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Review

Slow-release L-cysteine Lozenges in Smoking Cessation: Meta-analysis of Two Randomized Controlled Trials

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Abstract

Background/Aim: The hypothesis that elimination of cigarette smoke-derived acetaldehyde in the saliva by slow-release L-cysteine would eliminate acetaldehyde-enhanced nicotine addiction among smokers has been tested in two randomized controlled trials (RCT) using Acetium® lozenge (Biohit Oyj, Helsinki, Finland). Both RCTs showed a similar direction and magnitude of the effect size, but only the larger study was adequately powered to reach statistical significance.

Materials and Methods: The two published RCTs on Acetium® in smoking intervention included in this formal meta-analysis include: a cohort of 423 cigarette smokers, randomly allocated to intervention (n=212) and placebo arms (n=211) in Study 1, as well as a cohort of 1,998 smokers, with 996 and 1,002 subjects in the intervention and placebo arms, respectively, in Study 2. Both studies analyzed the results for intention-to-treat (ITT) and per protocol (PP) compliance groups. Random-effects (RE) meta-analysis was used to compute the summary effect size.

Results: In the ITT group of Study 1, Acetium® was more effective than placebo, with OR=1.48 (95% CI=0.87-2.54), and in Study 2, the respective OR=1.26 (95% CI=0.99-1.59). In the PP groups, the success rates in both studies were better: OR=1.65 (95% CI=0.75-3.62) and OR=1.51 (95% CI=1.12-2.02), respectively. In RE meta-analysis, the summary estimates of Acetium® efficacy were statistically significant in both the ITT (n=2,421) and PP (n=863) analysis: OR=1.29 (95% CI=1.04-1.60, p=0.018) and OR=1.53 (95% CI=1.16-2.01, p=0.0025), respectively.

Conclusion: Although meta-analyses with a limited number of studies should be interpreted with caution, these data provide clear support to the concept that Acetium® lozenge significantly (1.5-fold) increases the likelihood of successful smoking cessation as compared to placebo.

Keywords: Smoking intervention, slow-release L-cysteine, lozenge, randomized controlled trial, meta-analysis, review.

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Introduction

Nicotine is the key psychoactive component of tobacco smoke (1). Particularly adolescents seem to be highly sensitive to the rewarding effects of nicotine and prone to develop nicotine dependence. Addiction develops when nicotine acts on nicotinic acetylcholine receptors in the central nervous system (CNS) releasing neurotransmitters, like dopamine, glutamate and gamma-aminobutyric acid (1). It is known, however, that smoking dependence is much more complex than simply nicotine addiction.

Animal experiments suggest that acetaldehyde, the most common carcinogenic compound in cigarette smoke (2, 3), enhances endocrine, neuronal and behavioral responses to nicotine, most likely mediated by the condensation products of acetaldehyde and biogenic amines (4-6). These condensation products (*e.g.*, harman, nor-harman and salsolinol) act as MAO-inhibitors, being the prime culprits for the lower MAO-activity found in the brain of regular smokers (7). These experiments gave rise to the idea that cigarette smoke-derived acetaldehyde may increase the addictive potential of smoking via formation of these adducts also in human smokers (4-7).

Fortunately, acetaldehyde can be effectively eliminated by a patented (8) formulation based on slow-release L-cysteine lozenge (Acetium® lozenge, Biohit Oyj, Helsinki, Finland), converting acetaldehyde to the inactive MTCA (2-methylthiazolidine-4-carboxylic acid) compound (9-11). Captivated by this novel concept (7), we hypothesized that an effective elimination of acetaldehyde in the saliva during cigarette smoking by L-cysteine lozenge might effectively i) block (or reduce) the formation of harmans, ii) reduce their blood levels, and iii) by reducing MAO-inhibition, counteract the reinforcing effects of acetaldehyde on nicotine dependence.

This hypothesis was tested in human smokers by two placebo-controlled, randomized trials (RCT) (12-14). Unfortunately, the first of these trials, with 423 study subjects, was not adequately powered to give a statistically significant effect size (12). The second RCT with 1,998 smokers was adequately powered and confirmed Acetium® lozenge to be an effective new tool supporting smoking cessation nicotine-free (13, 14).

No additional clinical trials with Acetium® lozenge have been conducted, are underway or planned, justifying the generation of evidence by other approaches. One possible approach is to perform a meta-analysis of the published RCTs (12-14), to assess whether the summary estimates for Acetium® efficacy in smoking cessation reach statistical significance. The consistent positive direction and parallel magnitude of the effect size (OR between 1.51 and 1.65) in these two RCTs (12-14) suggest a genuine treatment benefit of Acetium® lozenges in supporting smoking cessation.

Materials and Methods

Study subjects. In the current situation, where only two published RCTs of interest are known to exist, it was not necessary to go through all the steps that a systematic review and the literature search for meta-analyses are expected to include (15). Accordingly, the present meta-analysis includes only the two existing RCTs (here labelled as Study 1 and Study 2), in which the efficacy of Acetium® lozenge in smoking intervention was compared in a double-blind, placebo-controlled randomized design (12, 13).

