

Mecamylamine (a nicotine antagonist) for smoking cessation (Review)

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[Intervention Review]

Mecamylamine (a nicotine antagonist) for smoking cessation

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ABSTRACT

Background

Mecamylamine is a nicotine antagonist (that is, it blocks the effect of nicotine). The rationale for its use in smoking cessation is that it may block the rewarding effect of nicotine and thus reduce the urge to smoke.

Objectives

The objective of this review was to determine the effectiveness of mecamylamine in promoting smoking cessation, either alone or in combination with nicotine replacement therapy.

Search strategy

We searched the Cochrane Tobacco Addiction Group trials register for trials using mecamylamine in October 2010.

Selection criteria

Randomized trials of mecamylamine, either alone or in combination with nicotine replacement therapy, which reported smoking cessation rates at least six months after intervention.

Data collection and analysis

The main outcome measure was sustained abstinence from smoking (biochemically validated) after at least six months follow up in patients smoking at baseline. Smokers lost to follow up were regarded as being continuing smokers. Because of the preliminary nature of available data, we did not perform meta-analysis but report the results narratively.

Main results

We identified two studies, both from the same investigators. In a study of 48 volunteers, a combination of mecamylamine plus nicotine patch was more effective than nicotine patch alone (abstinence rate at one year 37.5% vs 4.2%). In a second study, 80 volunteers were treated for four weeks prior to cessation with one of four treatments: 1. Nicotine patch plus mecamylamine capsules 2. Nicotine alone 3. Mecamylamine alone 4. No active drug. All four groups received combination treatment with nicotine and mecamylamine after the scheduled quit date. The abstinence rates in these four groups were respectively 40%, 20%, 15% and 15%. The higher abstinence rate in the group treated with combination therapy was not statistically significant. The authors reported a statistically significant benefit of mecamylamine using Kaplan-Meier survival analysis.

In the doses used, mecamylamine was well tolerated, although up to 40% of subjects required reductions in dose, usually because of constipation.

Authors' conclusions

Data from two small studies suggest that the combination of nicotine and mecamylamine may be superior to nicotine alone in promoting smoking cessation. However, these results require confirmation in larger studies before the treatment can be recommended clinically.

PLAIN LANGUAGE SUMMARY

Does mecamylamine help people to stop smoking

Mecamylamine is a drug originally marketed for lowering blood pressure, which was found to block the rewarding effects of nicotine. At doses high enough to do this, though, mecamylamine can have significant adverse effects, including drowsiness, hypotension and constipation. It has been suggested that smaller doses may work well with nicotine replacement therapy (NRT), and the two therapies may offset each other's adverse effects. Our review of trials found that while mecamylamine did not have a great effect on quitting rates, it may enhance the effectiveness of NRT and is worth further research.

BACKGROUND

Mecamylamine is a nicotine antagonist. It is a ganglionic cholinergic blocker which was originally marketed for blood pressure lowering. The rationale for its use in smoking cessation is to block the rewarding effects of nicotine, and therefore reduce the urge to smoke. This contrasts with nicotine replacement which provides a substitute for nicotine from cigarettes. The aim of substitution therapy is to relieve withdrawal symptoms, and thus wean the individual from cigarettes.

In studies of nicotine dependence in humans, mecamylamine, administered in a dose of 2.5-20 mg/day, has been found to produce a dose-related blockade of the perceived effects of nicotine (Hughes 1994; Tennant 1984a; Tennant 1984b). However, at these doses, it produced significant side effects, including drowsiness, postural hypotension and constipation.

Rose and colleagues have suggested that co-administration of mecamylamine and nicotine replacement might allow the use of smaller doses of mecamylamine (Rose 1996). One hypothesized mechanism of action is that the combined therapy occupies more nicotinic receptors than either alone, thereby better blocking the rewarding effects of cigarettes. By using mecamylamine prior to smoking cessation, smokers should learn that smoking no longer produces the expected effects. Combination therapy is also hypothesized to improve the tolerability of both treatments, as they may offset each other's side effects.

OBJECTIVES

To determine the effectiveness of mecamylamine, or mecamylamine combined with nicotine replacement, in promoting smoking

cessation.

