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Slow-release L-Cysteine (Acetium®) Lozenge Is an Effective New Method in Smoking Cessation. A Randomized, Double-blind, Placebo-controlled Intervention

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Abstract. *Background/Aim: Because of the major health problems and annual economic burden caused by cigarette smoking, effective new tools for smoking intervention are urgently needed. Our previous randomized controlled trial (RCT) provided promising results on the efficacy of slow-release L-cysteine lozenge in smoking intervention, but the study was not adequately powered. To confirm in an adequately-powered study the results of the previous RCT implicating that effective elimination of acetaldehyde in saliva by slow-release L-cysteine (Acetium® lozenge, Biohit Oyj, Helsinki), would assist in smoking cessation by reducing acetaldehyde-enhanced nicotine addiction. On this matter, we undertook a double-blind, randomized, placebo-controlled trial comparing Acetium® lozenge and placebo in smoking intervention. Materials and Methods: A cohort of 1,998 cigarette smokers were randomly allocated to intervention (n=996) and placebo arms (n=1,002). At baseline, smoking history was recorded by a questionnaire, with nicotine dependence testing according to the Fagerström scale (FTND). The subjects used smoking diary recording the daily numbers of cigarettes, lozenges and subjective sensations of smoking. The data were analysed separately for point prevalence of abstinence (PPA) and prolonged abstinence (PA) endpoints. Results: Altogether, 753 study subjects completed the trial per protocol (PP), 944 with violations (mITT), and the rest (n=301) were lost to follow-up (LTF). During the 6-month intervention, 331 subjects stopped smoking; 181 (18.2%) in the intervention arm and 150 (15.0%) in the placebo arm (OR=1.43; 95%CI=1.09-1.88); p=0.010). In the PP group, 170 (45.3%) quitted smoking in the intervention arm compared to 134 (35.4%) in the placebo arm (OR=1.51, 95%CI=1.12-2.02; p=0.006). In multivariate (Poisson regression) model, decreased level of smoking pleasure (p=0.010) and "smoking sensations changed" were powerful independent predictors of quit events (IRR=12.01; 95%CI=1.5-95.6). Conclusion: Acetium® lozenge, herein confirmed in an adequately powered study to be an effective means to aid smoking quit, represents a major breakthrough in the development of smoking intervention methods, because slow-release L-cysteine is non-toxic, with no side-effects or limitations of use.*

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Although smoking rates declined in many Western countries during the 1970's-1980's, this trend seems to be leveling off but instead increasing in countries like China (1-3). It is estimated that a) 1.1 billion adults are smokers, and b) smoking causes over 500 billion dollars of economic damage every year, emphasizing an urgent need of effective measures for smoking interventions (3-7). Albeit the risk of lung cancer remains increased for several years after smoking cessation (4, 5, 8, 9), it is gradually decreasing to the level of non-smokers, making cessation meaningful even after long-term smoking (6, 10, 11).

Smoking intervention can be attempted by two principally different approaches; i) with and ii) without assistance by healthcare professionals (12, 13). However, which of the multitude of intervention methods is the most effective remains under dispute (14, 15). Nicotine is the main psychoactive component of tobacco, and addiction develops when nicotine acts on nicotinic acetylcholine receptors in the CNS to release neurotransmitters *e.g.* dopamine (16).

However, smoking dependence is much more complex than simply nicotine addiction (16). Recent experiments suggest that acetaldehyde, the most common carcinogenic compound in tobacco smoke (17, 18), enhances behavioral, endocrine and neuronal responses to nicotine in animals, most likely mediated by harman and salsolinol (19-21). These condensation products of acetaldehyde and biogenic amines (*e.g.* tryptamine) act as MAO-inhibitors and readily pass the blood brain barrier (BBB), being the prime culprits for the lower MAO-activity in the brain of smokers (24). This led to reasoning that cigarette smoke-derived acetaldehyde may increase the addictive potential of tobacco via formation of these adducts (harmans) *in vivo*.

Acetaldehyde can be effectively eliminated by a patented formulation based on slow-release L-cysteine lozenge (Acetium® lozenge, Biohit Oyj, Helsinki, Finland), converting acetaldehyde to inactive MTCA (2-methylthiazolidine-4-carboxylic acid) compound (22, 23, 25). Driven by the novel harman concept (24), we reasoned that elimination of acetaldehyde in the saliva during cigarette smoking by Acetium® lozenge might effectively i) block (or reduce) the formation of harmans, ii) decrease their high blood levels, and iii) by reducing MAO-inhibition, minimize the reinforcing effects of acetaldehyde on smoking dependence.

To assess whether Acetium® lozenge is an effective measure to stop smoking, a randomized, double-blind trial (RCT) was recently conducted (26). The results suggested that the efficacy of Acetium® intervention in assisting smoking cessation was equivalent to that reported for nicotine replacement therapy (NRT) and only slightly inferior to the results obtained by the two most popular medications (bupropion and varenicline) (14). Unfortunately, the study (n=423) was not adequately powered to provide statistical significance to these encouraging results (26).

In the present RCT, the design of the first trial was reproduced (26), now in an adequately powered setting with almost 2000 smokers. The aim was to provide conclusive evidence that elimination of cigarette smoke-derived acetaldehyde in the saliva by slow-release L-cysteine (Acetium® lozenge), would, indeed, be an effective new tool in smoking intervention.