Design of the original studies. In Study 1, a cohort of 423 current cigarette smokers were enrolled between December 2013 and April 2015 (11). The enrolled participants were randomly allocated into two study arms receiving either Acetium® lozenges (n=212) or placebo (n=211), in a double-blind setting. Before enrolment, all participants signed a written consent and agreed to use the lozenges (Acetium or placebo) concomitantly with every single smoked cigarette throughout the whole intervention period (12). Each study participant was requested to fill in a structured questionnaire also including an estimation of their nicotine dependence, evaluated by the modified Fagerström Test for Nicotine Dependence (FTND) at baseline (16).

The description of the study conduction, including the randomization and monitoring by daily smoking diary, repeated FTND as well as study compliance (PP, ITT) have been detailed in the original report (12). The two most common outcome measures in smoking intervention trials are: i) prolonged abstinence (PA) and ii) point prevalence of abstinence (PPA) (17). In this study, the results were analyzed separately for these two primary endpoints, using the 2-month cut-off for a positive record of PA (12).

In Study 2, a total of 2,937 smokers volunteered to participate by responding electronically to the public invitations between May to October 2016 (13). Finally, a total of 1,998 regular cigarette smokers were enrolled in the trial and randomly allocated into two study arms receiving either Acetium® lozenges (*n*=996) or placebo (*n*=1,002), in a double-blind fashion (13). All agreed to use of the lozenges throughout the whole intervention period and refrained testing any other intervention methods. Nicotine dependence was monitored by the FTND (16).

Different to Study 1 (on-site visits), the whole monitoring of this study was done electronically, including the baseline questionnaire and follow-up (FU) records by electronic smoking diary, as explained in the original report (13). As to the subjects' compliance, the original report used three categories: i) lost to follow-up (LTF), 2) per protocol (PP), and 3) modified intention to treat (mITT) (13). Later, however, there has been an increasing demand of including in the analysis of the RCTs all the study subjects who have been originally randomized (18). This is called as intention to treat (ITT) analysis, which is considered equally important as the PP analysis (18). Because of this, the description of the study compliance was subsequently modified in an addendum (14) submitted to complement the original report (13), calculating the Acetium® efficacy data for the ITT group as well (14). Similarly to Study 1, the efficacy results in Study 2 were analyzed separately for the two primary study endpoints (PA, PPA) (17), using the 2-month cut-off for a positive record of PA (13). In this meta-analysis, only the data on PPA are given in Tables and Figures, following the reporting practice of the original studies (12-14).

Statistical analysis. For statistical analyses both SPSS 29.0.2.0 for Windows (IBM, Armonk, NY, USA) and STATA/SE 18.0 software (STATA Corp., College Station, TX, USA) were used. Using the data of the two original studies, the file (SPSS format) was re-arranged to make it suitable for meta-analysis by STATA. Two groups were formed (A & B). In Group A (Acetium® intervention), the data include success for treatment, and failure for treatment. Similarly, in Group B (Placebo), the data include success for placebo and failure for placebo. To conduct the meta-analysis by STATA, the SPSS file was saved in the STATA format. The meta-analysis was performed following the software guidelines (19). To calculate the summary estimates (pooled results), the random effects (RE) model was used, with the restricted maximum likelihood method (REML) to calculate the exponential effect sizes (odds ratio; OR), with 95% confidence intervals (CI). Forest plots were drawn up using the same settings (REML, OR). Study heterogeneity was tested using both Galbraith plot and L'Abbe plot for binary data. Data were also tested for eventual publication bias using funnel plots with Begg, Eggers, and fill-and-trim tests for small study effects (19). All these analyses were repeated separately for the PP group and ITT group of study compliance. The significance levels ($p<0.05$) are indicated where appropriate.

Results

Table I depicts the efficacy indicators (success and failure) of the two study arms in both studies, both in the ITT and PP analysis. The two studies differ considerably in their cohost size, but the success rates for Acetium® intervention are remarkably similar: 17.9% and 18.2% in the ITT group, and 42.9% and 45.3% in the PP group of Study 1 and Study 2, respectively. These figures were used in the meta-analytic calculations for two group comparison of binary data.

Figure 1 is the forest plot for the summary effect size estimate of Acetium® intervention in the ITT analysis. The ITT group comprises all study subjects originally randomized in Study 1 (*n*=423) and Study 2 (*n*=1,998), irrespective of their compliance with the study protocol.

Table I. *The efficacy indicators* for Acetium® intervention and placebo in the two studies stratified by the compliance groups PP and ITT.*

Study (Ref)	Compliance Group/No Cases	Acetium®		Placebo	
		Success	Failure	Success	Failure
Study 1 (12)	ITT (*n*=423)	38	174	27	184
	PP (*n*=110)	21	28	19	42
Study 2 (13)	ITT (*n*=1.998)	181	815	150	852
	PP (*n*=753)	170	205	134	244

*PPA, point prevalence of abstinence; PP, per protocol; ITT intention to treat.

The summary (pooled) effect size is statistically significant: OR=1.30 (95% CI=1.04-1.61).

The forest plot for the pooled efficacy estimate for Acetium® intervention in the PP group is shown in Figure 2. The PP group in both studies includes only the study subjects who completed the whole study according to the study protocol, including all control visits and return of all smoking diaries: 110 and 753 subjects in Study 1 and Study 2, respectively. The summary effect size is statistically significant: OR=1.53 (95% CI=1.16-2.01).

