Anxiolytics for smoking cessation (Review)

Hughes JR, Stead LF, Lancaster T

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 8

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Anxiolytics for smoking cessation

John R Hughes[1], Lindsay F Stead[2], Tim Lancaster[3]

[1]Dept of Psychiatry, University of Vermont, Burlington, Vermont, USA. [2]Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. [3]Department of Primary Health Care, University of Oxford, Oxford, UK

Contact address: John R Hughes, Dept of Psychiatry, University of Vermont, UHC Campus, OH3 Stop # 482, 1 South Prospect Street, Burlington, Vermont, 05401, USA. john.hughes@uvm.edu.

Editorial group: Cochrane Tobacco Addiction Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2011.
Review content assessed as up-to-date: 4 October 2009.

Citation: Hughes JR, Stead LF, Lancaster T. Anxiolytics for smoking cessation. *Cochrane Database of Systematic Reviews* 2000, Issue 4. Art. No.: CD002849. DOI: 10.1002/14651858.CD002849.

ABSTRACT

Background

There are two reasons to believe anxiolytics might help in smoking cessation. Anxiety may be a symptom of nicotine withdrawal. Secondly, smoking could be due to an attempt to self-medicate an anxiety problem.

Objectives

The aim of this review is to assess the effectiveness of anxiolytic pharmacotherapy in aiding long term smoking cessation. The drugs include buspirone; diazepam; doxepin; meprobamate; ondansetron; and the beta-blockers metoprolol, oxprenolol and propanolol.

Search strategy

We searched the Cochrane Tobacco Addiction Group specialised register (most recent search October 2009), which includes trials indexed in MEDLINE, EMBASE, SciSearch and PsycINFO, and conference abstracts.

Selection criteria

We considered randomized trials comparing anxiolytic drugs to placebo or an alternative therapeutic control for smoking cessation. We excluded trials with less than six months follow up.

Data collection and analysis

We extracted data in duplicate on the type of study population, the nature of the drug therapy, the outcome measures, method of randomization, and completeness of follow up.

The main outcome measure was abstinence from smoking after at least six months 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 of relative risks using a fixed effect model.

Main results

There was one trial each of the anxiolytics diazepam, meprobamate, metoprolol and oxprenolol. There were two trials of the anxiolytic buspirone. None of the trials showed strong evidence of an effect for any of these drugs in helping smokers to quit. However, confidence intervals were wide, and an effect of anxiolytics cannot be ruled out on current evidence.

Authors' conclusions

There is no consistent evidence that anxiolytics aid smoking cessation, but the available evidence does not rule out a possible effect.

PLAIN LANGUAGE SUMMARY

Do pharmacotherapies which reduce anxiety help smokers to quit

Anxiety can contribute to increased smoking, and may be a smoking withdrawal symptom. Medications to reduce anxiety (anxiolytics) may theoretically help smokers trying to quit. There have not been many trials, and none of them showed strong evidence of an effect on quitting.

BACKGROUND

Whilst nicotine replacement has become the most widely used pharmacotherapy for smoking cessation (Stead 2008), some smokers prefer a treatment which does not use nicotine. A range of other classes of pharmacotherapy have been tested for possible effectiveness, with the nicotine receptor agonist varenicline (Cahill 2008)and the antidepressants bupropion and nortriptyline (Hughes 2007a) identified as established therapies. Anxiolytics have also been proposed as treatments. Anxiety is a symptom of nicotine withdrawal (Hughes 2007b), and smoking may decrease anxiety (Morissette 2007; Zvolensky 2005). Anxiolytics may therefore aid cessation by abating a withdrawal symptom or by replacing the reinforcing effects of nicotine. Although clonidine is sometimes considered an anxiolytic, its efficacy for smoking cessation is covered in a separate Cochrane review (Gourlay 2004).

Short-term Trials

The focus of this review and meta-analysis is on trials which provide evidence for an effect on long-term smoking cessation and these are described in the Results section. Short-term trials investigating anxiolytics have also been completed, and they are described below.

Buspirone

Buspirone is a non-benzodiazepine anxiolytic with effects on serotonin neurotransmission. It is non-sedating and non-addicting. Doses used in smoking cessation trials have ranged from a maximum of 30 mg/day to 60 mg/day, over a period of nine to thirteen weeks, beginning therapy between two and three weeks before the quit date. Three short term studies have provided inconsistent evidence of an effect either on immediate abstinence rates or on withdrawal symptoms. West 1991 (61 smokers) found an effect on abstinence at four weeks (47% versus 16%, P < 0.025), but no differences on withdrawal symptom scores (including anxiety) amongst abstinent subjects. Robinson 1992 (54 smokers) failed to detect an effect of buspirone on any withdrawal symptoms or abstinence rates; two-week abstinence rates were 62% for buspirone and 52% for placebo. Hilleman 1992 (37 smokers) found statistically significant (P < 0.05) reductions in craving, anxiety, irritability, restlessness and sadness after seven days of attempted abstinence in the treated group.

