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Silver acetate for smoking cessation (Review)

Lancaster T, Stead LF

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[Intervention Review]

Silver acetate for smoking cessation

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ABSTRACT

Background

Silver acetate produces an unpleasant taste when combined with cigarettes, thereby producing an aversive stimulus. It has been marketed in various forms with the aim of extinguishing the urge to smoke, by pairing the urge with an unpleasant stimulus.

Objectives

The aim of this review was to determine the effectiveness of silver acetate products (gum, lozenge, spray) in promoting smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group specialised trials register. Most recent search was in July 2012.

Selection criteria

We included randomised trials of silver acetate for smoking cessation with reports of smoking status at least six months after the beginning of treatment.

Data collection and analysis

We extracted data in duplicate on the type of subjects, the dose and form of silver acetate, the outcome measures, method of randomisation, and completeness of follow-up.

The main outcome measure was biochemically validated abstinence from smoking after at least six months follow-up in patients smoking at baseline. Subjects lost to follow-up were counted as continuing smokers. Where appropriate, we performed meta-analysis using a fixed effects model.

Main results

Two studies provided long-term follow-up data on patients randomised to silver acetate or placebo. In one of these studies, there was a third arm, randomised to 2mg nicotine gum. The pooled risk ratio for quitting for silver acetate vs placebo was 1.04 (95% confidence interval 0.69 to 1.57).

Authors' conclusions

Existing trials show little evidence for a specific effect of silver acetate in promoting smoking cessation. The confidence intervals for the ratio are quite wide. However, the upper limit of the confidence intervals for a positive effect equates to an absolute increase in the smoking cessation rate of about 4%. Any effect of this agent is therefore likely to be smaller than nicotine replacement therapy. The lack of effect of silver acetate may reflect poor compliance with a treatment whose rationale is to create an unpleasant stimulus.

PLAIN LANGUAGE SUMMARY

Does silver acetate help people stop smoking

Silver acetate products (gum, lozenge, and spray) produce an unpleasant metallic taste when combined with cigarettes, so they are used as a form of aversion therapy for smoking. However, the review of trials found little evidence to show that silver acetate helps smokers quit. Any beneficial effect of silver acetate is likely to be very small, and less than the effect already proven for nicotine replacement therapy.

BACKGROUND

Silver acetate preparations produce an unpleasant, metallic taste when combined with cigarettes. Their use for smoking cessation is based on the principles of aversive conditioning, and is analogous to the use of disulfiram (Antabuse) for alcoholism. That is, an aversive stimulus (in this case taste) is systematically paired with a behaviour (smoking) that the subject wishes to stop. Various silver acetate products are available including lozenges, gum and sprays. The aim of treatment is to encourage smokers to use silver acetate, so that the act of smoking becomes unpleasant, and the urge to smoke therefore diminished, or ideally, extinguished. Excessive ingestion of silver can lead to the rare condition of argyrism. To avoid this, a total dose of silver no greater than 756mg is recommended, and this limits the duration of silver acetate treatment.

OBJECTIVES

To review the randomised evidence for the effectiveness of silver acetate in promoting smoking cessation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials which report smoking status at least six months after intervention. Studies reporting follow-up between 3 and 6 months only were reviewed, but data were not included in pooled analyses.

Types of participants

Adult patients who smoke.

Types of interventions

All randomised controlled comparisons of silver acetate with placebo, or with other smoking cessation treatments were included. Silver acetate products included lozenges, gums and sprays.

Types of outcome measures

The main outcome measure was sustained abstinence from smoking at 6 to12 months. Only participants who met criteria for biochemically validated cessation were counted as quitters.

Search methods for identification of studies

We searched the Tobacco Addiction Review Group specialised register for trials, using the term 'silver acetate' in the title or abstract, or as a keyword. This register has been developed from regular electronic searches of MEDLINE, EMBASE and PsycINFO, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. The most recent search for trials was in July 2102 when the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 7, 2012; MEDLINE (via OVID) to update 20120622; EMBASE (via OVID) to week 201227; and PsycINFO (via OVID) to update 20120625. See the Tobacco Addiction Group Module in the Cochrane Library for full search strategies and list of other resources searched. We also searched Clinicaltrials.gov using the terms 'silver acetate' and 'smoking'.

