Clonidine for smoking cessation (Review)

Gourlay SG, Stead LF, Benowitz N
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ABSTRACT

Background
Clonidine was originally used to lower blood pressure. It acts on the central nervous system and may reduce withdrawal symptoms in various addictive behaviours, including tobacco use.

Objectives
The aim of this review is to determine clonidine’s effectiveness in helping smokers to quit.

Search strategy
We searched the Cochrane Tobacco Addiction Group trials register for trials of clonidine. Date of the most recent search: June 2008.

Selection criteria
We considered randomized trials of clonidine versus placebo with a smoking cessation endpoint assessed at least 12 weeks following the end of treatment.

Data collection and analysis
We extracted data in duplicate on the type of subjects, the dose and duration of clonidine therapy, the outcome measures, method of randomization, and completeness of follow up.

The main outcome measure was abstinence from smoking after at least 12 weeks follow up in patients smoking at baseline. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. Where appropriate, we performed meta-analysis using a fixed effect model.

Main results
Six trials met the inclusion criteria. There were three trials of oral, and three of transdermal clonidine. Some form of behavioural counselling was offered to all participants in five of the six trials.

There was a statistically significant effect of clonidine in one of these trials. The pooled risk ratio for success with clonidine versus placebo was 1.63 (95% confidence interval 1.22 to 2.18). There was a high incidence of dose-dependent side-effects, particularly dry mouth and sedation.
Authors’ conclusions

Based on a small number of trials, in which there are potential sources of bias, clonidine is effective in promoting smoking cessation. Prominent side-effects limit the usefulness of clonidine for smoking cessation.

PLAIN LANGUAGE SUMMARY

Does clonidine help smokers to quit

Clonidine is a drug used to lower blood pressure, but it may also reduce drug and alcohol withdrawal symptoms. The review of trials found that clonidine can lead to a small increase in the number of people likely to quit smoking. However, the quality of the trials was poor, which makes the evidence less reliable. Adverse effects of clonidine included a dry mouth and sedation. Clonidine may not be the best option for people trying to quit smoking, but it might be useful for people who are not helped by nicotine replacement therapy or antidepressants.

BACKGROUND

Clonidine is marketed as an antihypertensive agent and has been recommended as treatment for chronic pain syndromes (Bredfeldt 1989), menopausal flushing (Edington 1980; Ginsburg 1985), Tourette’s syndrome (Leckman 1985) and withdrawal from opiate or alcohol abuse (Gold 1993; Manhem 1985). More recently, the use of clonidine as a smoking cessation therapy has been reported. Double blind tobacco withdrawal symptom studies have reported amelioration of craving, anxiety, restlessness, tension and hunger by clonidine therapy (Glassman 1984; Gourlay 1994a; Hao 1988; Ornish 1988; Prochazka 1992) whilst another study (Franks 1989) failed to find any effect. These same studies found that sedation and other undesirable central effects accompany clonidine therapy.

A previous review of trials which reported the frequency of adverse effects (Gourlay 1995) found these were common. An adverse experience (AE) was reported by 23% to 92% (median 71%) of patients taking clonidine compared to 4% to 61% (median 28%) of patients taking placebo. The most common reports were of dry mouth, sedation and dizziness. Symptomatic postural hypotension was reported by 10% of patients taking the 0.3 mg dosage. Twice as many patients taking clonidine discontinued the drug prematurely due to adverse experiences compared with placebo recipients (7%).

The aim of this review was to examine systematically the effectiveness of clonidine for smoking cessation.

OBJECTIVES

To determine the effectiveness of clonidine therapy in helping smokers to stop smoking.

The hypothesis tested was that treatment with clonidine is more effective than placebo in achieving long-term smoking cessation.

METHODS

Criteria for considering studies for this review

Types of studies
Randomized placebo-controlled studies.

Types of participants
Any smokers.

Types of interventions
Treatment with oral or transdermal clonidine with a maximum daily dosage of >=0.2 mg.