Diazepam

This tranquilliser has been used in one long-term smoking cessation trial described in the Results section.

Meprobamate

This tranquilliser has been used in one long-term smoking cessation trial described in the Results section.

Ondansetron

Ondansetron is a serotonin 5-HT3 antagonist, which has been proposed for smoking therapy on the basis that 5-HT3 antagonists should reduce the reinforcing effect of nicotine. Zacny 1993 investigated the effect of ondansetron on tobacco consumption under laboratory conditions and found no evidence that it altered smoking behaviour. West 1996 randomized 101 smokers to ondansetron 0.25 mg twice a day or to placebo for two weeks before and four weeks after a quit date. Subjects also received group-oriented behavioural therapy. At four-week follow up from the quit date, they found no significant difference in continuous abstinence rates, validated by salivary cotinine. Abstinence rates were 59% for

ondansetron and 66% for placebo. Although the relatively high success rate from the group therapy could have masked any effect of the drug, it would be less likely to have affected withdrawal symptom severity, which did not differ between the groups. Neither group showed any marked increase in anxiety.

Beta-blockers

Beta-blockers have potential anxiolytic effects, and for this reason have been tested for smoking withdrawal activity. Farebrother 1980 (73 subjects) failed to find any effect of propanolol (40 mg three times a day) on abstinence at the end of eight weeks treatment, with a high drop out rate and low success rates in both treated (9%) and placebo (8%) groups.

OBJECTIVES

To assess the evidence for the effectiveness in assisting long-term smoking cessation drugs with anxiolytic properties including: buspirone, diazepam, meprobamate, metoprolol, ondansetron, oxprenolol, propanolol.

For each drug identified as having been used in a smoking cessation trial, the hypothesis tested was that it 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 trials against placebo or an alternative therapeutic control.

Types of participants

Any smokers.

Types of interventions

Treatment with any drug with anxiolytic properties, including beta blockers, but excluding clonidine which is covered by a separate review (Gourlay 2004).

Types of outcome measures

Abstinence from smoking, assessed at follow up at least six months from start of treatment.

Search methods for identification of studies

Studies were identified from the Tobacco Addiction Group's specialised register. All trials using pharmacotherapy other than nicotine, bupropion, nortriptyline, varenicline, clonidine or lobeline for smoking cessation were found, and those using drugs generally classified as having an anxiolytic effect were selected for consideration for inclusion in this review. The citation lists of these studies, previous reviews of non-nicotine pharmacotherapy (Fagerstrom 2006; George 2004; McRobbie 2005; Siu 2007) and abstracts from the meetings of the Society for Research on Nicotine and Tobacco were checked. An additional search was made of MEDLINE (most recent search, via PubMed, October 5th 2009) and EMBASE (most recent search, via Ovid, 2009 week 40) using the search terms 'Anti-Anxiety Agents/exp' (MEDLINE) or 'Anxiolytic Agent /exp' (EMBASE) or any drug already identified as relevant from the register, combined with 'smok* or tobacco'.

Data collection and analysis

Data on the number of study participants who had ceased to smoke at final follow up were extracted by LS and TL independently.
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 that used biochemical validation of cessation, only those subjects meeting the criteria for biochemically confirmed abstinence were regarded as having stopped smoking. Subjects in either group lost to follow up were regarded as being continuing smokers. As far as possible an Intention-to-treat analysis is applied. Where subjects appeared to have been randomized but were not included in the data presented by the author this is noted in the study description (see Characteristics of included studies table).
Data on the number of quitters in the treatment and control groups, and a risk ratio with confidence intervals, is presented in the Summary of Analyses. For each type of drug where more than one eligible trial was identified, an estimate of the most likely effect size is calculated using the Mantel-Haenszel fixed-effect method, in line with the current recommendation of the Cochrane Handbook. Although a summary statistic is displayed, the conclusions which can be drawn from it must be cautious. Where trials are small and few in number the confidence intervals will be wide.
Unpublished studies or studies found only as abstracts were included where sufficient detail was available. Authors were contacted for further data if necessary.

We include 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.

Additonal details of included and studies are given in the Characteristics of included studies table. Studies that appeared relevant but were not included are listed in the Characteristics of excluded studies table.

Buspirone

Three trials with long-term follow up were identified. Cinciripini 1995 and Schneider 1996 compared buspirone to placebo. Cinciripini divided subjects into low and high anxiety groups on the basis of a Profile of Mood States Anxiety/Tension Scale (POMS) before randomization. Because there was evidence for a therapy/anxiety state interaction the two groups were entered separately into the meta-analysis (Cinciripini 1995 L; Cinciripini 1995 H). Hilleman 1994 compared buspirone with fixed-dose or tapered dose transdermal nicotine, and since this study lacks a placebo group it is not compared directly with the other two trials. Two studies compared a combination of sertraline (an antidepressant) and buspirone to placebo. We excluded these because the effect of buspirone could not be evaluated separately

Diazepam

Hao 1988 in China tested the benzodiazepine, diazepam in a randomized design against both placebo and clonidine. Suggested dosage was 7.5 - 15 mg per day for four weeks. Subjects also had three individual sessions with a psychiatrist. Long-term follow up was stated to be at an average of 4.5 months from the end of drug therapy, which has been treated as six months from the quit date, sufficiently long to meet the inclusion criteria.