The main hypotheses were:

1. Mecamylamine used before a specified quit date is more effective than placebo in achieving sustained abstinence from smoking.
2. Mecamylamine plus nicotine replacement is more effective than either mecamylamine or nicotine replacement alone in achieving abstinence from smoking.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials which report smoking status at least six months after intervention.

Types of participants

Adult smokers.

Types of interventions

Treatment with mecamylamine, with or without concurrent nicotine replacement therapy.

Types of outcome measures

We confined the review to a comparison of the effects of mecamylamine, plus or minus nicotine replacement, on smoking cessation, rather than withdrawal symptoms. We excluded trials in which follow up was of short duration (less than six months), or which did not include measurement of smoking cessation.

We required a sustained cessation rate, rather than point prevalence, and biochemical verification of self-reported quitting. We regarded smokers lost to follow up as being continuing smokers. We also noted adverse effects.

Search methods for identification of studies

We searched the Tobacco Addiction Review Group specialised register for trials, using the terms 'mecamylamine' and 'smoking' in the title or abstract, or as keywords. This register has been developed from electronic searching of MEDLINE, EMBASE, PsycINFO and Science Citation Index, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. We also contacted the authors of published studies of mecamylamine. Date of most recent search was October 2010.

Data collection and analysis

Two authors (TL and LS) reviewed potentially eligible studies. Data were abstracted onto a data form which detailed the methods of recruitment and randomization, types of participants, interventions and outcomes. We recorded whether abstinence was confirmed biochemically.

As the available evidence comes from two small studies, we made no attempt at meta-analysis. Instead, the results of the individual studies are reported in the Results section.

We have included in this updated review the Tobacco Addiction Group glossary of tobacco-specific terms ([Appendix 1](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

We identified two studies evaluating mecamylamine and giving data on long-term abstinence. Both were conducted by the same investigators, and examined the effects of treatment both on withdrawal symptoms (not considered in this review) and on abstinence.

In the first study ([Rose 1994](#)), 48 volunteers were randomized to receive either nicotine patch treatment plus oral mecamylamine capsules or nicotine patch plus placebo capsules. Treatment with mecamylamine started two weeks before the quit date, and half the subjects in each group were further randomized to begin patch use at the same time. The trial therefore tested the effect of four treatment combinations prior to the scheduled quit date: 1. Nicotine patch plus mecamylamine 2. Nicotine alone 3. Mecamylamine alone 4. No active drug, and two combinations after the quit date: 1. Nicotine patch plus mecamylamine 2. Nicotine patch plus placebo. All subjects wore nicotine patches after the cessation date, and continued mecamylamine or placebo capsules for three weeks after the quit date. The investigators reported continuous abstinence data to 12 months.

In the second study ([Rose 1996](#)), 80 volunteers were randomized to four weeks pre-cessation treatment in one of four groups: 1. Nicotine patch plus mecamylamine capsules 2. Nicotine patch alone 3. Mecamylamine alone 4. No active drug. Following the scheduled cessation date, all subjects received both mecamylamine and nicotine. The investigators reported continuous abstinence rates at six months.

Risk of bias in included studies

The studies were judged on their attempts to control bias in allocation, assessment and analysis. Both studies reviewed confirmed abstinence with biochemical verification. The studies were randomized and double-blind (with respect to mecamylamine administration), and randomization was performed using computer-generated random numbers.

Effects of interventions

In their first study, Rose and colleagues ([Rose 1994](#)) reported that the combination of mecamylamine capsules and nicotine patches compared to nicotine patches and placebo capsules led to a statistically significant difference in rates of sustained abstinence at six months (37.5% versus 12.5%, $P = 0.046$) and at 12 months (37.5% versus 4.2%, $P = 0.004$). There was no significant effect of early versus late initiation of nicotine patch treatment on continuous abstinence.