We also tested the REML estimator for τ^2 with Knapp-Hartung adjusted CI. In both ITT and PP analysis, the adjusted CIs are wider: OR=1.30 (95% CI=0.59-2.82, *p*=0.147), and OR=1.53 (95% CI=1.04-2.25, *p*=0.046). respectively. The conventional graphic evaluation of between-study heterogeneity is shown by the Galbraith plot for the ITT group in Figure 3. Albeit of limited relevance in a two-study meta-analysis, the plot shows that both studies fall within the 95% confidence area (close to the regression line), formally interpreted to indicate lack of heterogeneity across the two studies. Figure 4 shows a similar analysis for the PP group, again with no evidence of heterogeneity.

Funnel plots to test for eventual publication bias are presented in Figure 5 (ITT group) and Figure 6 (PP group). The funnel plots were accompanied by the conventional tests for publication bias (Begg, Eggers, and fill-and-trim test). None of these tests indicated any publication bias, consistent with the two funnel plots.

Discussion

The present study was undertaken to provide additional support to the results reported in two original RCTs, suggesting that slow-release L-cysteine is an effective new tool in assisting the smokers to quit (12-14). The results in both studies were very similar, implicating that among the smokers who completed the trial according to the PP compliance, the OR for smoking cessation (point prevalence of abstinence) varied between 1.51 to 1.65. The higher OR was obtained in the first RCT which was smaller in its sample size (*n*=423) and unfortunately proved to be inadequately powered to reach statistical significance to this OR (12). In the larger study (*n*=1,998 smokers), however, the OR for smoking cessation was 1.51 (95% CI=1.12-2.02) and was statistically significant (*p*=0.006) (13). It was of interest to see, whether the meta-analytical approach would yield a significant summary effect size (Acetium® efficacy) when both studies are included in a RE meta-analysis (19). Indeed, this proved to be the case, when the summary estimates of Acetium® efficacy were statistically significant in both the ITT (*n*=2,421) and PP (*n*=863) groups: OR=1.29 (95% CI=1.04-1.60, *p*=0.018) and OR=1.53 (95 CI%=1.16-2.01, *p*=0.0025), respectively. This data translates to risk ratios (RR) and risk difference as follows: in the ITT group, RR=1.24 (95%CI=1.03-1.48, *p*=0.019), and the risk difference is 3.5% (18.1%-14.6%), with the number needed to treat, NNT=28 (95% CI=15-168). In the PP group, the respective numbers are RR=1.29 (95% CI=1.09-1.52, *p*=0.0024), and the risk difference is 10.2% (45.0%-34.8%), with the NNT=10 (95% CI=6-27). In other words, in the ITT group one needs to treat 28 smokers to get one extra quitter, whereas in the PP group, this number is only 10 smokers.

The question arises: how to interpret these data based on a meta-analysis of two studies only? In a setting where only two studies are included in a meta-analysis, several methodological aspects need to be considered, including feasibility, statistical limitations and interpretation of the data (20-22). Regarding feasibility, it is statistically

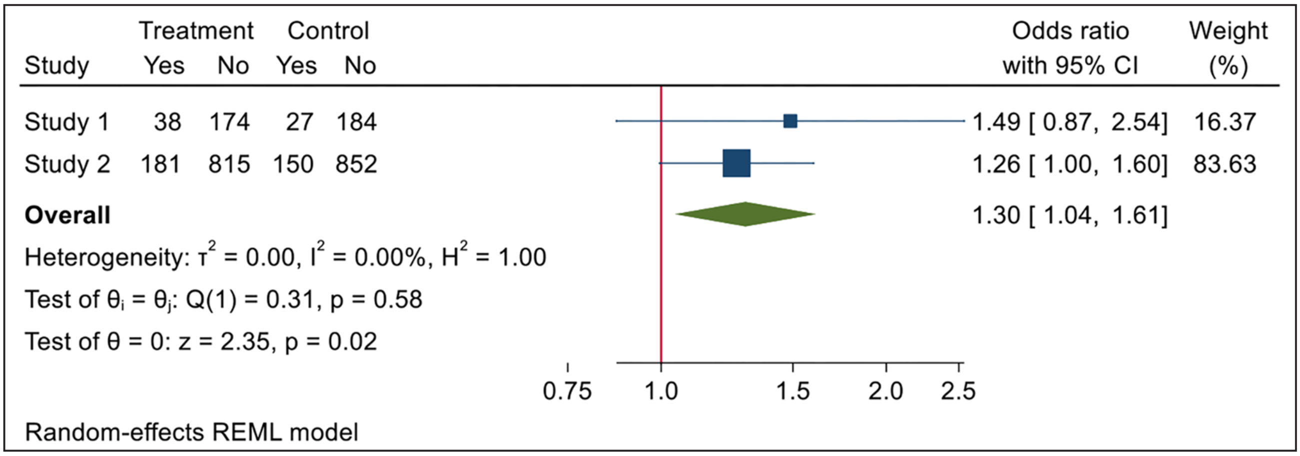

Figure 1. *Forest plot for the summary effect estimates* of Acetium® intervention in the intention-to-treat (ITT) group. *PPA, Point prevalence of abstinence.*