Meprobamate

Schwartz 1968 tested meprobamate (400 mg per day) in a factorial design trial which randomized subjects to prescription or placebo, alone or in combination with group or individual counselling. Although one-year and eighteen-month follow-up results are reported, absolute abstinence at any point is not used an outcome measure, with success being classified as a reduction of 85% or more in baseline smoking. Subjects could be counted as successes at any follow-up point, irrespective of their smoking status at previous points.

Ondansetron

No trials met the inclusion criteria.

Beta-blockers

Dow 1984 tested two types; metoprolol (100 mg twice a day) or oxprenolol (80 mg twice a day) against placebo, using a double dummy technique, with follow up at 12 months.

Risk of bias in included studies

Very few of the trials reported randomization methods in sufficient detail for the possibility of allocation bias to be discounted. The definition of abstinence was not always explicit and biochemical validation of self-reported smoking status was not always used. Descriptions of trial design are given in the table 'Characteristics of Included Studies'.

Effects of interventions

Buspirone

In the two trials comparing buspirone with placebo, the pooled risk ratio (RR) was 0.76; 95% confidence interval (CI) 0.42 to 1.37; *Analysis 1.1.1*). The point estimate does not suggest effectiveness but the confidence intervals do not rule out a clinically useful effect. The trial comparing buspirone with a known effective treatment, transdermal nicotine (Hilleman 1994), failed to detect evidence of a difference between the nicotine patch and buspirone therapies (RR 1.08; 95% CI 0.70 to 1.65; *Analysis 1.1.2*). Cinciripini found a significant benefit of buspirone among the high anxiety subjects at the end of drug therapy (88% versus 61%, $P < 0.01$). However, Schneider 1996 did not replicate this effect.

Diazepam

One trial (Hao 1988) found no difference between diazepam and placebo at long-term follow up, (RR 1.00, 95% CI 0.56 to 1.80; *Analysis 2.1*); both groups had behavioural therapy and quit rates were relatively high, 37% in each. Withdrawal symptom scores were also similar in each group. However the questionnaire contained 10 items so any effect on anxiety may have been obscured.

Meprobamate

One trial (Schwartz 1968; *Analysis 3*) found no evidence for a beneficial effect of this tranquilliser on reduction in smoking. Subjects on placebo did consistently better than those on meprobamate within each counselling condition. The authors suggest that side effects of the drug such as drowsiness and sensitivity to alcohol 'may have been detrimental to the subject's own determination to stop smoking'.

Ondansetron

There was no evidence from long-term trials.

Beta-blockers

One trial (Dow 1984) found a cessation rate at 12-month follow up of 17% for oxprenolol, 24% for metoprolol and 3% for placebo. The difference was statistically significant for metoprolol (*Analysis 4.1.2*) but not for oxprenolol (*Analysis 4.1.1*). However the marked difference between the groups on active drug and placebo developed after the end of drug treatment, which is surprising.

DISCUSSION

Trial data on anxiolytics for smoking cessation are limited. Although there are no strongly positive long-term studies, the confidence intervals for the available data do not rule out a possible effect. The rationale for studying anxiolytics is based on two assumptions: a) cessation causes increased anxiety (Hughes 2007b), and b) smoking relieves this (Morissette 2007; Zvolensky 2005). Some studies cast doubt on these assumptions (West 1997; Parrott 1999). On the other hand, people who are still smoking may be those with minor or major psychiatric comorbidity (Morissette 2007; Zvolensky 2005); thus, using anxiolytics for highly anxious patients may prove helpful. In one study high anxiety patients appeared to benefit more (Cinciripini 1995 H) whilst in the other they did not (Schneider 1996). Two trials combining buspirone with the selective serotonin reuptake inhibitor (SSRI) sertraline as an adjunct to cognitive behavioural therapy have both reported significant long tem effects (Carrão 2007, Ionescu 2008). These are excluded from the review because it is not possible to separate out the effect of the anxiolytic buspirone alone, from that of the SSRI. SSRIs alone do not appear to aid long term cessation (Hughes 2007a). However, the authors of the above two trials hypothesize a mechanism in which the combined use of these would be effective. Many of the anxiolytics have significant side effects such as a risk of abuse or dependence, and sedation. Given the reluctance of smokers to take medication for cessation, probably only anxiolytics with benign side-effect profiles (e.g. buspirone) would be acceptable to smokers.

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence neither supports nor rules out an effect of anxiolytics on smoking cessation. In view of this uncertainty and the side effects of the drugs, there is little justification for using them. One drug with some anxiolytic effects, clonidine, does show evidence of efficacy (Gourlay 2004), but the incidence of side effects from clonidine is relatively high.