Data collection and analysis

All potentially eligible studies were reviewed by two authors (TL and LS). Data were abstracted onto a data form which detailed the methods of recruitment and randomisation, types of participants, interventions and outcomes. A record was made of whether abstinence was confirmed biochemically.

Trial results were expressed as risk ratios (number of quitters in intervention group/total randomised to intervention)/(number of quitters in control group/total randomised to control). Pooled effects were estimated using a Mantel-Haenszel fixed-effect model (Deeks 2011).

RESULTS

Description of studies

Two randomised trials with follow-up greater than six months were identified. In the first (Jensen 1990) 6mg silver acetate chewing gum was compared to 2mg nicotine gum, and to ordinary chewing gum in a three armed, randomised, open study. In the second (Hymowitz 1996), 2.5mg silver acetate lozenges were compared to placebo lozenges in a randomised double-blind study. A third study (Malcolm 1986) was reviewed. In this study, participants were randomised to silver acetate chewing gum or placebo. This study was excluded from formal analysis because the maximum follow-up was only four months.

Risk of bias in included studies

The studies were judged on their attempts to control bias in allocation, assessment and analysis. All three were randomised, though the precise method of randomisation was not stated in any of the studies. One (Jensen 1990) was not blinded. Each of three studies reviewed confirmed abstinence with biochemical verification. In all studies, smokers lost to follow-up were counted as continuing smokers in the analysis.

Effects of interventions

Two studies provided long-term follow-up of patients randomised to silver acetate or placebo. In the first (Jensen 1990), there were no significant differences in smoking status between patients randomised to silver acetate chewing gum, nicotine gum or ordinary chewing gum. In the second (Hymowitz 1996), 11/ 239 subjects randomised to silver acetate lozenges had quit at one year, compared to 9/241 randomised to placebo. The combined estimate for the risk ratio for quitting was 1.04 (95% confidence interval 0.69 to 1.57).

In the comparison between silver acetate and nicotine gum in Jensen 1990 the risk ratio was 0.98 95% (CI 0.69 to 1.39).

In one further study (Malcolm 1986) 9/127 randomised to silver acetate gum quit, compared to 4/142 randomised to placebo. This study was not included in meta-analysis because follow-up was only four months.

In all trials, the total dose of silver acetate was restricted to reduce the chance of developing the rare outcome of argyrism (silver deposition in body tissues), and no subject suffered this side-effect. The main adverse effects reported were those expected from this aversive stimulus; unpleasant tastes and sensations in the mouth, and gastrointestinal disturbances.

DISCUSSION

There is little evidence for a specific effect of silver acetate in promoting smoking cessation. The confidence intervals for the pooled risk ratio are quite wide, because the total number of subjects studied with long-term follow-up is relatively small. The upper limit of the confidence intervals for a positive effect equates to an absolute increase in smoking cessation rate of about 4%. Such an effect would, of course, be worth having. However, given that other smoking cessation interventions produce effects comparable to or larger than this (Stead 2008; Cahill 2012), proving or disproving a small effect of silver acetate is unlikely to have much clinical relevance. In a direct comparison between silver acetate and nicotine gum, no advantages were seen for either product over the other, but the numbers studied were small (Jensen 1990).

In part, the results may reflect the difficulties of complying with a treatment whose rationale is to create an unpleasant stimulus.

A recent laboratory based study (Rose 2010) assessed the effect of silver acetate on the taste of nicotine-containing or denicotinized cigarettes, and nicotine inhaler. Silver acetate mouth wash made the taste of both types of cigarette less pleasant but did not affect the taste of the inhaler, implying that silver acetate interacts with components other than nicotine. The authors suggest that silver acetate could potentially be used in combination with NRT products to reduce the chance that a recent quitter who slipped and tried a cigarette would relapse completely.

AUTHORS' CONCLUSIONS

Implications for practice

Although a possible small effect of silver acetate in promoting smoking cessation has not been disproved, any such effect is likely to be very small, and less than that proven for nicotine replacement therapy. There is therefore little role for silver acetate for promoting smoking cessation in the clinical setting.