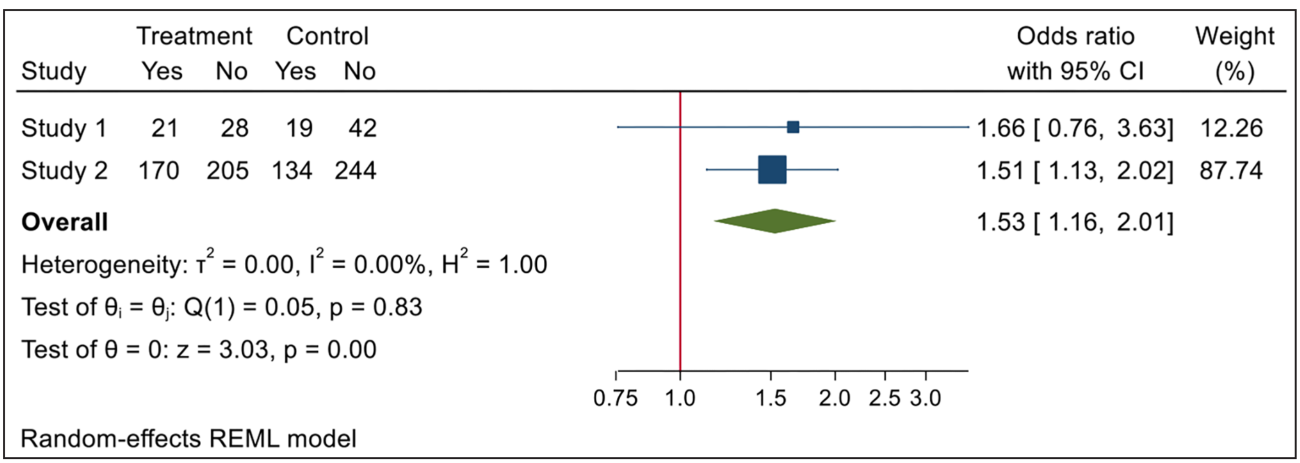

Figure 2. *Forest plot for the summary effect estimates* of Acetium® intervention in the per protocol (PP) group. *PPA, Point prevalence of abstinence.*

permissible to perform a meta-analysis with only two studies (19, 21, 22). Modern meta-analytical techniques (both fixed- and random-effects models) (19) can compute a pooled estimate from as few as two data points, provided that: 1) the studies are comparable in their i) design, ii) population, iii) intervention, iv) control, and v) outcomes, and 2) the effect size and its variance (95% CI) are available for each study (20-23).

All these conditions are fulfilled in the present setting, where the two studies of interest (12, 13) are practically identical in their design, *i.e.*, double-blind, randomized placebo-controlled trials using a population-derived cohort of active cigarette smoker volunteers (12, 13). The only difference is the study execution; while the first one was based on personal, on-site monitoring (12), the latter was conducted fully electronically (13). Yet, the key results of both studies were practically identical, including the results of the multivariate analysis for the significant co-variates of smoking quit (12, 13). As to the study population, both RCTs included only cigarette smokers who volunteered to participate in the trial and committed themselves to adhere to the study protocol

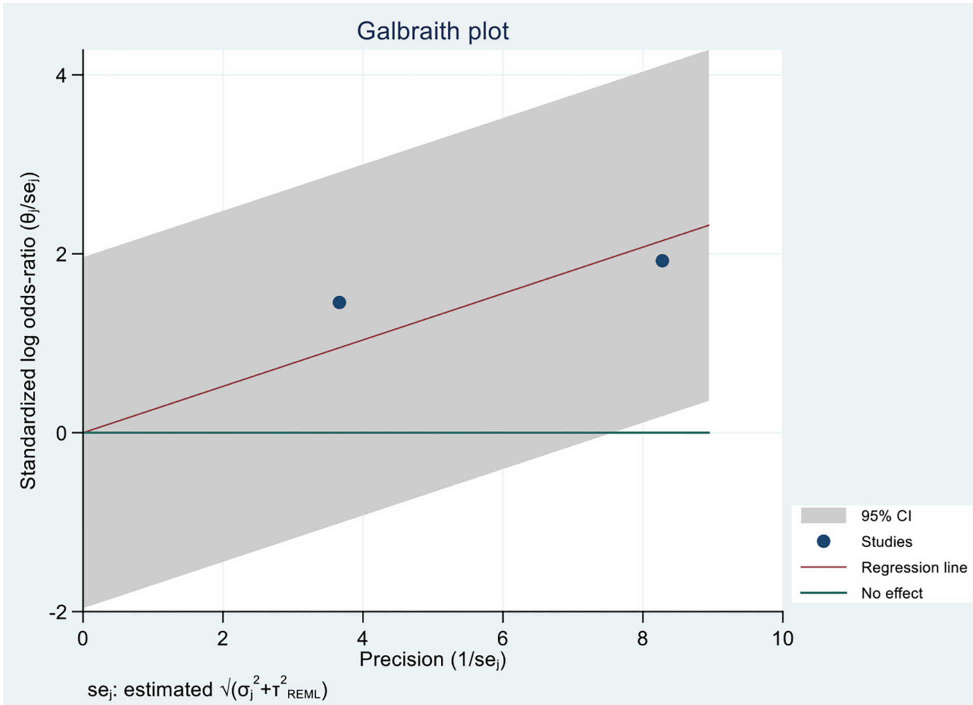

Figure 3. *Study heterogeneity evaluated by Galbraith plot in the intention-to-treat (ITT) compliance group.*