Implications for research

Further studies of anxiolytics for highly anxious smokers may be reasonable.

ACKNOWLEDGEMENTS

JR Hughes is supported by Research Scientist Development Award DA-00490 from the National Institute on Drug Abuse.

REFERENCES

References to studies included in this review

Cinciripini 1995 L *{published data only}*
Cinciripini PM, Lapitsky LG, Seay S, Wallfisch A, Meyer WJ, Vanvunakis H. A placebo-controlled evaluation of the effects of buspirone on smoking cessation - differences between high-anxiety and low-anxiety smokers [published erratum appears in J Clin Psychopharmacol 1995;15:408]. *Journal of Clinical Psychopharmacology* 1995;**15**:182–91.

Cinciripini 1995 H *{published data only}*
Cinciripini PM, Lapitsky LG, Seay S, Wallfisch A, Meyer WJ, Vanvunakis H. A placebo-controlled evaluation of the effects of buspirone on smoking cessation - differences between high-anxiety and low-anxiety smokers [published erratum appears in J Clin Psychopharmacol 1995;15:408]. *Journal of Clinical Psychopharmacology* 1995;**15**:182–91.

Dow 1984 *{published data only}*
Dow RJ, Fee WM. Use of beta-blocking agents with group therapy in a smoking withdrawal clinic. *Journal of the Royal*

Society of Medicine 1984;**77**:648–51.

Hao 1988 ***{published data only}***
Hao W, Young D, Wei H [corrected to Hao-W]. Effect of clonidine on cigarette cessation and in the alleviation of withdrawal symptoms [published erratum appears in Br J Addict 1988;83:1467]. *British Journal of Addiction* 1988; **83**:1221–6.

Hilleman 1994 ***{published data only}***
Hilleman DE, Mohiuddin SM, Delcore MG. Comparison of fixed-dose transdermal nicotine, tapered-dose transdermal nicotine, and buspirone in smoking cessation. *Journal of Clinical Pharmacology* 1994;**34**:222–4.

Schneider 1996 ***{published data only}***
Schneider NG, Olmstead RE, Steinberg C, Sloan K, Daims RM, Brown HV. Efficacy of buspirone in smoking cessation - a placebo-controlled trial. *Clinical Pharmacology and Therapeutics* 1996;**60**:568–75.

Schwartz 1968 ***{published data only}***
* Schwartz JL, Dubitzky M. One-year follow-up results of a smoking cessation program. *Canadian Journal of Public Health* 1968;**59**:161–5.
Schwartz JL, Dubitzky M. The smoking control research project: purpose, design, and initial results. *Psychological Reports* 1967;**20**:367–76.

References to studies excluded from this review

Bartlett 1957 ***{published data only}***
Bartlett WA, Whitehead RW. The effectiveness of meprobamate and lobeline as smoking deterrents. *Journal of Laboratory and Clinical Medicine* 1957;**50**(2):278–81.

Carrão 2007 ***{published data only}***
Carrão JL, Moreira LB, Fuchs FD. The efficacy of the combination of sertraline with buspirone for smoking cessation. A randomized clinical trial in nondepressed smokers. *European Archives of Psychiatry & Clinical Neuroscience* 2007;**257**:383–8.

Farebrother 1980 ***{published data only}***
Farebrother MJ, Pearce SJ, Turner P, Appleton DR. Propranolol and giving up smoking. *British Journal of Diseases of the Chest* 1980;**74**:95–6.

Gawin 1989 ***{published data only}***
Gawin F, Compton M, Byck R. Buspirone reduces smoking [letter]. *Archives of General Psychiatry* 1989;**46**(3):288–9.

Hatsukami 2003 ***{published data only}***
Hatsukami DK, Jensen J, Brauer LH, Mooney M, Schulte S, Sofuoglu M, et al.Lack of effect of 5HT(3) antagonist in mediating subjective and behavioral responses to cotinine. *Pharmacology Biochemistry and Behavior* 2003;**75**:1–7.

Hilleman 1992 ***{published data only}***
Hilleman DE, Mohiuddin SM, del Core MG, Sketch MH. Effect of buspirone on withdrawal symptoms associated with smoking cessation. *Archives of Internal Medicine* 1992; **152**:350–2.

Ionescu 2008 ***{unpublished data only}***
Daniela Ionescu, Carmen Cristescu. The combination of sertraline with buspirone for smoking cessation process - the effectiveness and adverse events. *Toxicology Letters* 2008; **180**(Suppl 1):S130. [DOI: 10.1016/j.toxlet.2008.06.751]

Robinson 1991 ***{published data only}***
Robinson MD, Smith WA, Cederstrom EA, Sutherland DE. Buspirone effect on tobacco withdrawal symptoms: a pilot study. *Journal of the American Board of Family Practice* 1991;**4**(2):89–94.