Materials and Methods

Study design. This randomised, double-blind, placebo-controlled trial (RCT) was designed to evaluate the efficacy of Acetium® lozenge intervention as a new means of quit smoking. Active cigarette smokers (all personally motivated to quit) were invited by public invitations to participate in the trial. Different from the first trial (26), an independent research agency (Kuulas, Helsinki) was engaged, taking care of all the practical steps in the study conduction, everything based on an online system with no personal contacts.

All responders to the public invitations were instructed to register in the study website. They were first requested to fill in a structured questionnaire recoding their detailed smoking history and other clinical data pertinent to this study. All those who were considered eligible, were then asked to sign (electronically) a consent to participate. Written signed consents were also accepted as an option. The study design was approved by the HUS (Helsinki University Hospital) Coordinating Ethical Committee (DNo: 84/13/03/00/16, April 12, 2016). The trial is also registered in the https://clinicaltrials.gov/ -database, identifier: NCT02758743.

Study subjects. Between May to October 2016, a total of 2.937 smokers volunteered by responding electronically to the public invitations (3 rounds in different media). Of all those who contacted, 939 never completed the registration and/or consenting process necessary for eligibility assessment. Finally, a total of 1.998 regular cigarette smokers were enrolled. Subjects eligible for the study were current regular smokers (adult women and men), who were motivated to quit smoking, with no limitations in smoking duration and daily cigarettes (pack years). However, the following subjects were considered non-eligible: 1) the individuals who smoked other types of tobacco than cigarettes, 2) those who refused to sign a written consent, 3) those who were not motivated to quit smoking, 4) those who did not commit themselves for not using other interventions during the 6-month follow-up time, and 5) those who used MAO-inhibitor type of antidepressants.

The flowchart of the study is illustrated in Figure 1. The enrolled subjects were randomly allocated into two study arms receiving either Acetium® lozenge (n=996) or placebo (n=1.002), in a double-blind fashion, where both the examiners and the test subjects were blinded to the test substance. For randomization, a random number generator was used, with the block size of 4 and creating unique randomization codes for each subject (https://www.sealedenvelope.com/simple-randomiser/v1/lists). Printed lists (CSV Excel) were sealed and stored in the safety box until opened at study completion (May 2017). Before signing the consent to participate, all subjects received a detailed information of the study and its goals, as well as instructions about the practical conduct. All agreed to use the lozenges (Acetium® or placebo) concomitantly with every single smoked cigarette throughout the whole intervention period, without adopting any other intervention methods. The test lozenges were delivered to each study subjects by regular mail (3 times), in quantities sufficient to satisfy the need of two months of smoking, as determined from their baseline smoking history.

Baseline data. Having consented to participate, each study subject was instructed to fill in an electronically-structured questionnaire to record their detailed smoking history, including the previous attempts of smoking cessation. This questionnaire also includes a more objective estimation of the nicotine dependence, evaluated by using the modified Fagerström Test for Nicotine Dependence (FTND) at baseline (27). Complete recording of the items in the electronic questionnaire was a prerequisite to continue the registration process, and for this reason, these baseline data are complete for the entire cohort of 1,998 smokers (Figure 1).

Follow-up (FU) records by electronic smoking diary. The essential research tool was the electronic smoking diary recorded on daily basis and submitted to the study monitor at the end of each month. This regular submission of the diaries was one of the measures whereby the study monitors controlled the compliance of each subject with the study protocol, accurate recording of the date of

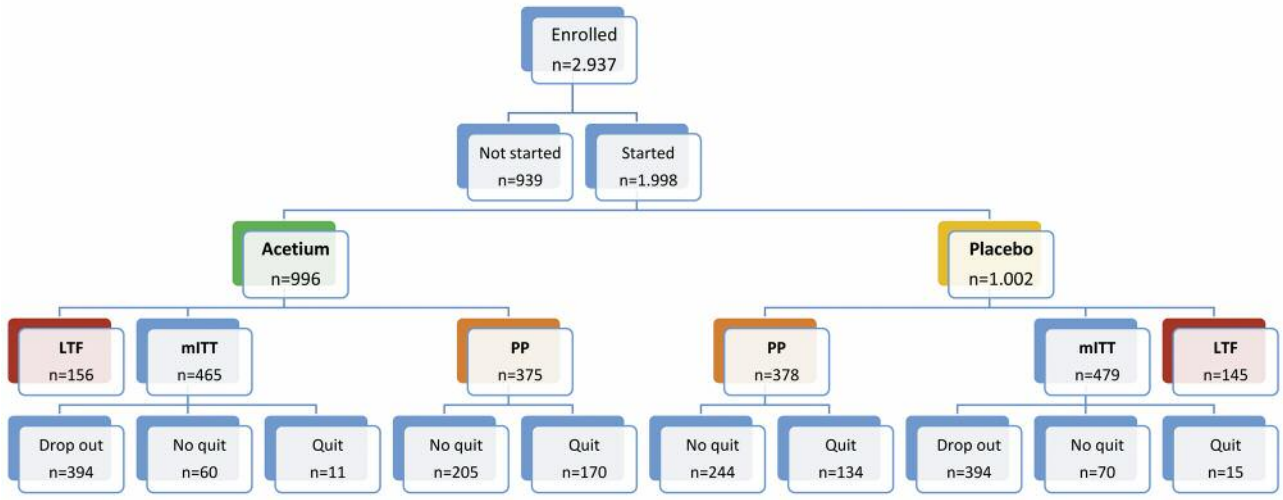

Figure 1. *Flow Chart of the study.*

eventual smoking quit events, violations in the protocol or censoring due to other reasons.