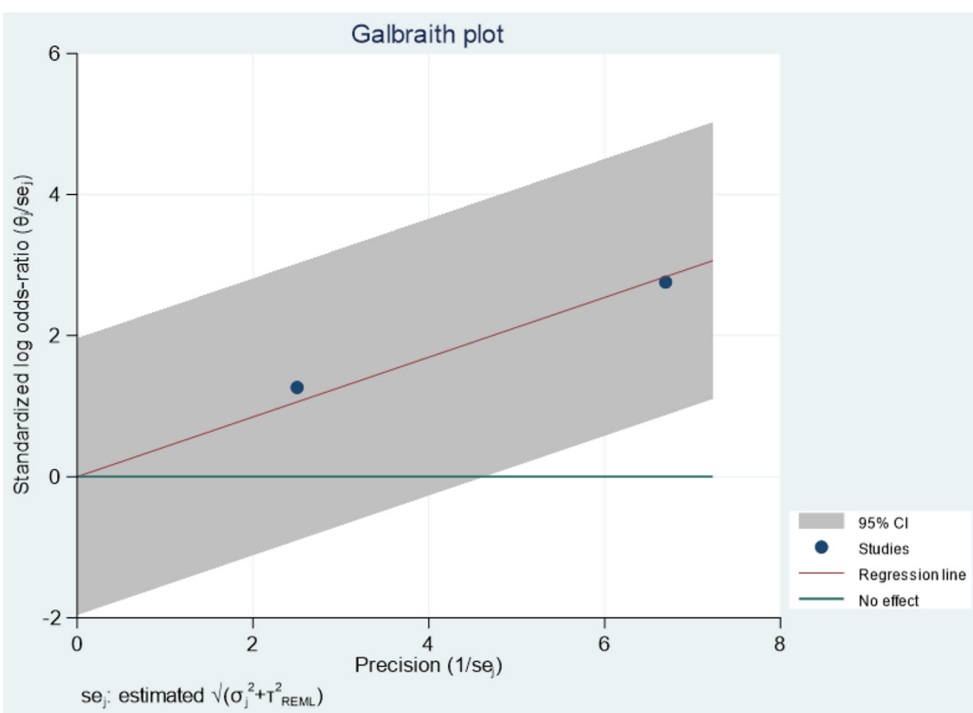

Figure 4. *Study heterogeneity evaluated by Galbraith plot in the per protocol (PP) compliance group.*

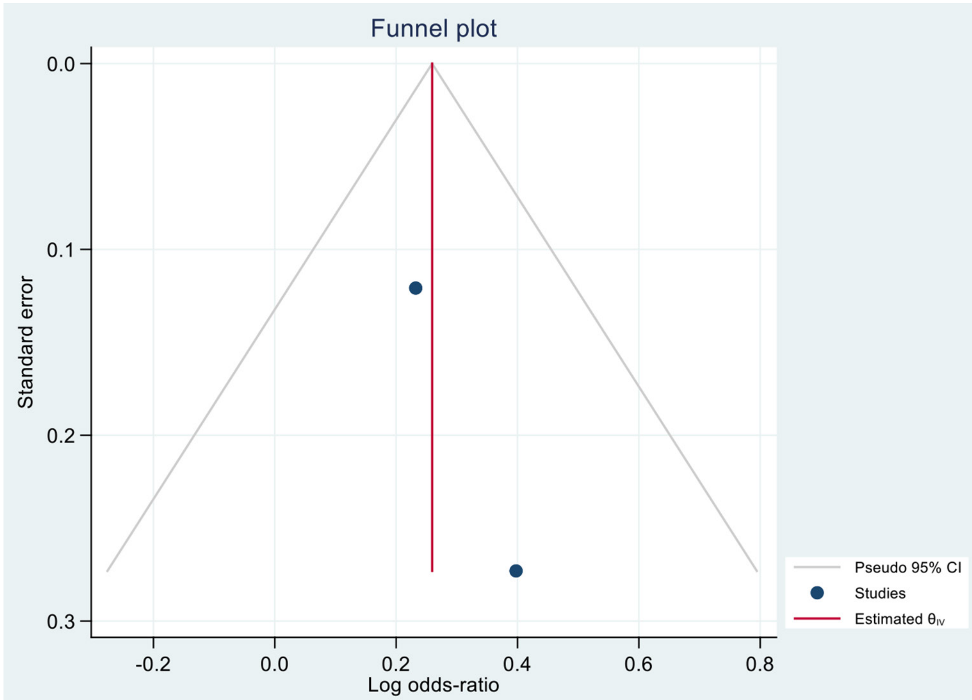

Figure 5. *Funnel plot for the eventual publication bias in the intention-to-treat (ITT) analysis.*