Robinson 1992 ***{published data only}***
Robinson MD, Pettice YL, Smith WA, Cederstrom EA, Sutherland DE, Davis H. Buspirone effect on tobacco withdrawal symptoms: a randomized placebo-controlled trial. *Journal of the American Board of Family Practice* 1992; **5**(1):1–9.

West 1991 ***{published data only}***
West R, Hajek P, McNeill A. Effect of buspirone on cigarette withdrawal symptoms and short-term abstinence rates in a smokers clinic. *Psychopharmacology Berlin* 1991;**104**:91–6.

West 1996 ***{published data only}***
West R, Hajek P. Randomized controlled trial of ondansetron in smoking cessation. *Psychopharmacology Berlin* 1996;**126**:95–6.

Zacny 1993 ***{published data only}***
Zacny JP, Apfelbaum JL, Lichtor JL, Zaragoza JG. Effects of 5-hydroxytryptamine3 antagonist, ondansetron, on cigarette smoking, smoke exposure and mood in humans. *Pharmacology, Biochemistry, and Behavior* 1992;**44**:387–91.

Additional references

Cahill 2008
Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD006103.pub3]

Cochrane Handbook
Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions 4.2.6 [updated September 2006]. http://www.cochrane.org/resources/handbook/hbook.htm (accessed 18th April 2007) 2006.

Fagerstrom 2006
Fagerstrom K, Balfour DJK. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. *Expert Opinion on Investigational Drugs* 2006;**15**(2):107–16.

George 2004
George TP, O'Malley SS. Current pharmacological treatments for nicotine dependence. *Trends in Pharmacological Sciences* 2004;**25**(1):42–8.

Gourlay 2004
Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000058.pub2]

Hughes 2007a
Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD000031.pub3]

Hughes 2007b
Hughes JR. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine & Tobacco Research* 2007;**9**(3):315–27.

McRobbie 2005
McRobbie H, Lee M, Juniper Z. Non-nicotine pharmacotherapies for smoking cessation. *Respiratory Medicine* 2005;**99**:1203–12.

Morissette 2007
Morisette SB, Tull MT, Gulliver SB, Kamholz BW, Zimering RT. Anxiety, anxiety disorders, tobacco use, and nicotine: a critical review of interrelationships. *Psychological Bulletin* 2007;**133**(2):245–72.

Parrott 1999
Parrott AC. Does cigarette smoking cause stress?. *The American Psychologist* 1999;**54**:817–20.

Siu 2007
Siu ECK, Tyndale RF. Non-nicotinic therapies for smoking cessation. *Annual Review of Pharmacology and Toxicology* 2007;**47**:541–64.

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]

West 1997
West R, Hajek P. What happens to anxiety levels on giving up smoking?. *American Journal of Psychiatry* 1997;**154**: 1589–92.

Zvolensky 2005
Zvolensky MJ, Feldner MT, Leen-Feldner EW, McLeish AC. Smoking and panic attacks, panic disorder, and agoraphobia: a review of the empirical literature. *Clinical Psychology Review* 2005;**6**:761–89.

References to other published versions of this review

Hughes 1997
Hughes JR, Stead LF, Lancaster T. Anxiolytics and antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 1997, Issue 3.

Hughes 2000
Hughes JR, Stead LF, Lancaster T. Anxiolytics for smoking cessation. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002849]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Cinciripini 1995 L

Methods	BUSPIRONE Country: USA Recruitment: volunteers
Participants	101 subjects with > 3 yr history of >=15 cigs/day, divided into 'high anxiety' and 'low anxiety' groups on the basis of POMS anxiety score above or below 44. (48 smokers in low anxiety group)
Interventions	1. Buspirone, for 12 wks, max 45mg/day for 4 wks pre quit date, increasing to max 60mg/day after quit. 2. Placebo Both groups received 9 sessions of a cognitive behavioural intervention, and were required to pay a deposit of US$140 dollars, repayable in stages.
Outcomes	Cessation validated by salivary cotinine <14 ng/ml at 12ms after end of group therapy. Slips were allowed if smoking occurred on less than 5 days since previous assessment.
Notes	High anxiety and low anxiety groups entered separately, since there was evidence of interaction. Numbers worked back from percentages and rounded up.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned 'balanced on sex ratio and screening level of cotinine'.
Allocation concealment (selection bias)	Unclear risk	No details given

Cinciripini 1995 H

Methods	BUSPIRONE See Cinciripini 1995 L - trial stratified by anxiety levels
Participants	53 smokers in high anxiety group
Interventions	see above
Outcomes	see above
Notes	High anxiety and low anxiety groups entered separately, since there was evidence of interaction.