Types of outcome measures
Smoking cessation, assessed through follow up at least 12 weeks following the end of drug treatment.
Search methods for identification of studies

Studies were identified from the Tobacco Addiction Group’s specialised register which has been developed using the strategy defined in the Review Group details. This was checked against the citation lists of previous reviews and meta-analyses of the subject, and MEDLINE and PsyCIT searches combining the MeSH terms ‘clonidine’ and ‘smoking’. We also checked for ongoing clinical trials registered on www.controlled-trials.com. Date of the most recent search: June 2008. Information on unpublished studies was requested through the email newsgroup of the Society for Research on Nicotine and Tobacco.

Data collection and analysis

Data on numbers of participants who had ceased to smoke at the final follow up were extracted independently by two reviewers (SG and LS).

In each study the strictest available criteria to define cessation were used, so figures for sustained abstinence were extracted in preference to point prevalence where both were presented. In studies where biochemical validation of cessation was available, only those participants who met the criteria for biochemically confirmed abstinence were regarded as having stopped smoking. If patients were lost to follow up they were regarded as being continuing smokers.

Following changes to the Cochrane Tobacco Addiction Group’s recommended method of data analysis the risk ratio is now used rather than the odds ratio for summarizing individual trial outcomes and for estimates of pooled effect. We estimated a pooled weighted average of risk ratios using a Mantel-Haenszel method, with 95% confidence intervals.

Unpublished data were obtained from three authors (Cummings 1991; Glassman 1993; Villagra 1989).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

A total of 21 trials which appeared to assess the efficacy of clonidine in smoking cessation were identified. Some of these only recorded withdrawal symptom endpoints but most were excluded because the follow up for cessation was too short. Two trials compared clonidine to other therapies (one to nicotine gum (Aparici 1994), and the other to nicotine gum and to naltrexone (Ahmadi 2003)) but without a placebo group. Brief details of these trials are given in the Excluded Studies section.

Six trials meeting the criteria for inclusion in the meta-analysis were identified, involving a total of 776 participants. Participants were volunteers recruited from community settings (five trials) and an internal medicine clinic. Four trials described the participants as heavy smokers.

Clonidine was taken orally in three trials and transdermally in three. The oral dosage varied from a maximum allowed of 0.15 mg per day to 0.45 mg per day. Dosage was generally individualised according to tolerance and/or body weight, and was built up prior to quit day. Transdermal dosages were 0.1 to 0.3 mg per day.

Five of the trials offered some form of behavioural therapy or counselling to all participants. One trial (Hilleman 1993) randomized half the clonidine and control groups to receive behaviour therapy, and the outcomes with and without therapy have been combined in the analysis.

Risk of bias in included studies

None of the studies reported details of randomization procedures in sufficient detail to assess the possibility of allocation bias. Assessment of blinding was not reported by any of the included studies. There was no biochemical verification of abstinence at maximum follow up in two trials. Plasma cotinine < 15 µg/ml was used in one trial, salivary cotinine < 20 µg/ml in one, expired CO in one and partial verification by random plasma thiocyanate in one. It was not clear in any of the trials whether sustained abstinence was required.

Effects of interventions

All six studies meeting the criteria favoured clonidine treatment, although only one (Glassman 1988) reached a statistically significant conclusion. Combining the results of the six studies gives a pooled risk ratio [RR] of 1.63; 95% confidence interval [CI] 1.22 to 2.18, suggesting that clonidine is effective. This equates to an absolute increase in the likelihood of quitting using clonidine of about 9%, given the quit rate amongst the pooled control groups of 14%.

There is a potential bias in excluding studies with short-term follow up from the meta-analysis. To address this, we performed a second meta-analysis including all 15 available randomized placebo-controlled studies where smoking cessation rates were reported (see list of included and excluded studies) using post-treatment cessation rates for the longer term studies. In this analysis the pooled RR was 1.31 (95% CI: 1.14 to 1.51, data not shown).