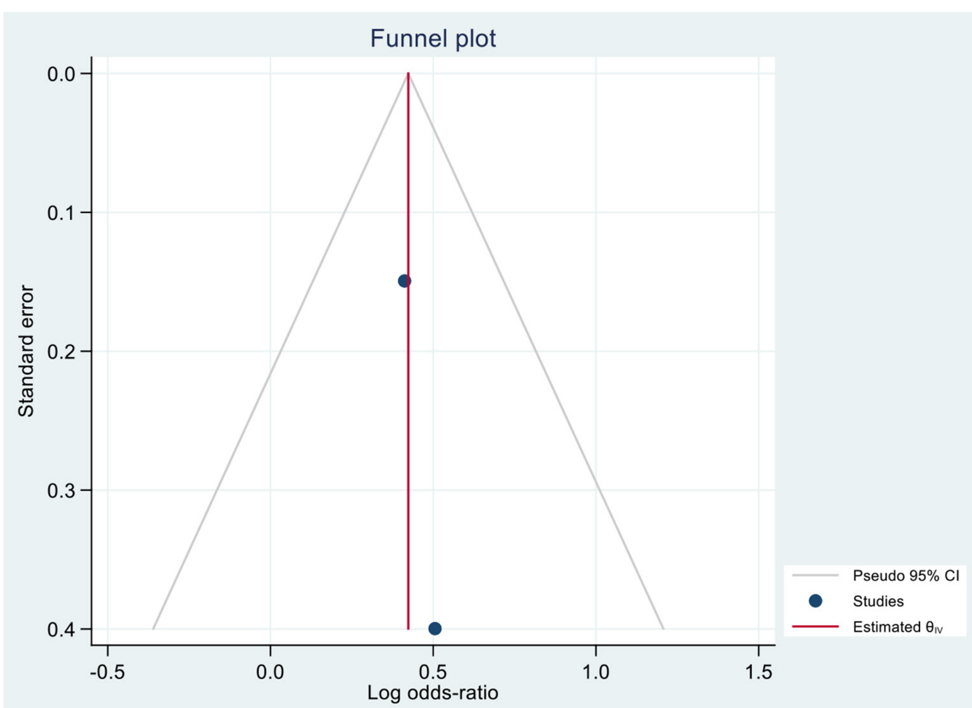

Figure 6. *Funnel plot for the eventual publication in the per protocol (PP) analysis.*

(12, 13). The only difference between the two studies was in how the study subjects were recruited. In the first study (12), the invitations included different media (mostly newspaper announcements), whereas in the latter (13) only electronic media were used. As to the intervention, this was exactly the same in both studies, using the same preparations for Acetium® lozenge with the same mode of administration, *i.e.*, one lozenge used in context with every smoked cigarette (12,13). As to the control, the same placebo preparation (a lozenge) was used in both studies, specially manufactured for this purpose. Importantly, the control group was randomized, double-blinded to the study subjects and study monitors and only disclosed after the completion of the trial (12, 13). Thus, there were no dissimilarities in the controls between the two studies. Finally, the outcomes of both studies were recorded similarly, using the same primary endpoints (PA and PPA), recorded separately for all randomized subjects (ITT group) and for those completing the study per protocol (PP group) (12-14).

As to the prerequisite for effect size and variance, this condition was also perfectly matched in these two RCTs, reporting the key results in an identical manner in the original reports (12, 13), and supplemented later by an addendum to report the ITT group (14). The effect size in both RCTs was very similar, including the variance (95% CI) within narrow limits. Accordingly, these critical points are in good control, and this two-study meta-analysis can be considered valid, as it was done transparently and the results interpreted with caution (20-22). In this meta-analysis including two studies only, also the use of Knapp-Hartung (also known as Sidik-Jonkman) method (KH) could be considered to provide adjusted CIs for the pooled effect (19). KH method is considered to improve the accuracy of the CI when the i) number of studies is small or ii) between-study heterogeneity (τ^2) is substantial. In this analysis, only the first is true (two studies), whereas the study heterogeneity is non-existent (see below). Because KH adjusts the standard error (SE) and uses a t-distribution instead of a normal distribution, it will produce wider CIs than those estimated by the traditional DerSimonian–Laird (DL) RE method (19). Indeed, this was the case in the present analysis, for both the ITT and PP groups, and in fact, the effect size in the ITT group lost its significance (OR=1.30; 95% CI=0.59-2.82, p=0.147). This result needs to be interpreted with caution, however, because the KH is known to perform poorly in settings with <5 studies, and its use is questionable when there is no documented heterogeneity between the studies (19).

Referring to statistical limitations, these are inevitable in a meta-analysis with two studies as compared with a similar meta-analysis with a larger number of studies (19-23). Most importantly, a meta-analysis of two studies is underpowered for assessing certain aspects of larger meta-analyses (20-23). First of those is the evaluation of study heterogeneity. More precisely, the I^2 and Cochran's Q statistic have very low power, and a non-significant heterogeneity with these tests does not mean that the studies are truly homogeneous (20-22). In the present analysis, I^2 reached the value 0.00 in both ITT and PP analysis (Figure 1 and Figure 2), and Q=0.31 (p=0.58) and 0.05 (p=0.83), respectively. Similarly, the variance component estimator of heterogeneity (τ^2) gives the value 0.00 in both ITT and PP analysis, indicating that RE model and fixed effects (FE) model give identical results. Indeed, this was confirmed by running both RE and FE models for these data. In a larger meta-analysis (23), this would certainly indicate lack of any heterogeneity at all, and indeed, indicates that the studies included in the meta-analysis are homogeneous. In this respect, however, the present meta-analysis can be concluded to represent a special setting in that the two studies included in the analysis are practically identical in most key aspects, including the design, population, intervention and outcome measures. Accordingly, it seems warranted to conclude that there is no heterogeneity between the two studies, as also confirmed by the conventional statistics (I^2 and Cochran's Q), formally suggesting the lack of heterogeneity, as did the Galbraith plots (Figure 3 and Figure 4). The latter, however, can be ignored because these are generally considered meaningless with only two data points (20-22).