The design and the contents of the smoking diary closely followed those in the first trial (26), except being fully electronic. Apart from the detailed records on the daily numbers of cigarettes smoked and the number of lozenges consumed concomitantly, the test subjects were asked to subjectively assess, how they felt the particular cigarette and estimate the degree of smoking-related sensations of pleasure. The monthly diary ends up with an overall estimation of each month of smoking (monthly conclusion), recording total numbers of cigarettes and lozenges used as well as the summary pleasure scale. Three additional questions of each month were: 1) Any change in your smoking habits? 2) Sensations of smoking changed? 3) Smoking-associated pleasure in the scale 1-10, similar as in the first trial (26).

Fagerström Test for Nicotine Dependence (FTND). Originally introduced in 1978, the latest modification of this test consists of 6 simple questions recording the key variables of the smoker's daily practices (27). FTND has been extensively validated and shown valuable in monitoring the psychological dependence on nicotine. In addition to the baseline testing, FTND was recorded on each monthly smoking diary. For statistical treatment, the FTND scores (1-10) were used as categorical variables: 0-2 (very low), 3-4 (low), 5 (moderate), 6-7 (high), and 8-10 (very high) (27).

Compliance and study endpoints

Lost to follow-up (LTF). Inherent to all longitudinal study designs, lost to follow-up is an inevitable outcome for a proportion of study subjects. In the present trial, this category consists of subjects who terminated the trial due to a wide variety of reasons, including cases who registered, consented and were even randomized, but never truly initiated the trial. Such a group of study subjects with no recordable FU data and outcome measure is not compatible with the data analysis, and in this trial, had to be treated as a compliance category LTF (lost to follow-up). The size of the LTF category was very similar in the Acetium® arm (n=156) and in the placebo arm (n=145), reducing the total number of the study subjects accessible for full data analysis to 1,697 (Figure 1). Following the usual practice for RCTs, the results were analysed separately for the PP and mITT groups.

Per protocol (PP). As usual for RCTs, the two categories of compliance that consist the target of the analysis are: 1) PP (Per Protocol), and 2) Modified Intention to Treat (mITT). The same principles as used in the first trial (26) were also followed in the present study. To be eligible for the PP compliance group, the subjects had to strictly follow the study protocol at all steps. Most importantly, this necessitates a complete series of adequately recorded smoking diaries covering the entire 6-month intervention period (in case with no quit). Alternatively, in cases of smoking cessation, the complete series of diaries preceding the quit was the requirement, including the record of the date of cessation (the quit event) in the last diary. In an otherwise perfect series, one incompletely filled or missing smoking diary was allowed, as far as the study endpoint was clearly recordable from the last diary. The size of the PP compliance category was practically identical in the two study arms, n=375 and n=378, respectively, for the Acetium® and placebo arms (Figure 1).

Modified intention to treat (mITT). Compared to the first trial (26), the criteria of the mITT category followed the same principles, albeit slightly more stringent. The minimum requirement to be eligible for mITT category was a complete series of 4 smoking diaries (*i.e.*, 16 weeks of intervention), for the subjects with no quit. For the subjects with smoking quit, the diary record was judged incomplete enough to justify the inclusion into the PP category. All those who failed to be compliant with the intervention for 16 weeks were classified as dropouts. In such cases, the number of returned diaries varied from 1-3, clearly indicating a failure to comply with the agreed study protocol after randomization. The mITT subjects classified as drop-outs differ from the LTF subjects in that they returned at least one diary (*i.e.*, initiated the trial), instead of no diary returned by the LTF subjects, who never truly initiated the intervention despite having been randomized and received the test lozenges. As shown in Figure 1, the number of mITT dropouts was exactly the same (n=394) in the two study arms.

Primary study end-points. The two most common outcome measures in smoking intervention trials are: 1) prolonged abstinence (PA) and 2) point prevalence of abstinence (PPA) (28, 29). PA, a sustained or continuous abstinence is typically defined as not smoking for a period of months after an attempt to quit. PPA is typically defined as not smoking on the day of concluding the FU. Like in the first study (26), the present results were analysed separately for these two primary study endpoints, using the 2-month cut-off for a positive record of PA (26, 28, 29).

Statistical analysis. All statistical analyses were performed using the SPSS 24.0.0.2 for Windows (IBM, NY, USA) and STATA/SE 14.2 software (STATA Corp., TX, USA). The descriptive statistics was done according to routine procedures. Frequency tables were analysed using the χ^2 test, with the likelihood ratio (LR) or Fisher's exact test for categorical variables. Differences in the means of continuous variables were analysed using ANOVA or a non-parametric (Mann-Whitney) test for two independent samples. The risk estimates of PA and PPA in the two study arms were calculated using conventional univariate regression models, expressed as odds ratio (OR), and their 95% (CI) confidence interval. The data were arranged in the panel format, suitable for analyses with generalized linear models, *e.g.* panel Poisson regression. In this study, the covariates of smoking quit were estimated using population-averaged (PA) Poisson regression model, where study subjects were clustered by their subject-ID, monthly diary as the time variable, and incident quit events (events/person days at risk) as the dependent count variable (26, 30, 31). The results for all covariates were expressed as the incidence rate ratio (IRR) with 95%CI. All covariates recorded at the baseline questionnaire (fixed variables) and all smoking-related variables from the smoking diaries (random variables) were first tested in univariate model. The final multivariate model was adjusted for age and all covariates that were significant in univariate analysis. All statistical tests were two-sided and declared significant at p-value <0.05 level.