Some studies of clonidine have reported trends towards greater efficacy of clonidine for women (Glassman 1988; Glassman 1993; Hilleman 1993; Villagra 1989). Since these findings are largely based on subgroup analysis they have to be interpreted cautiously. Amongst the included studies only one (Glassman 1993) stratified by gender before randomization. Unfortunately, the study included insufficient numbers in each stratum and, as a result, the trend favouring clonidine therapy for women at 12 months follow
up may not have been statistically significant due to a type two error (i.e., failing to detect a true effect). In the Glassman 1993 study men and women in the clonidine treatment had the same rate of smoking cessation at the end of treatment (31% versus 32% at 10 weeks). A gender difference was apparent because women in the placebo group were less successful than men (20% versus 31%), suggesting that women in this study were from the outset less likely to stop than the men. Women treated with placebo were less successful than men in two other randomized studies of clonidine (Glassman 1988; Villagra 1989).

**DISCUSSION**

The result as measured by the pooled RR compares favourably with that for all forms of nicotine replacement therapy of 1.58 (95% CI: 1.50 to 1.66) found in the most recent update of the Cochrane review of NRT (Stead 2008) and for the antidepressant bupropion (Hughes 2007). Compared to nicotine replacement, the precision of the pooled clonidine result is less in comparison because there are fewer studies and the confidence intervals are wider. Bias favourable to clonidine treatment may have arisen from many sources including: unsatisfactory randomization, inadequate blinding of participants or investigators, the existence of unknown negative studies, and lax definitions of smoking cessation outcome. However, the finding of a significant effect of clonidine remained when the analysis was broadened to include studies which reported only short-term follow up. There were insufficient data available to confirm or refute differences in the effectiveness of clonidine by gender.

In considering whether to use any type of therapy, efficacy must be weighed against adverse effects for the group or individual to be treated. Clonidine has clinically significant symptoms of sedation and postural hypotension occurring in a dose-dependent manner in parallel with efficacy.

The adverse effects of clonidine make it unsuitable as the pharmacotherapy component of “first-line” smoking cessation interventions. Nicotine replacement therapies are preferable for general use because, unlike clonidine, they rarely cause adverse effects that interfere with normal daily living (ICRF GPRG 1993; Russell 1993; TNSG 1991). Similarly, while bupropion may be associated with serious adverse reactions such as seizures, it is generally better tolerated than clonidine (Hughes 2007).

Clonidine therapy is most appealing for situations where it will have multiple beneficial effects or when withdrawal symptoms are intense. For example, sedative effects may be desirable during the period of nicotine withdrawal if a smoker experiences extreme agitation and anxiety unrelieved by nicotine replacement therapy. Clonidine could be added to, or used instead of, nicotine replacement therapy in that circumstance. Clonidine therapy could also have a role in treating withdrawal from a period of multiple drug abuse because it can relieve the withdrawal symptoms from drugs other than nicotine.

The recommended dose from the available studies is 100 µg twice daily (oral or the equivalent transdermal patch), titrated up to a maximum of about 400 µg per day, as tolerated. If clonidine therapy is planned prior to the quit day it should be initiated 48 to 72 hours before smoking cessation. This will allow time for steady state plasma concentrations to be reached before the onset of tobacco withdrawal symptoms. However, given the second-line nature of clonidine therapy for smoking cessation, treatment is most likely to be initiated after the quit day, when alternative strategies have been unsuccessful, or when severe withdrawal symptoms occur. As the efficacy of clonidine treatment relates to the acute nicotine withdrawal syndrome (US DHHS 1988) (i.e., lasting three to four weeks after smoking cessation), treatment should probably not extend beyond this period. Tapering of dosing over several days at the end of therapy is recommended to avoid withdrawal effects of clonidine itself. The need for tapering particularly applies to hypertensive patients, who are at risk of rebound hypertension, and to patients with diabetes who may experience relative hypoglycaemia.

In conclusion, clonidine is effective in promoting smoking cessation. However because of a high incidence of adverse effects, such as dry mouth and sedation, clonidine is not a first-line treatment. Rather it might be targeted to the subgroup of smokers who would also benefit from its sedative effects, for example smokers expected to experience high levels of agitation and anxiety when they stop smoking.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

On the basis of available studies it is reasonable to consider oral or transdermal clonidine as a second-line pharmacotherapy for smoking cessation. Close medical supervision is essential to titrate the dose appropriately and monitor for potentially severe adverse effects. The increasing use of antidepressants as an alternative, or complement, to nicotine replacement means that clonidine is unlikely to be used in primary care settings, but may play some role in specialist treatment.