The second shortcoming of the two-study meta-analysis is the formal evaluation of the publication bias. As recently discussed in expert reviews, the funnel plots as well as the Egger's and Begg's test are meaningless with only two studies (20-22). When these tests were done with the present data, the results indicated no publication bias. The same was true with the funnel plots (Figure 5 and Figure 6). This is, however, consistent with the reality, because these two studies (12, 13) are the only ones ever conducted and published, and no additional studies are underway or even planned. With these two studies giving practically identical results, it is hard to imagine any "publication bias" with the common meaning of the term. An additional hypothetical study failing to report a significant effect for Acetium® might generate a publication bias, if subjected to the same meta-analysis with the existing studies.

Yet the third point of concern (a potential limitation) in two-study meta-analysis is the precision of the pooled (summary) estimates (20-22). If the included studies are small, there is a danger that the confidence intervals may be broad, in which case even small changes in either study can substantially shift the combined effect. In the present meta-analysis, however, this was not an issue (Figure 1 and Figure 2). In both ITT and PP analysis for the summary effect size, the 95% CI was quite narrow (less than 1.0 unit), being narrower in the ITT analysis, with substantially more cases included. Thus, the combined effect was not significantly shifted from the values of the individual studies (20-22).

Following the stringent statistical principles (19-23), the results of the present meta-analysis clearly permit an estimation of the average (summary) effect, but one cannot robustly evaluate heterogeneity or publication bias. Accordingly, the pooled estimates for Acetium® efficacy in smoking intervention are statistically significant both in the ITT and PP analysis (Figure 1 and Figure 2). This result is important as such, because the first RCT (12) failed to demonstrate a statistically significant effect size even in the PP analysis, simply due to an insufficient statistical power. In the second trial, the effect size reached statistical significance in both ITT and PP analysis (13, 14). The summary estimates of the present meta-analysis indicate a significant efficacy for Acetium® intervention in both the PP and ITT analysis. In all RCTs, the ITT group is considered equally important as the PP analysis, both having different scopes and interpretations depending on the context (18). In the current context, we can state that smoking intervention by Acetium® lozenge seems to be more effective than placebo among all smokers randomized in two trials, irrespective of whether they complete the study following the protocol or with some degree of violations (12-14).

As to the value of such a small meta-analysis like this, there are several points that support undertaking of a two-study meta-analysis. At a general level, even though small, such a meta-analysis can 1) summarize evidence from geographically or temporally distinct populations, 2) provide a more stable overall estimate than either study alone (if both estimates point to the same direction), 3) serve as an evidence bridge until further studies become available, and 4) support regulatory or marketing documentation, especially when both trials meet good clinical practice standards. In the case of Acetium® lozenge in smoking intervention, most of these points are valid. Two independent, double-blind RCTs showing nearly identical results in two different cohorts of smoker volunteers in Finland substantially strengthen the external validity of the original RCTs, even if some of the formal meta-analytic tools have limited statistical power (heterogeneity and publication bias). A discussion about the significance of these results in comparison with the other (conventional) smoking intervention methods falls outside the scope of this communication; this is comprehensively addressed in the original reports (12, 13).

Conclusion

Meta-analyses with a limited number of studies must be interpreted with caution, because the statistical tools for assessing study heterogeneity and publication bias have a low power in such settings (20-23). Nevertheless, when both original studies show a similar direction and magnitude of the effect size, Acetium® efficacy in this case, the pooled analysis remains informative and helps consolidate the evidence across different settings (20-22).

Taken together, these meta-analytical data provide coherent support for the concept that Acetium® lozenge significantly increases the likelihood of successful smoking cessation (PPA in the PP group) compared with similarly administered placebo (OR=1.53, 95% CI=1.16–2.01). The reproduction of the results in two independent RCTs strengthens the external validity of the Acetium® concept and provides a solid foundation for future confirmatory trials in other populations.

Conflicts of Interest

The first Author (KS) is the former Chief Medical Director of Biohit Oyj, and the principal investigator of the two RCTs cited in this article. He has been retired since 2019 and currently continues as a scientific consultant for the company. OS is a member of the Board of Directors, Biohit Oyj, and the major shareholder of the company. OS is also the inventor of the Acetium® concept and the owner of the European patent (EP 2 197 436 B1) entitled: "Sucking Tablet for Use in Reducing Tobacco and/or Alcohol Dependence", from 2009.

Authors' Contributions

Both authors substantially contributed to the design and conceptualization of the work. Acquisition and data analysis was performed by KS, and both authors contributed to interpretation of the results. The first draft of the manuscript was written by KS and critically commented and revised by OS. The final version of the manuscript was approved by both KS and OS.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation or presentation of any part of this manuscript.