While planning this study, calculations were completed using the estimates of the previous trial (26) as the basis of calculating the statistical power. With the obtained effect size in that trial, it was estimated that 786 subjects would be needed in both study arms to make the new trial adequately powered (Type I error 0.05; Type II error 0.80).

Results

Randomization into the Acetium® and placebo arms resulted in groups of 996 and 1,002 subjects, respectively (Table I). Randomization was effective, as indicated by the fact that the two arms were practically identical in most of their smoking history variables. This applies to their mean age, gender balance, compliance with the intervention (PP, mITT, LTF groups), alcohol drinking habits, age of smoking onset, daily smoking habits and regularity, number of previous attempts to quit, type of interventions used for assisting quit, as well as efficacy of the previous interventions (*i.e.*, the longest time of smoking abstinence). The subjects in the placebo arm had experienced previous attempts to quit slightly more often than those in Acetium® arm (p=0.044). Most importantly, the subjects in the intervention and the placebo arm were similar as to their pack years (PY) of smoking; 15.9 and 14.7 PYs, respectively (p=0.057), as well as to their nicotine dependence measured by the FTND score (p=0.318). Interestingly, the vast majority (78.3% and 78.0%, respectively) of smokers in both study arms were categorized as having high or very high nicotine dependence (FTND scores 6-10). Adverse effects reported by the two groups during the intervention were equally rare (p=0.452).

The outcomes of intervention are summarized in Table II, separately for i) the two study arms, for ii) the two compliance groups (PP, mITT), and for iii) the study arms stratified by compliance. The distribution of the 5 outcomes: 1) quit smoking, 2) reduced smoking, 3) no objective effect, 4) moved to another method, 5) dropout, was significantly different in the two arms (p=0.008). Altogether, 3.2% more subjects quitted smoking in the intervention arm (18.2% *vs.* 15.0%) than in the placebo arm, compensated by the higher proportion of those with no effect in the latter (13.6% and 18.3%, respectively). When stratified by the study compliance, significantly more subjects stopped smoking in the PP group than in the mITT group, 40.4% and 2.8%, respectively (p=0.0001).

When analyzed separately, in the PP group, 9.9% more subjects (45.3% *vs.* 35.4%) quitted smoking in the Acetium® arm than in the placebo arm, and the overall outcome profile was also significant (p=0.004). In the mITT group, this difference in the effect size was only 0.7% in favor of the placebo arm, 2.4% and 3.1%, respectively, with no significance in the overall outcome profile (p=0.381).

The primary study end-points (PPA and PA) in the two study arms, and compliance groups (crude and stratified by study arms) are shown in Table III. The probability of PPA in the intervention arm compared to the placebo arm has OR=1.43 (95%CI=1.09-1.88, p=0.010). Also PA is more common in the Acetium® arm (OR=1.26) (p=0.317). As expected, the probability of quit smoking was significantly (p=0.0001) higher in the PP than in the mITT group (OR=23.9), and the same is true for experiencing PA (OR=1.6; NS). In the PP group, Acetium® intervention increased the likelihood of smoking quit significantly (p=0.006) as compared with placebo: OR=1.51, 95%CI=1.12-2.02.

Panel Poisson regression analysis was used to estimate the significant covariates of smoking cessation (Table IV), using the quit event as a count variable recorded in the smoking diaries during FU. In the univariate model, 6 covariates were significant predictors of the smoking quit event: 1) number of previous quit attempts (more attempts more likely to success); 2) pack years (higher number prohibitive); 3) FTND at FU visits (higher scores decrease the likelihood); 4) daily number of cigarettes smoked during intervention (higher number, less likely to quit), 5) pleasure experienced from smoking (high score prohibitive); and 6) subjective sensations of smoking changed/not changed (sensations changed favor quit). When all these significant univariates (together with age) were entered

Table I. *Key characteristics of the study subjects in the intervention and placebo arms.*