Cinciripini 1995 H (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Cinciripini 1995 L
Allocation concealment (selection bias)	Unclear risk	See Cinciripini 1995 L

Dow 1984

Methods	BETA-BLOCKERS Country: Scotland Recruitment: Smoking withdrawal clinic waiting list
Participants	101/277 subjects found to be suitable for beta-blocker therapy
Interventions	1. Oxprenolol 160 mg/day for 40 days 2. Metoprolol 200 mg/day for 40 days 3. Double dummy placebo All received a standard course of group therapy and health education
Outcomes	Cessation (not defined) at 12ms No validation
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given

Hao 1988

Methods	DIAZEPAM Country: China Recruitment: no details
Participants	118 smokers, (111 males, 7 females) >20cigs/day
Interventions	1. Diazepam ('Valium') recommended dosage 7.5mg/day for 4 wks 2. Clonidine, recommended dosage 0.225 mg/day for 4 wks 3. Matched placebo

Hao 1988 (*Continued*)

	All participants had 3 individual sessions with a psychiatrist	
Outcomes	Continuous abstinence at follow up on average 4.5ms from end of treatment. No biochemical validation, but confirmation sought from family and co-workers.	
Notes	Efficacy of clonidine has been assessed in a separate Cochrane review (Gourlay 2004)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given

Hilleman 1994

Methods	BUSPIRONE Country: USA Recruitment: advertisement	
Participants	208 smokers, >1 pack/day, with more than one serious attempt to stop smoking, no history of psychiatric disorder	
Interventions	1. Buspirone 15mg for 7 days then 30mg for 21 days 2. Fixed dose transdermal nicotine 21 or 22mg patch 3. Tapered dose 21 or 22mg, 14mg, 7mg patch Behavioural support consisted of 12 weekly sessions	
Outcomes	Abstinence at 24 wks (criteria not specified), partial validation by random plasma thiocyanate testing.	
Notes	Buspirone group compared with 2 and 3 combined	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given

Schneider 1996

Methods	BUSPIRONE Country: USA Recruitment: advertisements
Participants	100 subjects, >10 cigs/day for >5 years, previous attempt at quitting. No history of diagnosed anxiety or depression.
Interventions	1. Buspirone max 30mg/day for 3 wks pre quit date, max 60mg/day for further 6 wks 2. Matched placebo Both groups received controlled presentation (by video) of coping and relapse prevention skills. A total of 17 visits
Outcomes	1 yr abstinence, with no reported slips, validated by CO =< 8ppm
Notes	24/124 smokers dropped out pre quit day, not included in analysis Post hoc division into high and low anxiety groups. No evidence of differential effect.

Risk of bias

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

Schwartz 1968

Methods	MEPROBAMATE Country; USA Recruitment: Volunteers in a health care plan
Participants	324 smokers, >10cigs/day
Interventions	1. Tranquillizer alone 2. Placebo 3. Tranquilizer + individual counselling 4. Placebo + individual counselling 5. Tranquilizer + group counselling 6. Placebo + group counselling 7. Group counselling, no pill 8. Control I - no intervention 9. Control II - Completed psychosocial questionnaires and medical screening but no further intervention
Outcomes	Success was defined by a reduction of >85% from baseline smoking at follow up. Follow up at end of treatment (8 wks), 4ms and 1 yr, with telephone follow up of successes at 18ms

Schwartz 1968 (*Continued*)

Notes	One year success rates used. 1 compared with 2, 3 with 4, and 5 with 6 as separate subgroups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, stratified by social class, method not described
Allocation concealment (selection bias)	Unclear risk	No details given

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

Study	Reason for exclusion
Bartlett 1957	Meprobamate - Two trials: 1st a cross-over trial comparing it with lobeline and placebo. 2nd comparing meprobamate and placebo, to be taken when withdrawal symptoms were felt by subjects. There were 16 subjects and no indication of the follow up period was given
Carrão 2007	Buspirone - Pharmacotherapy was combined buspirone and sertraline, vs placebo, as adjunct to cognitive behavioural therapy. Effect of buspirone could not be separated.
Farebrother 1980	Propanolol - short follow up 40mg x3/day for 8 wks vs placebo, subjects advised to try to quit after 1 wk of treatment
Gawin 1989	Buspirone - open trial
Hatsukami 2003	Granisetron - short-term study of withdrawal symptoms during 15 days of abstinence
Hilleman 1992	Buspirone - short follow up 15mg/day for 1 wk, 30mg/day for 3 wks. Abstinence at 7 days post-cessation.
Ionescu 2008	Buspirone - Pharmacotherapy was combined buspirone and sertraline, vs placebo, as adjunct to cognitive behavioural therapy. Effect of buspirone could not be separated.
Robinson 1991	Buspirone - case series
Robinson 1992	Buspirone - short follow up Buspirone 30mg/day beginning 3 wks before abrupt cessation. Abstinence assessed 2 wks after quit day.
West 1991	Buspirone - short follow up

(*Continued*)

West 1996	Ondansetron - short follow up 0.25 mg/day 2 wks before and 4 wks after quit date
Zacny 1993	Ondansetron - Crossover trial of smoking behaviour in an inpatient laboratory