References

1 Benowitz NL: Nicotine addiction. N Engl J Med 362(24): 2295-2303, 2010. DOI: 10.1056/NEJMra0809890
2 Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Cogliano V, WHO International Agency for Research on Cancer Monograph Working Group: A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 10(11): 1033-1034, 2009. DOI: 10.1016/s1470-2045(09)70326-2
3 Haussman HJ: Use of hazard indices for a theoretical evaluation of cigarette smoke composition. Chem Res Toxicol 25(4): 794-810, 2012. DOI: 10.1021/tx200536w
4 Cao J, Belluzzi JD, Loughlin SE, Keyler DE, Pentel PR, Leslie FM: Acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats. Neuropsychopharmacol 32(9): 2025-2035, 2007. DOI: 10.1038/sj.npp.1301327
5 Belluzzi JD, Wang R, Leslie FM: Acetaldehyde enhances acquisition of nicotine self-administration in adolescent rats. Neuropsychopharmacol 30(4): 705-712, 2005. DOI: 10.1038/sj.npp.1300586
6 Quertemont E, Tambour S, Tirelli E: The role of acetaldehyde in the neurobehavioral effects of ethanol: A comprehensive review of animal studies. Prog Neurobiol 75(4): 247-274, 2005. DOI: 10.1016/j.pneurobio.2005.03.003
7 Talhout R, Opperhuizen A, van Amsterdam JG: Role of acetaldehyde in tobacco smoke addiction. Eur Neuropsychopharmacol 17(10): 627-636, 2007. DOI: 10.1016/j.euroneuro.2007.02.013
8 Suovaniemi O, Salaspuro M, Salaspuro V, Marvola M: Sucking tablet for use in reducing tobacco and/or alcohol dependence. European Patent: EP 2 197 436 B1. Available at: https://register.epo.org/application?number=EP08805430&tab=main [Last accessed on November 17, 2025]
9 Salaspuro V, Hietala J, Kaihovaara P, Pihlajarinne L, Marvola M, Salaspuro M: Removal of acetaldehyde from saliva by a slow-release buccal tablet of L-cysteine. Int J Cancer 97(3): 361-364, 2002. DOI: 10.1002/ijc.1620
10 Salaspuro VJ, Hietala JM, Marvola ML, Salaspuro MP: Eliminating carcinogenic acetaldehyde by cysteine from saliva during smoking. Cancer Epidemiol Biomarkers Prev 15(1): 146-149, 2006. DOI: 10.1158/1055-9965.EPI-05-0248

11 Sprince H, Parker CM, Smith GG, Gonzales LJ: Protective action of ascorbic acid and sulfur compounds against acetaldehyde toxicity: Implications in alcoholism and smoking. Agents Actions 5(2): 164-173, 1975. DOI: 10.1007/BF02027359
12 Syrjänen K, Salminen J, Aresvuo U, Hendolin P, Paloheimo L, Eklund C, Salaspuro M, Suovaniemi O: Elimination of cigarette smoke-derived acetaldehyde in saliva by slow-release L-cysteine lozenge is an effective new method to assist smoking cessation. A randomised, double-blind, placebo-controlled intervention. Anticancer Res 36(5): 2297-2306, 2016.
13 Syrjänen K, Eronen K, Hendolin P, Paloheimo L, Eklund C, Bäckström A, Suovaniemi O: Slow-release L-cysteine (Acetium®) lozenge is an effective new method in smoking cessation. A randomized, double-blind, placebo-controlled intervention. Anticancer Res 37(7): 3639-3648, 2017. DOI: 10.21873/anticanres.11734
14 Syrjänen K, Eronen K, Hendolin P, Paloheimo L, Eklund C, Bäckström A, Suovaniemi O: Addendum to: Slow-release L-cysteine (Acetium®) lozenge is an effective new method in smoking cessation. A randomized, double-blind, placebo-controlled intervention. Anticancer Res 43(5): 2379, 2023. DOI: 10.21873/anticanres.16404
15 Syrjänen K: Accuracy of Serum Biomarker Panel (GastroPanel®) in the diagnosis of atrophic gastritis of the corpus. Systematic review and meta-analysis. Anticancer Res 42(4): 1679-1696, 2022. DOI: 10.21873/anticanres.15645
16 Heatherton TF, Kozlowski LT, Frecker RC, Fagerström KO: The Fagerström test for nicotine dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 86(9): 1119-1127, 1991. DOI: 10.1111/j.1360-0443.1991.tb01879.x
17 Hughes JR, Carpenter MJ, Naud S: Do point prevalence and prolonged abstinence measures produce similar results in smoking cessation studies? A systematic review. Nicotine Tob Res 12(7): 756-762, 2010. DOI: 10.1093/ntr/ntq078
18 Tripepi G, Chesnaye NC, Dekker FW, Zoccali C, Jager KJ: Intention to treat and per protocol analysis in clinical trials. Nephrology (Calton) 25(7): 513-517, 2020. DOI: 10.1111/nep.13709
19 Stata 19 Meta-Analysis Reference Manual. StataCorp. College Station, TX, USA, Stata Press, pp. 1-435, 2025.
20 Friede T, Röver C, Wandel S, Neuenschwander B: Meta-analysis of two studies in the presence of heterogeneity with applications in rare diseases. Biom J 59(4): 658-671, 2017. DOI: 10.1002/bimj.201500236
21 Chen DG, Fang D, Wilson JR: Meta-analysis of two studies with random effects? J Minim Invasive Gynecol 24(5): 689-690, 2017. DOI: 10.1016/j.jmig.2017.05.008
22 Bender R, Friede T, Koch A, Kuss O, Schlattmann P, Schwarzer G, Skipka G: Methods for evidence synthesis in the case of very few studies. Res Synth Methods 9(3): 382-392, 2018. DOI: 10.1002/jrsm.1297
23 Hedges LV, Vevea JL: Fixed- and random-effects models in meta-analysis. Psychol Meth 3(4): 486-504, 1998. DOI: 10.1037/1082-989X.3.4.486