Implications for research

Further research on silver acetate for smoking cessation is unlikely to be helpful.

ACKNOWLEDGEMENTS

None

REFERENCES

References to studies included in this review

Hymowitz 1996 *{published data only}*

Hymowitz N, Eckholdt H. Effects of a 2.5-mg silver acetate lozenge on initial and long-term smoking cessation. *Preventive Medicine* 1996;**25**:537-46.

Jensen 1990 *{published data only}*

* Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect of nicotine, silver acetate, and ordinary chewing gum in combination with group counselling on smoking cessation. *Thorax* 1990;**45**:831-4.

Jensen EJ, Schmidt E, Pedersen B, Dahl R. Effect on smoking cessation of silver acetate, nicotine and ordinary chewing gum. Influence of smoking history. *Psychopharmacology Berl* 1991;**104**:470-4.

Jensen EJ, Schmidt E, Pedersen B, Dahl R. The effect of nicotine, silver acetate, and placebo chewing gum on the cessation of smoking. The influence of smoking type and nicotine dependence. *International Journal of the Addictions* 1991;**26**:1223-31.

Malcolm 1986 *{published data only}*

Malcolm RE, Currey HS, Mitchell MA, Keil JE. Silver acetate gum as a deterrent to smoking. *Chest* 1986;**90**:107-11.

References to studies excluded from this review

Hymowitz 1993 *{published data only}*

Hymowitz N, Feuerman M, Hollander M, Frances RJ. Smoking deterrence using silver acetate. *Hospital and Community Psychiatry* 1993;**44**:113-114, 118.

Morrow 1993 *{published data only}*

Morrow R, Nepps P, McIntosh M. Silver acetate mouth spray as an aid in smoking cessation: results of a double-blind trial. *Journal of the American Board of Family Practice* 1993;**6**(4):353-7.

Rose 2010 *{published data only}*

Rose JE, Behm FM, Murugesan T, McClernon FJ. Silver acetate interactions with nicotine and non-nicotine smoke components. *Experimental and Clinical Psychopharmacology* 2010;**18**:462-9.

Rosenberg 1977 *{published data only}*

Rosenberg A. An investigation into the effect on cigarette smoking of a new anti-smoking chewing gum. *Journal of International Medical Research* 1977;**5**:68-70.

Zmeili 1999 *{published data only}*

Zmeili S, Salhab A, Shubair K, Gharaibeh M, Suliman N, Al-Kayed A, et al. Clinical evaluation of a new AS mouth wash 881010 as an antismoking agent: a placebo-controlled double-blind trial. *International Journal of Clinical Pharmacology and Therapeutics* 1999;**37**:41-50.

Additional references

Cahill 2012

Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD006103.pub6]

Deeks 2011

Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Available from www.cochrane-handbook.org.. The Cochrane Collaboration, 2011.

Stead 2008

Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD000146.pub3]

References to other published versions of this review

Lancaster 1997

Lancaster T, Stead LF. Silver acetate for smoking cessation. *Cochrane Database of Systematic Reviews* 1997, Issue 3. [DOI: 10.1002/14651858.CD000191]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Hymowitz 1996

Methods	Randomised, double-blind trial. Country: USA
Participants	Adult smokers of more than 10 cigarettes/day. Motivated volunteers recruited by advertisement.

Hymowitz 1996 *(Continued)*

Interventions	2.5mg silver acetate lozenge vs placebo lozenge. To be used six times daily for 3 weeks. Successful quitters were given further lozenges to assist relapse prevention. All participants received self-help materials, videos and follow-up visits.
Outcomes	Sustained abstinence at 12 months, validated by urinary cotinine/expired carbon monoxide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, method not described
Allocation concealment (selection bias)	Unclear risk	No details reported

Jensen 1990

Methods	Randomised, open, controlled trial. Country: Denmark
Participants	496 motivated adult smokers, smoking >10 cigarettes/day for >5years.
Interventions	1. 6mg Silver acetate chewing gum, up to six pieces daily. 2. 2 mg Nicotine chewing gum 3. Ordinary chewing gum The gums were recommended for six weeks, with a reducing dose for a further six weeks. Treatments were not blinded.
Outcomes	Sustained abstinence at one year, validated by expired carbon monoxide.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised to 24 smaller groups, each group then randomly allocated to treatment
Allocation concealment (selection bias)	Unclear risk	No details reported

Malcolm 1986

Methods	Randomised, double-blind trial, method of randomisation not stated Country: USA
Participants	Adult smokers, at least 1 pack/day for 2 years. Motivated volunteers who responded to an advertisement.