DATA AND ANALYSES

Comparison 1. Buspirone versus placebo/NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long term abstinence	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Buspirone vs placebo	3	201	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.42, 1.37]
1.2 Buspirone vs nicotine patch	1	208	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.65]

Comparison 2. Diazepam versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous abstinence (6m)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Meprobamate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Reduction of >85% at 12 month f/up	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Prescription only	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Prescription and individual counselling	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Prescription and group counselling	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 4. Beta-blockers versus placebo

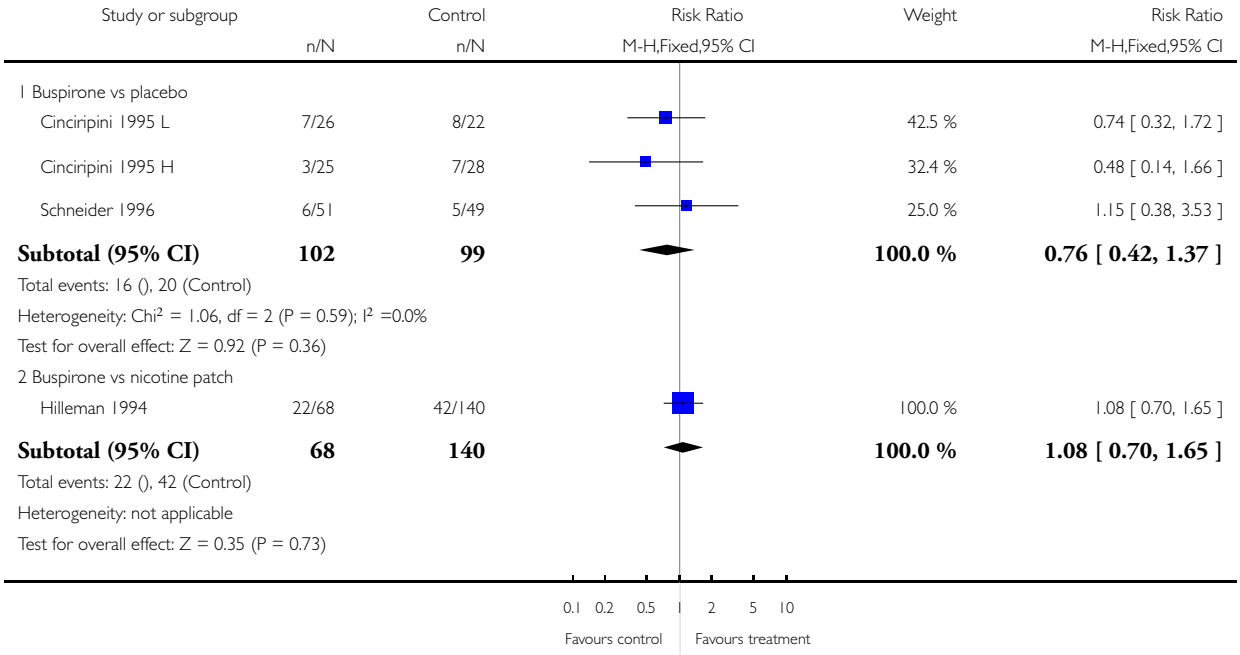
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long term abstinence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Oxprenolol versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Metoprolol versus placebo	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Buspirone versus placebo/NRT, Outcome 1 Long term abstinence.

Review: Anxiolytics for smoking cessation

Comparison: 1 Buspirone versus placebo/NRT

Outcome: 1 Long term abstinence

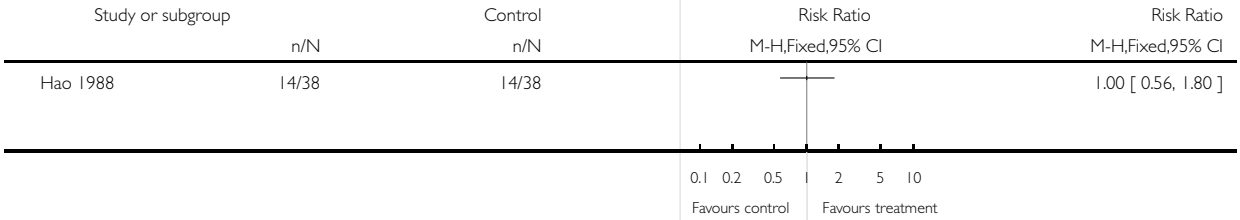


Analysis 2.1. Comparison 2 Diazepam versus placebo, Outcome 1 Continuous abstinence (6m).

