plasma cotinine and thiocyanate and hematologic parameters. Measured parameters included white blood cell count and levels of high- and low-density lipoprotein, total cholesterol, triglycerides, fibrinogen, and C-reactive protein (CRP).

Clinic visits were performed at participant's convenience during the day. Although it was recorded, fasting was not mandatory, and thus lipid changes were not analyzed.

All samples were analyzed for hematologic parameters at local hospital laboratories. Cotinine and thiocyanate levels were measured from a blood sample deposited in a 10-mL heparinized tube, centrifuged at 1400*g* for 10 minutes, and frozen within 4 hours. Samples for cotinine and thiocyanate measurement were transferred for analysis to Pfizer Consumer Healthcare, Helsingborg, Sweden. Cotinine analyses were performed by use of gas chromatography after a single-step liquid-liquid extraction of the plasma samples. Thiocyanate levels were determined by use of a colorimetric method based on the Koenig reaction. Exhaled-air CO was measured by use of a Bedfont Smokerlyzer (Bedfont Scientific, Rochester, United Kingdom).

Participant withdrawal. Participants were withdrawn from the study if the investigator determined it to be medically necessary or if the participants decided to discontinue. If a participant did not return for a scheduled visit, every effort was made to contact him or her. Participants who did not return to the clinic after 2 requests were classified as "treatment failures."

Outcome measures. The primary outcome measure was smoking reduction, which was defined as a 50% or greater reduction in cigarette consumption from baseline to 6-week, 4-month, and 13-month follow-up visits. Participants who managed to quit smoking (100% reduction) were included in these analyses. Self-reported reductions were verified by use of expired-air CO measures.

Secondary study parameters included 1-day and 7-day point-prevalence abstinence (based on self-report and verified by expired-air CO levels <10 ppm), expired-air CO levels, intention to quit, and baseline–to–follow-up changes in hematologic risk markers (fibrinogen, CRP, and white blood cell count).

Table I. Baseline characteristics

Characteristic	*Nicotine gum, 4 mg (n = 184)*	*Placebo gum (n = 180)*
Female gender (%)	45.9	35.2
Age (y)	42.6 ± 9.9	43.5 ± 10.3
Age at onset of smoking (y)	17.6 ± 3.7	17.4 ± 2.9
No. of cigarettes smoked per day	27.9 ± 9.2	29.6 ± 9.5
Exhaled-air carbon monoxide (ppm)	29.1 ± 10.8	28.2 ± 10.2
FTND score	5.7 ± 1.8	5.9 ± 1.9

Data are given as mean ± SD.
FTND, Fagerström Test of Nicotine Dependence.

Statistical analysis. On the basis of results from previous smoking cessation and smoking reduction studies, it was hypothesized that 20% of the nicotine treatment group and 10% of the placebo group would achieve sustained reduction in smoking between the 6-week and 4-month follow-up visits. Power analyses indicated that a sample size of 197 participants was needed in each treatment group to yield a power of 0.80 at a 2-tailed significance level of .05.

The data set for statistical analyses included all participants who enrolled in the study (intention-to-treat analysis). Two-tailed statistical tests were used throughout. Confidence intervals (CIs) for effect parameters have a nominal coverage probability of 95%. Approximate intervals, relying on normality assumptions, were used.

Treatment efficacy (the proportion of successful reducers) was analyzed by use of the Fisher exact test, supplemented by point estimates and 95% CIs for odds ratios. Changes from baseline for continuous outcome variables were evaluated by use of the Wilcoxon signed rank sum test. Linear models were applied to regress changes in the outcome variables on different covariates such as treatment status, mean cigarette reduction, mean CO reduction, age, and sex. Categoric, ordinal-scale variables were investigated by use of the sign test (binary data). Comparisons of different subgroups with respect to score changes were made by use of the Kruskal-Wallis test.