**Implications for research**

The finding that clonidine, an alpha-2 adrenergic and imidazoline receptor agonist, has efficacy in smoking cessation suggests that further work in this area is warranted. A key aspect of future research will be whether the efficacy of drugs acting via these mechanisms can be dissociated from adverse effects. Such improvements
in the benefit/risk ratio might allow first-line use in a broad population of smokers.

ACKNOWLEDGEMENTS

Steven Gourlay was supported by a National Heart Foundation of Australia Overseas Research Fellowship and is now an employee of the biotechnology company, Genentech Inc. Neal Benowitz is supported by US Public Health Service grants DA02277 and DA01696.

REFERENCES

References to studies included in this review

Glassman 1988 (published data only)

Glassman 1993 (published and unpublished data)

Hao 1988 (published data only)

Hilleman 1993 (published data only)

Niaura 1996 (published data only)

Villagra 1989 (published and unpublished data)
Villagra VG. Transdermal clonidine for smoking cessation: a randomized trial. Clinical Research 1991;39:640A.


References to studies excluded from this review

Ahmadi 2003 (published data only)

Aparici 1994 (published data only)

Appel 1987 (published data only)
Appel D. Clonidine helps cigarette smokers stop smoking, American Review of Respiratory Disease 1987;135(Suppl):A354.

Cummings 1991 (unpublished data only)
Cummings KM. A double-blind placebo controlled multi-center trial of two dosage strengths of Catapres-TTS in smoking cessation. Unpublished draft manuscript.

Davison 1988 (published data only)

Franks 1989 (published data only)

Glassman 1984 (published data only)

Gourlay 1994 (published data only)

Grimaldi 1987 (published data only)

Hilleman 1989 (published data only)
Hughes 2007

ICRF GPRG 1993

Leckman 1985

Manhem 1985

Russell 1993

Stead 2008

Additional references

Bredfeldt 1989

Edington 1980

Ginsburg 1985

Gold 1993

Gourlay 1994a

Gourlay 1995
## Characteristics of included studies  [ordered by study ID]

### Glassman 1988

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Random allocation, double blind</td>
</tr>
<tr>
<td>Participants</td>
<td>71 volunteer heavy (&gt;20/day) smokers aged 18-55, with previous failed quit attempts</td>
</tr>
</tbody>
</table>
| Interventions | All participants received individual behavioural counselling  
Treatment: 150-300 µg clonidine/day  
Control: matched placebo |
| Outcomes | Cessation at 4 weeks verified by serum cotinine  
Cessation at 26 weeks by self report. |
| Notes | Only subjects who had reduced their smoking level to less than 50% of baseline by quit day were entered in study (post-randomization exclusions) Variable dosage. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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### Glassman 1993

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Random allocation, double-blind, stratified by sex and history of depression</td>
</tr>
<tr>
<td>Participants</td>
<td>300 volunteer heavy (&gt;20/day) smokers</td>
</tr>
</tbody>
</table>
| Interventions | All participants received individual behavioural counselling  
Treatment: Oral clonidine, 150-750 µg/day  
Control: Matched placebo |
| Outcomes | Abstinence at 10 weeks, 6 months and 12 months, verified by plasma cotinine. |
| Notes | Only subjects who had reduced their smoking level to less than 50% of baseline by quit day were entered in study. Variable dosage. |

### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors’ judgement</th>
<th>Description</th>
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<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
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</tbody>
</table>
### Hao 1988

<table>
<thead>
<tr>
<th>Methods</th>
<th>Random allocation, double blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>118 heavy (over 20/day) smokers</td>
</tr>
</tbody>
</table>
| Interventions            | Treatment 1: Oral clonidine, 0.075 µg, 1 or 2 three times/day for 4 weeks  
Treatment 2: Oral diazepam, 2.5 µg, 1 or 2 three times/day for 4 weeks  
Control: placebo tablets |
| Outcomes                 | Smoking cessation at end of treatment (4 weeks), and at follow-up (av 4.5 months later). No biochemical validation, although checks made with co-workers and family. |
| Notes                    | Treatment 1 vs control used for comparison  
All participants received at least 3 one hour sessions with a psychiatrist |