Review: Anxiolytics for smoking cessation

Comparison: 2 Diazepam versus placebo

Outcome: 1 Continuous abstinence (6m)

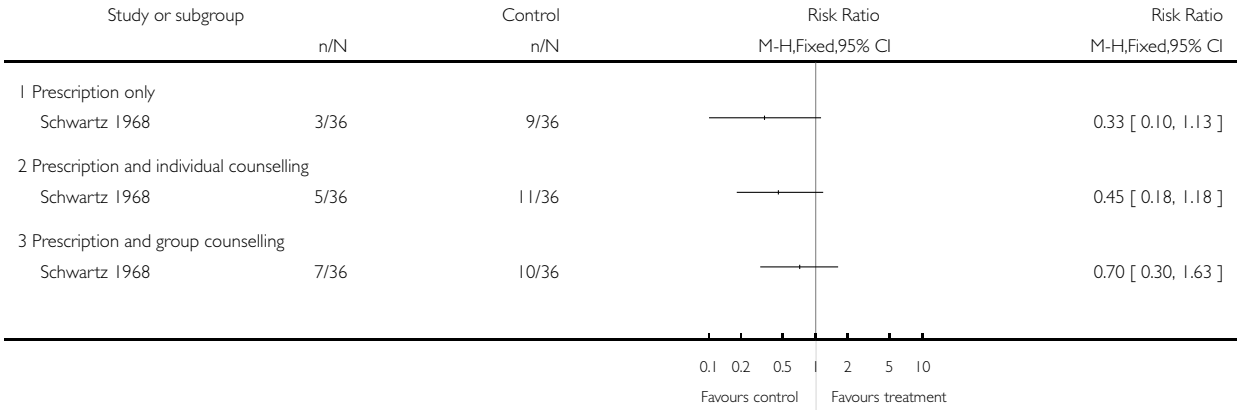


Analysis 3.1. Comparison 3 Meprobamate versus placebo, Outcome 1 Reduction of >85% at 12 month f/up.

Review: Anxiolytics for smoking cessation

Comparison: 3 Meprobamate versus placebo

Outcome: 1 Reduction of >85% at 12 month f/up

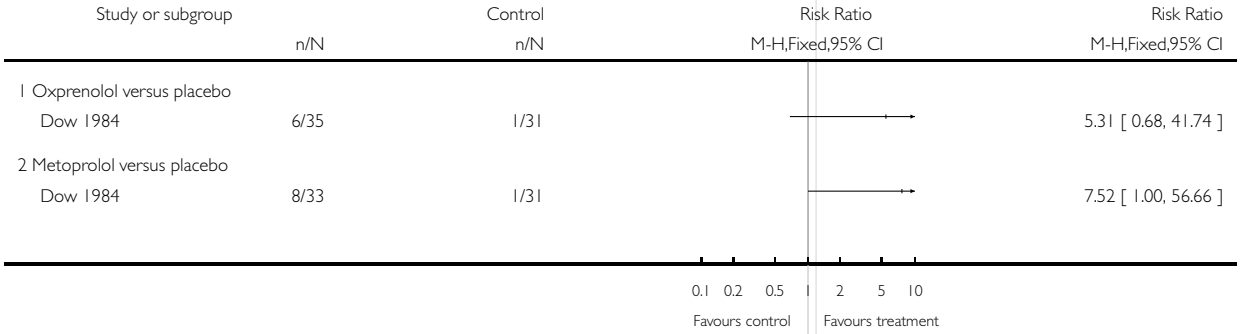


Analysis 4.1. Comparison 4 Beta-blockers versus placebo, Outcome 1 Long term abstinence.

Review: Anxiolytics for smoking cessation

Comparison: 4 Beta-blockers versus placebo

Outcome: 1 Long term abstinence



APPENDICES

Appendix 1. 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
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.

(*Continued*)

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
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.

(*Continued*)

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: 4 October 2009.

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

HISTORY

Protocol first published: Issue 3, 1997

Review first published: Issue 3, 1997

Date	Event	Description
6 October 2009	New search has been performed	Searches updated; no new included studies. Effects expressed as risk ratios instead of odds ratios
8 May 2008	Amended	Converted to new review format.
26 April 2007	New search has been performed	Search updated, no new trials found
27 August 2003	New search has been performed	Search updated. One study (Hatsukami 2003) added to excluded studies list.
15 November 2001	New search has been performed	Search updated, no new trials found

(*Continued*)

29 August 2000	New citation required and conclusions have changed	This review was first published as part of the review 'Anxiolytics and antidepressants for smoking cessation'. From Issue 4 2000 of the Cochrane Library the two classes of pharmacotherapies are reviewed separately

CONTRIBUTIONS OF AUTHORS

Authors jointly conceived and prepared review.

DECLARATIONS OF INTEREST

JR Hughes has received consultancy fees from pharmaceutical companies.

SOURCES OF SUPPORT

Internal sources

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

External sources

- National Institute on Drug Abuse (NIDA), USA.
- NHS Research and Development National Cancer Programme, England, UK.

NOTES

This review was first published as part of the review 'Anxiolytics and antidepressants for smoking cessation'. From Issue 4 2000 of the Cochrane Library the two classes of drugs are reviewed separately.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [*therapeutic use]; Anti-Anxiety Agents [*therapeutic use]; Smoking [*drug therapy]; Smoking Cessation [*methods]

MeSH check words

Humans