RESULTS

Preliminary and process analyses. A total of 953 participants were screened, of whom 364 were eligible

Table II. Smoking reduction and smoking cessation

Parameter	*Time point*	*Nicotine gum, 4 mg (n = 184) (No. and %)*	*Placebo gum (n = 180) (No. and %)*	*P value**
Sustained smoking	10 wk	37 (20.1)	20 (11.1)	.021
reduction from wk 6	4 mo	29 (15.8)	12 (6.7)	.008
including quitters	13 mo	15 (8.2)	5 (2.8)	.036
Sustained smoking	10 wk	32 (17.4)	20 (11.1)	.100
reduction from wk 6	4 mo	24 (13.0)	12 (6.7)	.052
excluding quitters	13 mo	13 (7.1)	5 (2.8)	.088
1-Day point-prevalence	10 wk	9 (4.9)	1 (0.6)	.020
abstinence	4 mo	12 (6.5)	4 (2.2)	.071
	13 mo	22 (12.0)	8 (4.5)	.012
7-Day point-prevalence	10 wk	8 (4.4)	1 (0.6)	.037
abstinence	4 mo	12 (6.5)	2 (1.1)	.011
	13 mo	20 (10.9)	7 (3.9)	.015

*Fisher exact test (2-tailed).

to enroll in the study. Baseline characteristics for the nicotine gum (n = 184) and placebo (n = 180) groups are shown in Table I. There were no differences between groups with respect to smoking characteristics and demographics. The study sample consisted 148 women (40.6%) and 216 men (59.4%), with a mean age of 43 years (range, 18-71 years). The mean age at the onset of smoking was 17.5 years (range, 10-40 years), and the mean cigarette consumption at baseline was 28 cigarettes per day (range, 20-70 cigarettes per day).

Attrition analyses indicated that 124 nicotine participants (67%) and 105 placebo participants (58%) were seen for the 4-month follow-up and that 98 nicotine participants (53%) and 69 placebo participants (38%) were seen for the 13-month follow-up. A further 82 participants were followed up by telephone or letter at 13 months, yielding a total of 249 participants who completed the study (n = 138 in nicotine group and n = 111 in placebo group). The most common reasons for attrition were being "lost to follow-up" (n = 10 in nicotine group and n = 19 in placebo group) or "no longer willing to participate" (n = 16 in nicotine group and n = 28 in placebo group). One participant in the placebo group was excluded from the primary analysis because the blinding code was broken during the study.

Compliance. Gum use in the nicotine and placebo groups was similar across time points and did not decrease during the initial 4-month period. At 2 weeks, daily gum users in the nicotine group used a mean of 6.5 pieces in the 4-mg nicotine group (n = 116) and 6.4 pieces in the placebo group (n = 108); the corresponding mean figure at 4 months was 6.5 pieces in both treatment groups (n = 54 in nicotine group and n = 38 in placebo group). After 12 months, participants who were still using gum on a daily basis (n = 15 in nicotine group and n = 13 in placebo group) were using a mean of 6.1 pieces of 4-mg nicotine gum, as compared with 4.3 pieces of placebo gum.

Smoking reduction and smoking cessation. The sustained successful smoking reduction rate from week 6 to month 4 in the nicotine gum group was 15.8% (29/184) compared with 6.7% (12/179) in the placebo group (P = .008, Fisher exact test). Corresponding figures at month 13 were 15 of 184 (8.2%) versus 5 of 179 (2.8%) (P = .036). The smoking status results are shown in Table II.

After exclusion of abstainers, the actual number of cigarettes at 13 months was 5.25 (n = 4; SD, 5.5; range, 0-10) in the placebo gum group and 9.14 in the nicotine gum group (n = 7; SD, 6.3; range, 4-20).

Nicotine gum promoted smoking cessation to a greater extent than placebo, although the 1-day point-prevalence abstinence analysis at month 4 failed to reach statistical significance: 6.5% of participants in the nicotine group (12/184) were abstinent compared with 2.2% in the placebo group (4/179) (P = .07). However, at month 13, 12% of participants in the nicotine gum group (22/184) were abstinent, as compared with 4.5% in the placebo gum group (8/179) (P = .012). By use of a 7-day point-prevalence cessation definition, active treatment was superior to placebo at all 3 time points.

Treatment effects on intention to quit. At month 13, more than half of the participants (n = 150 [60%]) stated that participation in the study had increased their interest in quitting, as compared with one third (n = 92 [36.6%]) who felt that study participation had no effect

on their intention to quit. There was, however, no difference between the nicotine and placebo groups with regard to intention to quit.