Variable		Intervention arm (n=996)	Placebo arm (N=1002)	Significance
Gender	Women	635 (63.8%)	648 (64.7%)	p=0.669
	Men	361 (36.2%)	354 (35.3%)	
Mean age (years±SD)		44.9 (12.1)	44.2 (12.3)	p=0.183
Compliance	PP	375 (37.7%)	378 (37.7%)	p=0.739
	mITT	465 (46.7%)	479 (47.8%)	
	LTF	156 (15.7%)	145 (14.5%)	
Education	Basic school	136 (13.7%)	161 (16.1%)	p=0.477
	Professional training	363 (36.4%)	335 (33.4%)	
	Student examination (no further)	82 (8.2%)	80 (8.0%)	
	High school/technical university	241 (24.2%)	252 (25.1%)	
	Academic degree	174 (17.5%)	174 (17.4%)	
Alcohol intake	Beer	467 (46.9%)	483 (48.2%)	p=0.950
	Wine	262 (26.3%)	254 (25.3%)	
	Liquors	7 (0.7%)	9 (0.9%)	
	Spirits	56 (5.6%)	53 (5.3%)	
	Other (*e.g.* cider, long drink, *etc.*)	204 (20.5%)	203 (20.3%)	
[1]Alcohol weekly dosage (Mean±SD)		6.0 (7.1)	5.9 (7.2)	p=0.719
Age initiated smoking (Mean±SD)		16.1 (4.3)	16.1 (4.4)	p=0.635
Regular smoker since start	No	391 (39.3%)	363 (36.2%)	p=0.162
	Yes	605 (60.7%)	639 (63.8%)	
If not regular, how long (years) regular		23.7 (10.4)	23.1 (10.9)	p=0.442
Smoking habits since initiation	Daily cigarette numbers remained stable	460 (46.2%)	468 (46.7%)	p=0.960
	Daily numbers increased	379 (38.1%)	380 (37.9%)	
	Daily numbers decreased	157 (15.8%)	154 (15.4%)	
Smoking by household members	Yes	509 (51.3%)	515 (51.4%)	p=0.964
	No	487 (48.7%)	487 (48.6%)	
Previous attempts to quit	No	163 (16.4%)	132 (13.2%)	p=0.044
	Yes	833 (83.6%)	870 (86.8%)	
No. of previous quit attempts (Mean±SD)		5.1 (7.8)	4.6 (7.8)	p=0.199
Intervention used for quit attempt	No	351 (35.2%)	331 (33.0%)	p=0.300
	Yes	645 (64.8%)	671 (67.0%)	
Intervention type offered:	NRT	176 (27.3%)	192 (28.6%)	p=0.646
	Electric cigarette	32 (5.0%)	37 (5.5%)	
	Medication	70 (10.9)	76 (11.3%)	
	Assisted by professional	1 (0.2%)	4 (0.6%)	
	Other	280 (56.6%)	309 (54.0%)	
Longest period without smoking (months)		14.3 (27.8)	13.4 (25.7)	p=0.484
Pack years of smoking (Mean±SD)		15.9 (15.2)	14.7 (13.7)	p=0.057
FTND at baseline	0-2	75 (7.5%)	82 (8.2%)	p=0.318
	3-4	60 (6.0%)	51 (5.1%)	
	5	81 (8.1%)	87 (8.7%)	
	6-7	489 (49.1%)	454 (45.3%)	
	8-10	291 (29.2%)	328 (32.7%)	
[2]Follow-Up time (days) (Mean±SD)		92.1 (61.4)	98.8 (63.4)	p=0.027
[3]Adverse effects during intervention	No	1635 (93.5%)	1838 (94.1%)	p=0.452
	Yes	114 (6.5%)	115 (5.9%)	

PP, Per protocol; mITT, modified intention to treat; LTF, lost to follow-up; [1]Glass of wine equivalent; FTND, Fagerström test for nicotine dependence; [2]Follow-up calculated for PP and mITT groups only (n=1,695); [3]Adverse effect reported by the subject at any visit during the follow-up.

in the multivariate Poisson model, 5 independent predictors remain: 1) previous attempts; 2) FTND; 3) daily cigarettes smoked during intervention; 4) pleasure obtained from smoking; and 5) smoking sensations changed. The latter has an impressive IRR=12.01 (95%CI=1.5-95.6).

Discussion

As previously discussed, the theoretical basis for considering the Acetium® lozenge (slow-release L-cysteine) as a potential new method in smoking intervention is highly

Table II. *The study outcomes in the intervention and placebo arms and related to study compliance.*

	Study Outcomes				
Study arm/compliance	Quit smoking	Reduced smoking	No objective effect	Moved to other method	Interrupted the study
*Study arm					
Intervention	181 (18.2%)	115 (11.5%)	135 (13.6%)	15 (1.5%)	550 (55.2%)
Placebo	150 (15.0%)	124 (12.4%)	183 (18.3%)	7 (0.7%)	539 (53.7%)
Total	331 (16.6%)	239 (12.0%)	318 (15.9%)	22 (1.1%)	1.089 (54.5%)
			Significance: p=0.008 (Likelihood Ratio statistics)		
Compliance					
PP	304 (40.4%)	196 (26.0%)	248 (32.9%)	5 (0.7%)	NA
mITT	27 (2.8%)	43 (4.6%)	70 (7.4%)	17 (1.8%)	788 (83.4%)
**Total	331 (18.9%)	239 (14.1%)	318 (18.7%)	22 (1.3%)	788 (46.4%)
			Significance: Significance: p=0.0001 (Likelihood Ratio statistics)		
Study arm by compliance					
PP					
Intervention	170 (45.3%)	98 (26.1%)	103 (27.5%)	4 (1.1%)	NA
Placebo	134 (35.4%)	98 (25.9%)	145 (38.4%)	1 (0.3%)	NA
Total	304 (40.4%)	196 (26.0%)	248 (32.9%)	5 (0.7%)	NA
			Significance: Significance: p=0.004 (Fisher's Exact test)		
mITT					
Intervention	11 (2.4%)	17 (3.7%)	32 (6.9%)	11 (2.4%)	394 (84.7%)
Placebo	16 (3.1%)	26 (5.4%)	38 (7.9%)	6 (1.3%)	394 (82.3%)
Total	27 (2.8%)	43 (4.6%)	70 (7.4%)	17 (1.8%)	788 (83.4%)
			Significance: Significance: p=0.381 (Fisher's Exact test)		