In their second study ([Rose 1996](#)), the reported rates of sustained abstinence at six months were 40% in the group pre-treated with nicotine/mecamylamine, 20% in the group treated with nicotine alone, and 15% in the groups treated with mecamylamine alone, and with no drug treatment. The higher rate of abstinence in the group pre-treated with nicotine and mecamylamine was not statistically significant. The authors reported that, using Kaplan-Meier survival analysis, they detected a significant benefit for the two groups receiving mecamylamine prior to cessation compared to the groups which did not.

In both these clinical trials, mecamylamine was reported to be well tolerated at the doses used. The main side effect was constipation, which improved with reduction in dose. In the first study (Rose 1994), 70% of subjects treated with mecamylamine reported constipation compared to 30% treated with placebo, and two subjects required a dose reduction. In the second study (Rose 1996), 40% of subjects required a reduction in dose of mecamylamine.

DISCUSSION

The available data on mecamylamine for smoking cessation are encouraging in showing that mecamylamine, used at low doses, can be tolerated.

The evidence from these two studies suggests that there is an effect of mecamylamine, started pre-cessation and continued post-cessation, in aiding smoking cessation. It is not clear whether this effect is significantly greater than that of nicotine replacement alone. The studies also suggest that the combination of mecamylamine with nicotine replacement, started before cessation, may increase the rates of cessation beyond those achieved with nicotine alone.

These results require confirmation in larger studies. One large multicentre study using a combined nicotine/mecamylamine transdermal patch has been completed but has not reported long-term follow up (Elan 2004), and another is not yet published (Stapleton 2002). Further trials are planned (Elan 2000).

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of a sustained effect on quitting from large scale studies, it is premature to recommend the addition of mecamylamine to nicotine replacement for smoking cessation.

However, existing research suggests that, used in low dose, mecamylamine can be tolerated, and that there is preliminary evidence to suggest that it may be a useful additional agent in smoking cessation, particularly in combination with nicotine replacement.

Implications for research

Further, large scale studies are required to determine whether mecamylamine, combined with nicotine replacement, is more effective than nicotine alone.

In addition, a number of questions remain to be answered about the best dose and timing if this therapy is used. In particular, questions remain about whether mecamylamine is more effective when given prior to, or following, cessation, and how it is best combined with nicotine replacement.

ACKNOWLEDGEMENTS

Dr J.E.Rose for comments and clarification of study details, and for unpublished data on an Elan Phase III RCT in August 2004.

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References to studies included in this review

Rose 1994 {published data only}

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Glover 2007 {published data only}

Glover ED, Laffin MT, Schuh KJ, Schuh LM, Nides M, Christen AG, Glover PN, Strnad JV. A randomized, controlled trial to assess the efficacy and safety of a transdermal delivery system of nicotine/mecamylamine in cigarette smokers. *Addiction* 2007;**102**:795–802.

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Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine & Tobacco Research* 2006;**8**:89–101.

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Stapleton 2002

Stapleton J. Personal communication Jan 16 2002.

Tennant 1984a

Tennant FS Jr, Tarver AL, Rawson RA. Clinical evaluation of mecamylamine for withdrawal from nicotine dependence. *NIDA Research Monograph* 1984;**49**:239–46.

Tennant 1984b

Tennant FS Jr, Tarver AL. Withdrawal from nicotine dependence using mecamylamine: comparison of three-week and six-week dosage schedules. *NIDA Research Monograph* 1984;**55**:291–7.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Rose 1994

Methods	Randomized, double-blind trial. The authors report that randomization was performed as follows: a list of random numbers, each corresponding to a subject identification number, was generated by computer. The random numbers conformed to a Gaussian distribution with mean=0 and standard deviation=1. The numbers were ranked in magnitude, and one fourth of the ranks were designated to each of the four treatments. This ensured equal numbers of subjects per condition.	
Participants	48 volunteers recruited through advertisements, 20-40 years old, smoking at least one pack of cigarettes for at least 2 years.	
Interventions	<p>Group 1. Mecamylamine capsules plus nicotine skin patch (21mg/24 hours, for 4 weeks after quit date, then reducing by 7mg/24 hours for two weeks).</p> <p>Group 2. Placebo capsule plus nicotine skin patch (21mg/24 hours, for 4 weeks after quit date then reducing by 7mg/24 hours for two weeks).</p> <p>The two groups were further divided to start nicotine patches two weeks before the quit date, or on the quit date.</p> <p>Mecamylamine was started at a dose of 2.5mg twice daily two weeks before the quit date, and increased to 5mg twice daily, continued for 3 weeks after quitting.</p> <p>All subjects received self-help materials to assist cessation (a minimal behavioural intervention).</p>	
Outcomes	Continuous abstinence at 12 months, Validation: Expired carbon monoxide less than or equal to 8 ppm	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No details given