#### Risk of bias

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<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Hilleman 1993

<table>
<thead>
<tr>
<th>Methods</th>
<th>Random allocation, double blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>150 volunteer heavy (&gt;1 pack/day for 3 years) cigarette smokers</td>
</tr>
</tbody>
</table>
| Interventions          | Treatment: Transdermal clonidine 0.1 - 0.2 µg/day with/without behaviour modification  
Control: Placebo patches with/without behaviour modification |
| Outcomes               | Cessation rates at 6, 12, 24 and 52 weeks of follow up, verified by random plasma thiocyanate monitoring |
| Notes                  | Behaviour modification consisted of one hour standardized group-training classes weekly for 12 months.  
With/without behaviour modification groups combined in comparison |

#### Risk of bias

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

### Niaura 1996

<table>
<thead>
<tr>
<th>Methods</th>
<th>Random allocation, double blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>72 volunteer smokers (&gt;10/day). 54 contribute to meta-analysis</td>
</tr>
</tbody>
</table>
Niaura 1996  (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>All participants received 4 sessions of individual behavioural treatment. Treatment: Transdermal clonidine 0.1 µg, 0.2 µg or 0.3 µg Control: Matched placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Abstinence at end of treatment, validated by CO &lt;10ppm, and at 12 months, verified by saliva cotinine &lt;20 µg/ml.</td>
</tr>
<tr>
<td>Notes</td>
<td>0.2 µg and 0.3 µg treatments compared with placebo.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

Villagra 1989

<table>
<thead>
<tr>
<th>Methods</th>
<th>Random allocation, double blind</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>121 smokers, no further information</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment: Transdermal clonidine 0.2 µg/day for 11 weeks Control: Placebo patch</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Abstinence at 1,4,8,12 and 24 weeks, verified by expired CO</td>
</tr>
<tr>
<td>Notes</td>
<td>Information from abstract only</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
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<th>Item</th>
<th>Authors' judgement</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>B - Unclear</td>
</tr>
</tbody>
</table>

CO: Carbon monoxide
## Characteristics of excluded studies [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmadi 2003</td>
<td>Clonidine vs nicotine gum and naltrexone. No placebo comparison group</td>
</tr>
<tr>
<td>Aparici 1994</td>
<td>Clonidine vs nicotine gum. No placebo comparison group</td>
</tr>
<tr>
<td>Appel 1987</td>
<td>Maximum follow up 10 weeks from start of Rx</td>
</tr>
<tr>
<td>Cummings 1991</td>
<td>Maximum follow up 12 weeks from quit day. Multicentre trial (350 participants) comparing 0.1 µg and 0.2 µg clonidine patch (Catapres) with placebo. 0.2 µg dose used for sensitivity analysis.</td>
</tr>
<tr>
<td>Davison 1988</td>
<td>10 week follow up from end of Rx</td>
</tr>
<tr>
<td>Franks 1989</td>
<td>Maximum follow up 4 weeks</td>
</tr>
<tr>
<td>Glassman 1984</td>
<td>Trial of effect on withdrawal symptoms not cessation</td>
</tr>
<tr>
<td>Gourlay 1994</td>
<td>Study of withdrawal symptoms</td>
</tr>
<tr>
<td>Grimaldi 1987</td>
<td>10 week follow up from end of Rx.</td>
</tr>
<tr>
<td>Hilleman 1989</td>
<td>Maximum follow up 3 months.</td>
</tr>
<tr>
<td>Murray 1989</td>
<td>Maximum follow up 4 weeks.</td>
</tr>
<tr>
<td>Nana 1998</td>
<td>Maximum follow up 4 weeks. Smoking cessation endpoint not defined.</td>
</tr>
<tr>
<td>Ornish 1988</td>
<td>Trial of effect on withdrawal symptoms not cessation</td>
</tr>
<tr>
<td>Prochazka 1992</td>
<td>5 week follow up from end of Rx</td>
</tr>
<tr>
<td>Wu 1997</td>
<td>Insufficient information in abstract on methods and results.</td>
</tr>
</tbody>
</table>
DATA AND ANALYSES

Comparison 1. Clonidine vs placebo

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Smoking Cessation</td>
<td>6</td>
<td>776</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.63 [1.22, 2.18]</td>
</tr>
</tbody>
</table>

Analysis 1.1. Comparison 1 Clonidine vs placebo, Outcome 1 Smoking Cessation.

