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Stead LF, Hughes JR

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[Intervention Review]

Lobeline for smoking cessation

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ABSTRACT

Background

Lobeline is a partial nicotine agonist, which has been used in a variety of commercially available preparations to help stop smoking.

Objectives

The objective of this review was to assess the effects of lobeline on long term smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group trials register (most recent search December 2011).

Selection criteria

Randomized trials comparing lobeline to placebo or an alternative therapeutic control, which reported smoking cessation with at least six months follow-up.

Data collection and analysis

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

Main results

We identified no trials meeting the full inclusion criteria including long term follow-up. One large trial failed to detect any effect on short-term abstinence.

Authors' conclusions

There is no evidence available from long term trials that lobeline can aid smoking cessation, and the short-term evidence suggests there is no benefit

PLAIN LANGUAGE SUMMARY

Can lobeline help people to quit smoking

Lobeline is an alkaloid derived from the leaves of an Indian tobacco plant, and has been widely used in commercial smoking remedies. Its adverse effects include dizziness, nausea, and vomiting, and tablets and pastilles containing Lobeline may lead to throat irritation. The review found no adequate long-term trials which could provide evidence that Lobeline can help people stop smoking. One large study with only s ix weeks follow-up did not detect any evidence of short-term b enefit , suggesting that lobeline is not an e ffective treatment.

BACKGROUND

Lobeline is an alkaloid derived from the leaves of an Indian tobacco plant (Lobelia inflata). It was synthesised in the early 1900s and classified as a partial nicotinic agonist. The first reported use in aiding smoking cessation was in the 1930s (Dorsey 1936), Since then it has been tested in a variety of doses and formulations, and has been quite widely used in proprietary smoking remedies.

Schwartz (Schwartz 1969) identified 16 studies or reviews of clinic success rates in which lobeline had been used. Few of these used placebo or other controls, or had follow-up beyond the end of treatment. Davison 1972 also reviewed the evidence and concluded that poor methodological quality prevented any conclusions on efficacy being drawn. In 1993 the FDA banned all OTC smoking cessation products in the United States, including lobeline, due to a lack of acceptable clinical efficacy data (FDA 1993). This led to renewed interest in investigating efficacy (Schneider 1996a; Glover 1998; Glover 2010).

The early use of high doses (8 mg tablets) of lobeline sulphate gave rise to considerable side effects; Wright (Wright 1937) cautioned against the drug's use because of the aversive gastric effects. Parenteral injection although reported as being particularly effective, caused dizziness, nausea and vomiting (Ejrup 1967). Even buffered tablets or flavoured pastilles may lead to local throat irritation, with the possibility that any short term efficacy could be due to a non-specific aversive effect.

OBJECTIVES

To assess the current evidence for the effectiveness of lobeline in assisting long-term smoking cessation.

The hypothesis tested was that lobeline was more effective than placebo, or an alternative treatment, in achieving long-term smoking cessation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized studies using a placebo or an alternative therapeutic control.

Types of participants

Any smokers.

Types of interventions

Treatment with any form of lobeline.

Types of outcome measures

Smoking cessation, assessed at follow-up at least 6 months from start of treatment.

Search methods for identification of studies

We searched the Tobacco Addiction Review Group Specialized Register of trials, using the free text or indexing term 'lobeline'. The most recent search of the Register was in December 2011, and included reports of trials indexed in MEDLINE to update 20110826, EMBASE to 2011 week 33, PsycINFO to 20110822 and the Cochrane Central Register of Controlled trials to Issue 3, 2011. See the Tobacco Addiction Group Module for details of the search strategies for these databases. We also searched clinicaltrials.gov using the terms lobeline and smoking. Review bibliographies were searched for the original review.

Data collection and analysis

In each study the strictest available criteria to define cessation would be used, with figures for sustained abstinence extracted in preference to point prevalence where both were presented. In studies which used biochemical validation of cessation, only those subjects meeting the criteria for biochemically confirmed abstinence

would be regarded as having stopped smoking. Subjects in either group lost to follow-up would be regarded as being continuing smokers. Two reviewers would extract data independently. Statistical meta-analysis would be used to derive a typical Odds Ratio and its associated confidence intervals, using a fixed-effects model (Yusuf 1985).

RESULTS

Description of studies

No studies were found which met all criteria for inclusion. A number of early reports of the use of lobeline did not use any control groups. Of those which used a placebo, a number employed a cross over design with smoking behaviour assessed over days rather than weeks. Percentage reduction in number of cigarettes smoked was more commonly used as an outcome than complete abstinence. Few trials followed up beyond the end of treatment, and none for the required 6 month period.

Risk of bias in included studies

Lack of long term follow-up was a reason for exclusion in all cases. A large number of the studies were not controlled. Where comparison was made with a placebo control or alternative treatment it was rarely clear that an appropriate method of randomization had been used.

Effects of interventions

On the basis of the trials which have been published in the past sixty years there is no evidence that lobeline has any long term effect on smoking cessation.

DISCUSSION

Trials with long-term follow-up using validated sustained abstinence are the gold standard for evaluating smoking cessation methods. Trials with short-term follow-up may overestimate both the overall abstinence rates and the size of any treatment effect.

Because short-term abstinence is not necessarily evidence of long-term cessation this review has not systematically synthesized and evaluated the evidence from short-term studies. However even these did not appear to provide consistent evidence that lobeline has an effect on smoking behaviour. A number of the early controlled short term trials concluded that lobeline had no effect on smoking; (Merry 1963; BTA 1963; Edwards 1964 A; Edwards 1964 B; Ross 1967; Leone 1968; Davison 1972).