*All enrolled subjects (n=1,998) included; PP, per protocol; mITT, modified intention to treat; NA, not applicable, **LTF subjects (n=301) omitted from analysis.

interesting (26). Acetium® lozenge is a patented formulation based on slow-release L-cysteine, known to effectively eliminate acetaldehyde to an inactive compound (MTCA) (25). In different animal experiments, acetaldehyde has been confirmed to reinforce the effects of nicotine and help maintaining the smoking-dependence by exerting a wide variety of behavioral, endocrine and neuronal responses to nicotine (19-21, 24). These effects take place through mediators called harmans, known to be synthesized as condensation products of acetaldehyde and biogenic amines, *e.g.* tryptamine (33, 34). It was recently proposed that acetaldehyde might increase the addictive potential of tobacco products *via* formation of these amine adducts (24). The concept was tested in a RCT to assess whether elimination of cigarette smoke-derived acetaldehyde in the saliva by slow-release L-cysteine (22, 23) would be an effective means to assist smoking quit (26).

Encouraged by these results (26), we also designed a small pilot study with 11 smokers to measure the levels of harman and norharman in the saliva and serum (35) before and after smoking (with Acetium® and placebo). As previously reported (35), harman and norharman levels in both saliva and serum increased almost immediately after smoking one cigarette. In 6/11 subjects, there was a minor reduction of these levels induced by the Acetium® lozenge, but the difference to placebo was not significant. However, our experiment was not well controlled *e.g.* for the confounding effects of dietary exposure, known to be a major source of harmans (35, 36). Thus, there is no reason to abandon the concept of harmans as mediators of acetaldehyde-induced reinforcing effects on smoking-dependence (24). It might well be that a circumstantial evidence on the validity of this concept is seen in the present study, where the subjective feeling of pleasure obtained from smoking was a powerful prohibitive covariate in smoking quit (IRR=0.60), while reporting "smoking sensation changed" was a powerful trigger of the quit event (IRR=12.01) (Table IV).

The studies on different smoking intervention methods have increased substantially during the past recent years, including reviews and meta-analysis (32, 37, 38). In a recent meta-analysis (14), the following assisted strategies were found to be effective in clinical trials: 1) group behavioral therapy (OR=2.17, 95%CI=1.37-3.45), 2) bupropion (OR=2.06, 95%CI=1.77-2.40), 3) intensive physician advice (OR=2.04, 95%Cl=1.71-2.43), 4) NRT (OR=1.77, 95%CI=1.66-1.88), 5) individual counselling (OR=1.56, 95%CI=1.32-1.84), 6) telephone counselling (OR=1.56, 95%CI=1.38-1.77), 7) nursing interventions (OR=1.47, 95%CI=1.29-1.67) and 8) tailored self-help interventions (OR=1.42, 95%CI=1.26-1.61).

Table III. *The primary study endpoints (PPA, PA) in the intervention and placebo arms and related to study compliance (PP, mITT).*

Study arm/compliance	Primary study endpoints					
	Point prevalence of abstinence (PPA)		Significance (OR; 95%CI)	Prolonged abstinence (PA)*		Significance (OR; 95%CI)
**Study Arm:	Yes	No		Yes	No	
Intervention	181 (40.6%)	265 (59.4%)	1.43 (1.09-1.88)	98 (54.4%)	82 (45.6%)	1.26 (0.81-1.96)
Placebo	150 (32.3%)	314 (67.7%)	p=0.010	71 (48.6%)	75 (51.4%)	p=0.317
#Compliance:						
PP	304 (40.4%)	449 (63.6%)	23.90 (15.77-36.24)	158 (52.7%)	142 (47.3%)	1.61 (0.73-3.60)
mITT	27 (2.8%)	918 (89.3%)	p=0.0001	11 (40.7%)	16 (59.3%)	p=0.315
**Study arm by compliance						
PP						
Intervention	170 (45.3%)	205 (54.7%)	1.51 (1.12-2.02)	93 (55.0%)	76 (45.0%)	1.24 (0.78-1.96)
Placebo	134 (35.4%)	244 (64.6%)	p=0.006	65 (49.6%)	66 (50.4%)	p=0.415
mITT						
Intervention	11 (15.5%)	60 (84.5%)	0.86 (0.36-2.04)	5 (45.5%)	6 (54.5%)	1.25 (0.25-6.02)
Placebo	16 (17,6%)	70 (82.4%)	p=0.830	6 (40.0%)	9 (60.0%)	p=0.781

*Prolonged abstinence (2-month cut-off); **Subjects who interrupted the study (n=1,089) are excluded; #Subjects lost to follow-up (LTF) are excluded; PP, per protocol; mITT, modified intention to treat.