Malcolm 1986 *(Continued)*

Interventions	Chewing gum (Tabmit) containing 6mg of silver acetate vs placebo gum. To be chewed six times daily for 3 weeks
Outcomes	Sustained abstinence at 4 months, validated by serum metabolites.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised, method not described
Allocation concealment (selection bias)	Unclear risk	No details reported

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Hymowitz 1993	A trial of 2.5 mg silver acetate lozenges vs placebo for smoking cessation with three week follow-up. Smokers who successfully quit were then randomised to silver acetate vs placebo for relapse prevention, and followed to one year. Excluded because does not present long-term follow-up of the initial randomisation to silver acetate or placebo for cessation.
Morrow 1993	A randomised controlled trial among 42 patients in US family practice, comparing silver acetate spray with placebo. Excluded on the grounds that follow-up less than six months (3 months).
Rose 2010	Laboratory study, cessation not an outcome.
Rosenberg 1977	Randomised trial of silver acetate gum vs placebo gum. Excluded because follow-up only four weeks.
Zmeili 1999	Silver nitrate mouthwash. Excluded because follow-up only six weeks post treatment.

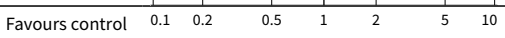
DATA AND ANALYSES

Comparison 1. Silver acetate vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sustained abstinence at 12 months	2	785	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.69, 1.57]

Analysis 1.1. Comparison 1 Silver acetate vs placebo, Outcome 1 Sustained abstinence at 12 months.

Study or subgroup	Silver acetate n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Jensen 1990	46/203	19/82		75.05%	0.98[0.61,1.56]
Hymowitz 1996	11/250	9/250		24.95%	1.22[0.52,2.9]
Total (95% CI)	**453**	**332**		**100%**	**1.04[0.69,1.57]**
Total events: 57 (Silver acetate), 28 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=0.18(P=0.86)					

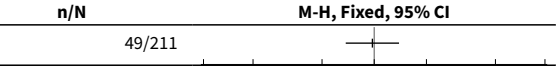


Comparison 2. Silver acetate vs nicotine gum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sustained abstinence at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Silver acetate vs nicotine gum, Outcome 1 Sustained abstinence at 12 months.

Study or subgroup	SIlver acetate n/N	Nicotine gum n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Jensen 1990	46/203	49/211		0.98[0.69,1.39]



WHAT'S NEW

Date	Event	Description
14 August 2012	New search has been performed	Searches updated. No new studies included. Effect sizes now expressed as risk ratios and pooled using a Mantel-Haenszel fixed-effect model.
14 August 2012	New citation required but conclusions have not changed	No change to conclusions.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 3, 1997

Date	Event	Description
8 January 2009	New search has been performed	No new trials found
29 October 2008	Amended	Converted to new review format.
26 April 2006	New search has been performed	Searches updated, no new trials found.
14 May 2003	New search has been performed	Searches updated, no new trials found.

CONTRIBUTIONS OF AUTHORS

TL extracted data and wrote the review. LS assisted in identifying studies and data extraction.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Primary Care Health Sciences, University of Oxford, UK.
- National School for Health Research School for Primary Care Research, UK.

External sources

- NHS Research and Development Fund, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Smoking Prevention; Acetates [*administration & dosage]; Administration, Buccal; Chewing Gum; Randomized Controlled Trials as Topic; Silver Compounds [*administration & dosage]; Smoking Cessation [*methods]; Tobacco Use Cessation Devices

MeSH check words

Humans