Biochemical and hematologic parameters. As shown in Table III, plasma cotinine and thiocyanate levels decreased from baseline to month 4. At month 12, plasma thiocyanate levels remained reduced compared with baseline values, but plasma cotinine levels had increased from baseline levels. Both cigarette consumption and expired CO levels progressively decreased throughout the study.

At month 4, a sustained reduction in expired-air CO levels of at least 20% (considered to be a clinically significant reduction) versus baseline was noted in 26.1% of the participants in the nicotine gum group (48/184), as compared with only 16.8% of participants in the placebo group (30/179) ($P = .04$; odds ratio, 1.75 [95% CI, 1.05-2.92]). Corresponding figures at 13 months were 25 of 184 (13.6%) in the active treatment group versus 10 of 179 (5.6%) in the placebo group ($P = .012$, Fisher exact test; odds ratio, 2.66 [95% CI, 1.24-5.71], Mantel-Haenszel test).

Reductions in cigarette consumption and CO, thiocyanate, and cotinine levels were compared between smokers who were treated with nicotine gum and those given placebo gum. Only the number of cigarettes after 4 months ($P = .02$) and cotinine levels after 4 months ($P = .01$) and 12 months ($P = .04$) showed significant differences.

There were no statistically significant changes in mean levels (by use of the Mann-Whitney test) in any of the cardiovascular risk markers (white blood cell count, fibrinogen, CRP) between baseline and month 4 in the 42 participants who successfully reduced their smoking by at least 50%. Nor were there any significant differences between baseline and month 12 in the 20 successful reducers (by use of the Wilcoxon signed rank sum test).

Safety. Concomitant use of 4-mg nicotine gum and cigarette smoking was well tolerated, and no unexpected adverse events occurred during the study. Participants in the placebo group (n = 180) reported a total of 370 adverse events. Of these, 13% were assessed as mild, 46% as moderate, and 40% as severe. Participants in the nicotine group (n = 184) reported a total of 506 adverse events, of which 16% were assessed as mild, 44% as moderate, and 40% as severe. Some of the adverse events in the nicotine gum group were reported more frequently than in the placebo gum group, such as nausea (19 versus 11; P = not significant [NS], Fisher exact test [2-tailed]), hiccups (28 versus 3, $P < .0001$), dyspepsia (12 versus 5, P = NS), and oral discomfort (8 versus 3, P = NS). The most common adverse event was headache (43 in active group versus 52 in placebo group, P = NS). No serious adverse event was related to nicotine treatment, and there were no discontinuations reportedly resulting from side effects.

DISCUSSION

This study compared 4-mg nicotine chewing gum with placebo gum as an aid to reducing smoking in participants who were not ready to quit but were willing to reduce their daily smoking. According to the primary definition of success (a reduction in daily cigarette smoking by at least 50% versus baseline from week 6 to month 4), treatment with nicotine gum resulted in a significantly higher success rate than placebo at 4 months (15.8% versus 6.7%). The superiority of the active treatment was maintained throughout the study. In addition, 64% of participants in the active group smoked fewer cigarettes per day at month 13 than at baseline, as compared with 51% in the placebo group ($P = .02$, Fisher exact test).

These findings corroborate those of prior studies which have reported that nicotine medications help smokers reduce their cigarette consumption and promote smoking cessation in smokers not ready to quit.[1,4,9,12,13] The population studied in our investigation was similar to those observed in the comparable studies. One study in which smokers were instructed to use the nicotine inhaler to reduce smoking reported a sustained reduction in smoking at 4 months in 26% of participants using the active inhaler versus 9% using placebo.[1] At 2 years, 10% of participants in the nicotine inhaler group were smoke-free (as measured by point-prevalence abstinence). Similarly, a study that used 2-mg and 4-mg nicotine gum for smoking reduction reported significantly higher sustained smoking reduction rates and point-prevalence cessation rates with active gum than placebo.[4]

Other investigators also recently reported that large (>50%) and even moderate (25%-50%) reductions in the smoking intensity predicted prospectively increased likelihood of cessation compared with no change in quantity. Moreover, participants who reduced smoking and then quit were somewhat less likely to have a relapse than those who did not reduce smoking in the 2 years before quitting.[14]

A reduction rate of 8% is not yet optimal but may be of clinical relevance, considering that, before the study, participants were unwilling to quit and unable to change their smoking behavior. Nevertheless, the goal in the treatment of tobacco dependence is for participants to become abstinent. In this study significantly