Review: Clonidine for smoking cessation

Comparison: 1 Clonidine vs placebo

Outcome: 1 Smoking Cessation

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Control</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glassman 1988</td>
<td>9/33</td>
<td>2/38</td>
<td>3.3 %</td>
<td>5.18 [ 1.20, 22.30 ]</td>
</tr>
<tr>
<td>Hao 1988</td>
<td>24/42</td>
<td>14/38</td>
<td>26.1 %</td>
<td>1.55 [ 0.95, 2.54 ]</td>
</tr>
<tr>
<td>Villagra 1989</td>
<td>9/53</td>
<td>9/68</td>
<td>14.0 %</td>
<td>1.55 [ 0.95, 2.54 ]</td>
</tr>
<tr>
<td>Glassman 1993</td>
<td>21/152</td>
<td>16/148</td>
<td>28.8 %</td>
<td>1.28 [ 0.69, 2.35 ]</td>
</tr>
<tr>
<td>Hilleman 1993</td>
<td>19/75</td>
<td>10/75</td>
<td>17.8 %</td>
<td>1.90 [ 0.95, 3.81 ]</td>
</tr>
<tr>
<td>Niaura 1996</td>
<td>16/38</td>
<td>4/16</td>
<td>10.0 %</td>
<td>1.68 [ 0.67, 4.26 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>393</td>
<td>383</td>
<td>100.0 %</td>
<td>1.63 [ 1.22, 2.18 ]</td>
</tr>
</tbody>
</table>

Total events: 98 (), 55 (Control)

Heterogeneity: Chi^2 = 3.56, df = 5 (P = 0.61); I^2 = 0%

Test for overall effect: Z = 3.28 (P = 0.0010)

WHAT'S NEW

Last assessed as up-to-date: 15 June 2008.

17 June 2008 | Amended
Converted to new review format.

17 June 2008 | New search has been performed
Search updated; no new studies found. Outcome metric changed from odds ratio to risk ratio.
**HISTORY**

Protocol first published: Issue 1, 1997

Review first published: Issue 1, 1997

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>27 April 2006</td>
<td>New search has been performed</td>
<td>Search updated; no new studies. Change of contact author.</td>
</tr>
<tr>
<td>12 May 2004</td>
<td>New citation required but conclusions have not changed</td>
<td>Updated for 2004 issue 3. One small study (Ahmadi 2003) added to Excludeds. No placebo comparison group.</td>
</tr>
<tr>
<td>10 June 2001</td>
<td>New search has been performed</td>
<td>Updated for 2001 issue 4. No major changes, but one large unpublished study without long term follow-up added to list of excluded studies and to a sensitivity analysis on impact of excluding short term studies. Implications for research added.</td>
</tr>
</tbody>
</table>

**CONTRIBUTIONS OF AUTHORS**

SG initiated the review, identified studies, extracted data and drafted the text. LS assisted with study identification and data extraction. NB contributed text and scientific editorial assistance.

**DECLARATIONS OF INTEREST**

Steven Gourlay received grant support 1990-1994 from makers of nicotine replacement therapies and clonidine. Neal Benowitz is a consultant to various pharmaceutical companies that manufacture and/or market nicotine replacement products.

**SOURCES OF SUPPORT**

**Internal sources**

- University of California, San Francisco, USA.
- Department of Primary Health Care, University of Oxford, UK.
External sources

- National Heart Foundation, Australia.
- US Public Health Service, USA.
- NHS Research and Development National Cancer Programme, England, UK.

INDEX TERMS

Medical Subject Headings (MeSH)
*Smoking Cessation; Clonidine [*therapeutic use]; Randomized Controlled Trials as Topic; Smoking [prevention & control]

MeSH check words
Humans