More recent laboratory studies suggested that a formulation of lobeline with better bioavailability could be efficacious (Schneider 1996a; Schneider 1996b). This research included a pilot study comparing a sublingual lobeline tablet (7.5 mg, 9 times/day) with placebo for 6 weeks. Both groups received weekly individual counselling (Glover 1998). This study did not demonstrate short-term efficacy but there was a trend towards a benefit in more dependent participants and results were considered promising enough for a phase 3 trial. A multicentre study of sublingual lobeline sulfate tablets with 750 subjects was conducted by Dynagen in 1997 and identified as unpublished in previous versions of this review. It was published in 2010 (Glover 2010). There was no statistically significant difference in quitting between placebo (15% abstinent) and lobeline (17%) at 6 week follow-up. DynaGen discontinued its research programme, but it remains possible that formulations of lobeline for nasal, transdermal patch or transbuccal patch use may be further investigated by other companies. Since then, other nicotinic receptor partial agonists have been shown to be effective. Varenicline has been licensed widely for smoking cessation (Cahill 2011), whilst cytisine, like lobeline a plant-derived compound, and used as a cessation medication in Eastern Europe, has now shown efficacy in one high quality trial with 12 month follow-up (West 2011).

AUTHORS' CONCLUSIONS

Implications for practice

There are no well conducted trials with long-term follow-up and one large short-term trial did not detect evidence of benefit. There is therefore no evidence that lobeline can aid smoking cessation.

Implications for research

Given the established efficacy of nicotine replacement therapy (Stead 2008) and of partial nicotinic agonists (Cahill 2011), further trials are unlikely unless lobeline is shown to have potential advantages. In this case formulations that increase bioavailability and have good compliance would need to be developed.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bachman 1964	Double blind crossover evaluation of Nikoban.
Bartlett 1957	Crossover trial comparing lobeline, meprobamate and placebo. Smokers not attempting to cut down
BTA 1963	Only six week follow-up
Davison 1972	No follow-up after 4 weeks treatment.
Dorsey 1936	Not controlled
Edwards 1964 A	Double blind trial, follow-up only 3 months after 4 weeks of treatment
Edwards 1964 B	Subjects alternated to lobeline or hypnosis. Only 3 month follow-up after treatment
Ejrup 1959	Not controlled. Used lobeline injections in a smoking clinic
Ejrup 1967	Not controlled. Used lobeline injections in smoking clinics.
Farago 1968	Not controlled. Cited by Schneider 1996a for use of parenteral lobeline.
Glover 1998	No follow-up after 6 weeks of treatment.
Glover 2010	No follow-up after 6 weeks of treatment.
Golledge 1965	Only 28 day follow-up.
Graff 1966	Only 3 month follow-up.
Hoffstaedt 1964	No control group. Lobeline, hydroxyzine and discussion in a smoking clinic
Hoffstaedt 1965	No control group. Lobeline, hydroxyzine and discussion in a smoking clinic
Jacobs 1971	Only 10 week follow-up.
Jochum 1961	Lobeline compared with psychotherapy. No follow-up.
Kalyuzhny 1968	No long term follow-up. Cited by Schneider 1996a for use of parenteral lobeline.
Kaufman 1960	Not controlled.
Leone 1968	Describes a number of clinics. Outcomes not reported for lobeline and placebo separately. 6 week follow-up

(*Continued*)

London 1963	Controlled trial of 0.5 mg pastilles. No follow-up after 4 weeks treatment
McChargue 2002	Controlled trial of lobeline and moist snuff replacement with placebos over four weeks (one week for each condition). Follow-up for each measured 48 hours later
Merry 1963	Controlled trial of lobeline or placebo after failure to quit with one week without medication and one week on placebo. No post treatment follow-up
Perlstein 1964	No post-treatment follow-up reported
Rapp 1955	Crossover trial of lobeline and placebo. Smoking behaviour recorded for one week on each
Rapp 1959	Crossover study of lobeline sulphate in capsules, Bantron in capsules or starch placebo
Rosenberg 1959	Controlled trial, no long term follow-up data reported.
Rosnick 1965	No long term follow-up.
Ross 1967	Long term quit rates not reported by treatment group.
Schneider 1996a	Short follow-up. See Glover 1998 for full study report.
Schneider 1996b	Not a cessation study; effect of lobeline on withdrawal symptoms after overnight abstinence
Scott 1962	Crossover study with no long term follow-up.
Swartz 1964	Not controlled.
Wright 1937	Not controlled.

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Date	Event	Description
4 January 2012	New search has been performed	One new excluded study added
3 January 2012	New citation required but conclusions have not changed	Excluded study described in discussion. Evidence for absence of effect is strengthened

HISTORY

Date	Event	Description
8 January 2009	New search has been performed	No new trials found
28 October 2008	Amended	Converted to new review format.
27 April 2006	New search has been performed	Searches rerun, no new studies
19 May 2003	New search has been performed	One reference added to excluded studies list

CONTRIBUTIONS OF AUTHORS

LS and JH conceived the review; both extracted data, and collaborated on original text and subsequent updates

DECLARATIONS OF INTEREST

JH has received consulting fees from several for-profit and nonprofit organizations that provide smoking cessation medications and services.

SOURCES OF SUPPORT

Internal sources

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

External sources

- NHS National Institute for Health Research, NIHR Evaluation Trials and Studies Coordinating Centre, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

*Smoking Prevention; Lobeline [*therapeutic use]; Nicotinic Antagonists [*therapeutic use]; Smoking Cessation [*methods]

MeSH check words

Humans