Table III. Daily gum consumption and percentage change in number of cigarettes smoked per day and expired-air carbon monoxide, plasma thiocyanate, and plasma cotinine levels

Time point		*Pieces of gum per day (%)*					*Cigarette reduction (%)*				
		No.	*Mean*	*SD*	*Min*	*Max*	*No.*	*Mean*	*SD*	*Min*	*Max*
Baseline*	Placebo	39	0.0	0.0	0.0	0.0	39	31.0	11.1	20.0	60.0
	Active	55	0.0	0.0	0.0	0.0	55	26.7	8.5	20.0	50.0
6 wk	Placebo	39	5.8	3.3	1.0	18.0	39	39.5†	19.7	10.0	100
	Active	55	5.7	3.3	1.0	14.0	55	45.8†	25.3	0.0	100
4 mo	Placebo	39	4.1	2.6	0.0	11.0	39	39.3†	22.3	−15	85.0
	Active	55	4.8	3.2	0.0	13.0	55	52.0†	27.2	0.0	100
12 mo	Placebo	39	1.6	1.7	0.0	5.0	37	50.6†	33.3	−17	100
	Active	55	2.3	3.1	0.0	15.0	55	61.4†	33.1	0.0	100
13 mo	Placebo	39	0.3	0.8	0.0	3.0	39	51.0†	33.9	−15	100
	Active	55	0.8	2.5	0.0	12.0	55	64.0†	33.1	0.0	100

Min, Minimum; Max, maximum.
*Values at baseline represent actual numbers or results rather than reductions. Data are presented for participants who attended all visits.
†Significant changes were shown by *t* tests comparing values with baseline results ($P < .001$).

more participants had stopped smoking in the 4-mg nicotine gum group than in the placebo group at the final 13-month follow-up (12% versus 4.5%, $P = .012$).

The point-prevalence abstinence rates observed in this study increased over time, which is not commonly observed in smoking cessation studies but has been found in some reduction studies.[1,14] This finding indicated that smokers not ready to quit may need more time to quit smoking and that the nicotine gum facilitates this step.

Furthermore, when asked if their interest in quitting had grown or diminished, participants in the nicotine group reported a more positive change in their attitude toward quitting smoking compared with participants in the placebo group. These results must be interpreted with caution because subjects who dropped out did not answer this question and because the item assessing intention to quit might not be adequately reliable. This preliminary finding regarding an increase in the motivation to quit should be investigated in future studies by use of established questionnaires.

Findings regarding the effects of smoking reduction on health outcomes indicated that smoking reduction had a minor and statistically nonsignificant effect on some laboratory variables regarded as markers of risk factors for long-term health. In recent years an intense discussion has taken place regarding opportunities for and potential dangers of using nicotine substitution as a harm-reduction approach. Kozlowski et al[3] came to the conclusion that there was no plausible argument against the use of nicotine medications for achieving smoking reduction, and a number of studies have shown that a reduction in cigarette consumption also led to a reduction in expired-air CO levels.[8] Other researchers, however, expressed doubts about the clinical significance of the effects of smoking reduction on intake of harmful substances and health outcomes.[15,16] Only a few authors (eg, Jimenez-Ruiz et al[7]) suggest an improvement in lung function after smoking reduction. Our data indicate that smoking reduction is accompanied by a notable change in the CO level. Although CO level is very dependent on when the last cigarette was consumed, an overall decrease in CO level for the group of reducers confirms a decrease in smoke exposure. The reduction in thiocyanate level (although it is not a reliable biomarker because of high background levels in nonsmokers) is supposed to correlate with a decrease in the intake of other harmful substances. The stable cotinine levels underline the effectiveness of nicotine substitution.