Rose 1996

Methods	Randomized, double-blind trial. The authors report that randomization was performed as follows: a list of random numbers, each corresponding to a subject identification number, was generated by computer. The random numbers conformed to a Gaussian distribution with mean=0 and standard deviation=1. The numbers were ranked in magnitude, and one fourth of the ranks were designated to each of the four treatments. This ensured equal numbers of subjects per condition.	
Participants	80 subjects, aged 19-54.	

Rose 1996 (Continued)

Interventions	Group 1: Nicotine patch/mecamylamine Group 2: Nicotine patch Group 3: Mecamylamine Group 4: No drug All drugs were administered for 4 weeks prior to cessation. After the quit date, all groups received nicotine/mecamylamine for 6 weeks.	
Outcomes	Continuous abstinence at six months. Validation: Expired carbon monoxide less than or equal to 8ppm	
Notes		
Risk of bias		
Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	No details given

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Elan 2004	RCT of nicotine, mecamylamine (alone and in combination) vs placebo, in 1191 smokers; follow up only four weeks
Glover 2007	RCT of three formulations of combined nicotine and mecamylamine patch; follow up only four weeks
Rose 2006	RCT of nicotine patch vs placebo, taken prior to quit date, in 96 smokers (6 groups, factorial design). All participants took mecamylamine 10mg daily during trial. This trial is included in our review of NRT.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Glossary of terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products. May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence
Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation': A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood.
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence.
Cessation	Also called 'quitting' The goal of treatment to help people achieve abstinence from smoking or other tobacco use, also used to describe the process of changing the behaviour
Continuous abstinence	Also called 'sustained abstinence' A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence
'Cold Turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support.
Craving	A very intense urge or desire [to smoke]. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004; 6(4): 599-614

(Continued)

Dopamine	A neurotransmitter in the brain which regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size': The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco.
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse.
nAChR	[neural nicotinic acetylcholine receptors]: Areas in the brain which are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking.
Nicotine Replacement Therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free. The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges.
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial.
Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. NRT, bupropion
Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation which typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes et al 'Measures of abstinence in clinical trials: issues and recommendations'; Nicotine & Tobacco Research, 2003; 5 (1); 13-25
Relapse	A return to regular smoking after a period of abstinence

(Continued)

Secondhand smoke	Also called passive smoking or environmental tobacco smoke [ETS] A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins.
Self-efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively.
Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects.
Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614

WHAT'S NEW

Last assessed as up-to-date: 1 December 2010.

Date	Event	Description
22 June 2011	Amended	Additional table converted to appendix to correct pdf format

HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1998

Date	Event	Description
16 February 2011	Amended	Date assessed up-to-date corrected
2 December 2010	New search has been performed	Searches updated, one trial added to excluded studies
28 October 2008	Amended	Converted to new review format.
25 April 2007	New search has been performed	Searches updated, one trial added to excluded studies
24 August 2004	New search has been performed	Searches updated, one trial added to excluded studies
27 February 2002	Amended	Minor change to discussion and implications

CONTRIBUTIONS OF AUTHORS

TL and LS jointly developed the protocol, extracted data and wrote the text.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- Department of Primary Health Care, Oxford University, UK.

External sources

- NHS Research and Development National Cancer Programme, England, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Cutaneous; Drug Therapy, Combination; Mecamylamine [*therapeutic use]; Nicotine [administration & dosage; therapeutic use]; Nicotinic Antagonists [*therapeutic use]; Smoking [*prevention & control]; Smoking Cessation [*methods]

MeSH check words

Humans