More results on medical treatment (bupropion and varenicline) are available elsewhere (38-40). Superiority of varenicline over bupropion was confirmed in a Cochrane review of 15 studies in 2011 (41). However, both these principal stand-alone medications have serious adverse effects or limitations for use, although tended to be overlooked in the most recent literature (42). Another clear trend seems to be that the efficacy of varenicline alone or in combination (with NRT or bupropion) is no longer at the same level (OR >2.0) as reported earlier (14, 43, 44). While assessing the efficacy and safety of the varenicline and bupropion combination, the authors found 4 studies including 1,193 patients (43). Of the prospective trials, one displayed a greater 4-week smoking abstinence for weeks 8-11 with combination (39.8%) *vs.* monotherapy (25.9%) (OR=1.89, 95%CI=1.07-3.35), and the other demonstrated greater PA at 12 weeks (OR=1.49, 95% CI=1.05-2.12)(43). In another meta-analysis, both the early and late outcomes were favorable for the varenicline & NRT combination (OR=1.50, 95%CI=1.14-1.97; and OR=1.62, 95%CI=1.18-2.23, respectively) (44).

In this scenario, it is obvious that the best available methods for smoking intervention (or their combination) can reach the success rates with OR slightly above 2.0 (at best), while most of the studies report ORs in the range of 1.5 (14, 32, 38-44). This level of success rate was already reached in our first RCT, where Acetium® lozenge proved to increase the likelihood of smoking quit at OR=1.65 in the PP group (26). Unfortunately, the cohort size (n=423) was not large enough to confer the results a statistical significance, and for this reason, the previous study was reproduced in a larger cohort of 1,998 smokers, as reported in this communication. In principle, the present study follows the same design as the original RCT (26), except for the larger cohort size.

However, there are some important differences between these two trials that deserve discussion to facilitate comparing the results of these two trials. These differences are related to both the practical conduction of the intervention and to the composition of the enrolled cohort itself. To start with the former, the present trial was completed entirely by using the website approach, with no face-to-face contacts between the researchers and the study subjects. This is the main difference to the first trial, where all study subjects were met in person by the study monitors both at baseline and during the intervention period, while returning their monthly diaries and received the next dosage of the test remedies. On the same occasion, they completed the FTND and CO- measurement. They were preserved the possibility of contacting the monitors at any time, and also the reverse happened when the monitors contacted the study subjects as soon as they noticed any irregularity in the return of monthly diaries. Inevitably, these personal contacts served the purpose of personal support and motivation to the subjects to maintain compliance (26). This type of personal communication was missing in the new trial where all steps were completed through the website and/or e-mails, and test remedies were delivered by mail.

Table IV. *Predictors of smoking quit* in panel Poisson regression[1] run in univariate mode and adjusted for all significant univariates.*

Covariates	Quit of smoking (event/FU diary)					
	Crude IRR	95% CI	*p*-Value	@Adjusted IRR	95% CI	*p*-Value
Age at study entry (cont.)	0.99	0.99-1.00	0.656	1.05	0.95-1.17	0.301
Intervention (intervention=ref)	0.82	0.67-1.01	0.055			
Gender (women=ref)	1.00	0.82-1.33	0.945			
Education (basic=ref)	0.99	0.92-1.06	0.799			
Alcohol type preferred (beer=ref)	0.98	0.92-1.05	0.662			
Alcohol weekly dose (cont.)	0.98	0.97-1.01	0.064			
Age initiated smoking (cont.)	1.01	0.99-1.03	0.139			
Regular smoker since start (no=ref)	0.98	0.80-1.20	0.893			
Smoking habits since initiation (stable=ref)	1.06	0.92-1.22	0.380			
Attempts to quit (no=ref)	1.22	0.90-1.65	0.189			
Number of previous attempts to quit (cont; low ref)	1.01	1.01-1.02	0.0001	1.02	1.01-1.04	0.0001
Intervention ever used for quit attempt (no=ref)	1.10	0.89-1.35	0.377			
Type of intervention (personal=ref)	NC	NC	NC			
Longest ever period without smoking (cont.)	1.01	0.99-1.01	0.142			
Pack years of smoking (cont.) (higher prohibitive)	0.98	0.98-0.99	0.036	0.96	0.90-1.02	0.218
FTND at FU visits (graded; 0-2 ref)	0.19	0.06-0.57	0.003	0.24	0.08-0.72	0.010
Adverse effects during intervention (no=ref)	0.99	0.22-1.43	0.665			
Cigarettes per day during intervention (cont.) (higher prohibitive)	0.80	0.77-0.83	0.0001	0.89	0.82-0.97	0.009
Pleasure obtained from smoking (scale 1-10) (cont.) (high prohibitive)	0.44	0.30-0.65	0.0001	0.60	0.41-0.88	0.010
Sensations of smoking changed during intervention (no change=ref)	13.24	1.66-105.73	0.015	12.01	1.50-95.56	0.019

*Count outcome (quit event), as defined by the quit event reported in the smoking diaries during intervention; [1]Population average (PA) model, clustered by subject ID number, monthly diaries (FU visit) as the time variable, exchangeable within-group correlation structure, 95%CI calculated by robust estimation; @adjusted for age and all other significant covariates of smoking quit in univariate model; IRR, incidence rate ratio; cont., continuous variable; ref., reference value; NC, non-calculable (too many options).

This basically different study logistics had an inevitable consequence that the study cohort in the first trial was enrolled exclusively from the capital city (Helsinki) region, in contrast to the present study, where the smokers were derived from all parts of the country. Another major consequence of the missing personal support is seen in the compliance of the study subjects in the current trial (Figure 1). While only 79 (18.7%) of the 423 enrolled subjects in the first trial were lost to follow-up, 939/2,937 (31.9%) of those who volunteered in the current trial never started, 301/1.998 (15.1%) of those who were randomized were lost to follow-up (with no single diary returned), and in addition, 788/1,697 (46.4%) of those remaining in the two arms interrupted the study (dropouts). At the end, 909/1.998 (45.5%) of the originally randomized subjects completed the study either according to PP or mITT criteria, which is in sharp contrast to 344/423 (81.3%) of the first trial (26).