Concurrent gum use and smoking were well tolerated in this study, and the incidence of treatment-related adverse events was generally no greater in the nicotine gum group than in placebo-treated participants. Concurrent gum and cigarette use may result in higher nicotine serum levels than with smoking alone, but data from clinical studies indicate that smoking while using nicotine medications is not associated with increased symptoms of nicotine overdose[17] or other safety issues.[1,4] One laboratory study, in which plasma nicotine levels were artificially raised during concurrent use of 4-mg nicotine chewing gum and smoking, reported no signs of myocardial ischemia during multiple submaximal exercise tests.[18]

A few limitations of this study deserve mention. First, the relatively high attrition rate reflects a problem

Carbon monoxide reduction (%)					*Thiocyanate reduction (%)*					*Cotinine reduction (%)*				
No.	*Mean*	*SD*	*Min*	*Max*	*No.*	*Mean*	*SD*	*Min*	*Max*	*No.*	*Mean*	*SD*	*Min*	*Max*
39	29.3	11.8	15.0	66.0	37	9.4	2.5	1.0	13.8	39	321	124	125	710
55	26.2	10.8	15.0	60.0	53	8.9	2.5	4.5	14.8	53	286	113	131	671
39	26.9†	26.8	−19	93.8	0	—	—	—	—	0	—	—	—	—
55	36.7†	27.4	−24	91.9	0	—	—	—	—	0	—	—	—	—
39	21.2†	34.3	−80	92.4	36	4.3†	20.3	−50	38.9	38	25.4†	26.3	−36	86.3
55	33.9†	39.4	−74	97.3	48	14.9†	27.1	−43	76.5	50	7.2†	37.8	−112	96.0
39	38.4†	42.6	−80	100	35	21.0†	25.0	−23	71.0	36	37.4†	36.2	−18	98.7
55	43.6†	40.5	−53	97.4	48	23.3†	31.4	−55	91.3	52	16.2†	53.0	−149	99.1
39	27.1†	40.5	−45	93.9	33	16.7†	22.8	−42	71.0	36	25.5†	40.0	−37	98.7
55	43.1†	39.3	−48	100	46	20.5†	30.5	−55	80.4	52	31.8†	44.2	−68	99.1

common to most smoking cessation and reduction trials with "healthy" smokers. The most common reasons for attrition in this study included discontinuation for unknown reasons (lost to follow-up) and those who reported not wanting to continue. In the intention-to-treat analyses, these participants are regarded as "treatment failures" even though their smoking status is unknown. Furthermore, this study found no effects of smoking reduction on health outcomes; however, this finding may reflect the difficulty in demonstrating statistically significant improvements in disease-risk biomarkers in a relatively healthy sample. The floor effects and resulting lack of variability that may have resulted from normal-range health parameters may have limited the capacity of these variables to provide useful predictors of treatment outcomes.

Offering smoking reduction as a treatment option engages a broader population of smokers compared with traditional smoking cessation interventions. Furthermore, smoking reduction appears to have a positive influence on the development of the motivation to quit.[19-21] Because current abrupt cessation strategies may not be attractive to discouraged smokers who have repeatedly failed to quit or to smokers who are not ready to quit, smoking reduction may provide a better treatment fit. Moreover, this study provided evidence that smoking-reduction treatment goals indeed help smokers decrease their cigarette consumption. In a harm-reduction context, the potential health benefits of such a strategy may outweigh the potential risks. The exact effect of smoking reduction on morbidity and mortality rates has not been consistently supported in the literature and should be considered in future treatment studies.

An expert group who developed World Health Organization guidelines for the regulation of nicotine replacement in 2001 came to the consensus that ". . .regulators and pharmaceutical companies should withdraw strong warnings against nicotine use and concomitant smoking" and ". . .research should be commissioned into the use of concomitant use of nicotine replacement and smoking among all smokers and particularly those in high risk groups such as patients with smoking related disease."[22] Of course, these WHO guidelines represent only experts' consensus and are not evidence-based. This strengthens the demand for further studies regarding both the efficacy, as determined by real long-term outcomes, and safety.

Further investigations are necessary to determine whether the offer of smoking reduction could impede abstinence-motivated smokers. Another point of interest is whether successful reduction can be maintained during the following years without nicotine substitution or whether nicotine replacement therapy has to be used permanently to guarantee success. Investigations carried out so far have left these questions unanswered. Moreover, the application of harm reduction should be regarded as an alternative solution for smokers who are not able to abstain or are not fully motivated to quit. This approach may be considered for smokers who have not been able to refrain from smoking despite serious health problems.

In conclusion, this study shows that 4-mg nicotine chewing gum can help to reduce smoking, is well

tolerated when used concomitantly with smoking, and promotes smoking cessation, which remains the ultimate goal in the treatment of tobacco dependence.

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