This different origin of the study subjects (capital region *vs.* whole country) also has some bearing to the composition of the final cohort (Table I). Compared to the first trial (26), the present study attracted more women. The present study also included markedly more those with academic degree, at the expense of those with high school training (26). Despite the fact that the mean age of the participants was practically identical in the two trials, there was a substantial difference in: 1) the total pack years (PY), and 2) the nicotine dependence measured by the FTND. The mean PYs in the present study was 5 years higher than in the first trial: 15 *vs.* 10 (Table I) (26). The age at onset of smoking being practically the same (around 16 years), the subjects in the present trial were more heavy smokers and also had a higher nicotine dependence. While 78.3% and 78.0% of the subjects in the Acetium® and placebo arms, respectively, had high or very high nicotine dependence in the present study (Table I), the corresponding figures in the first trial were only 45.2% and 41.7%, respectively (26).

Undeniably, the present trial had seemingly unfavorable prospects to success: 1) lack of personal support to the study subjects resulted in poor compliance, and 2) enrichment in both study arms of heavy smokers, with high or very high nicotine dependence. Against this background, the present results must be considered outstanding. Most importantly, among these heavy smokers who completed the study according to PP criteria, the users of Acetium® lozenge had an OR=1.51 (95%CI=1.12-2.02) (p=0.006) to quit smoking compared to placebo (Table III). Even if the study compliance (PP, mITT) is not considered, the likelihood of smoking cessation in the Acetium® arm had OR=1.43, which also reached statistical significance (p=0.010).

In the present study, the absolute difference between Acetium® and placebo arms in quit rate is 3.2%, the placebo effect being 15.0% (Table III). This is comparable to the rates reported in most intervention studies (14, 38-44), including our first trial (26). Accordingly, if a random sample of smokers are subjected to intervention with placebo, 15% succeed in smoking quit within 6 months, as compared with 18.2% with Acetium® intervention. This, however, does not take into account the study compliance (PP, mITT) and dropouts that certainly have a major impact on the efficacy (28, 29). Once optimally conducted according to PP, the success rate with placebo is much higher, *i.e.*, 35.4% in this study, and the difference to Acetium® intervention increased to 9.9% (Tables II and III). These quit rates (35.4% and 45.3%) are fully comparable with those reported in equivalent studies with NRT and current medication (varenicline, pubropion) (14, 32, 38-44). While using the RR (relative risk) analysis to calculate the NNT (number needed to treat) parameter, these figures translate to NNT of 10.1 (PP group only) and to 12.1 (PP and mITT). Accordingly, 10 and 12 people, respectively, need to use Acetium® intervention for one smoker to benefit (=quit). Using these data in the PP group, we can also calculate the population excess risk, which is 0.337 (33.7%) for Acetium intervention, and the population attributable fraction of 0.153 (15.3%). In lay terms, this means that 33.7% extra quit rate can be attributed to Acetium® intervention, while 15.3% is the proportion of new quits encountered in the smoking population attributable to this intervention.

Like in the first trial, we also analyzed the significant covariates of smoking quit using Poisson regression in univariate and multivariate mode (Table IV). The results confirm the key observations in the first trial (26), and also disclose a number of additional covariates that are significant in both univariate and multivariate analysis. Given that smoking quit is a complex issue, all of these covariates are quite rational in predicting the quit events. Thus, 1) number of previous quit attempts increases the success rate; 2) higher pack years decrease the likelihood of quit; 2) high scores in the FTND test (during intervention) are strongly prohibitive (IRR=0.19) for quit; 4) higher number of daily cigarettes make the quit more difficult; 5) high level of personal pleasure obtained from smoking makes quit less likely (IRR=0.44), and finally 6) reporting the sensations (taste, smell) of smoking changed during intervention is a powerful trigger of quit (IRR=13.24). Of these 6 variables, only the pack year (PY) loses its significance in multivariate model. It is tempting to speculate that the Acetium® lozenge is such a powerful trigger of smoking quit because: i) it decreases the subjective pleasure obtained from smoking, and ii) it makes the cigarette taste and smell different (unpleasant). Whether these effects are being mediated by the reduced levels of harmans, as recently suggested (19, 21-24, 26), remains to be demonstrated in carefully designed measurements of the salivary and serum levels of harmans.

Taken together, the present RCT with adequate statistical power confirms the results of the first trial (26), implicating that Acetium® lozenge is an effective new method in smoking intervention. The quit rate achieved in the intervention arm following the PP criteria (OR=1.5) favorably competes with the efficacy reported for NRT and currently available medication (14, 38-44), far exceeding the results of non-assisted and other assisted methods (12, 32). Being devoid of any side-effects, with no maximum dosage or other limitations of use, Acetium® lozenge represents a breakthrough in the development of smoking intervention methods. The feasible mechanism of action still remains to be elucidated, but the effect seems to be related to decreased levels of smoking-associated pleasure and changed subjective sensations of the smoked cigarette.

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