Opioid antagonists for smoking cessation (Review)

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[Intervention Review]

Opioid antagonists for smoking cessation

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ABSTRACT

Background

The reinforcing properties of nicotine may be mediated through release of various neurotransmitters both centrally and systemically. People who smoke report positive effects such as pleasure, arousal, and relaxation as well as relief of negative affect, tension, and anxiety. Opioid (narcotic) antagonists are of particular interest to investigators as potential agents to attenuate the rewarding effects of cigarette smoking.

Objectives

To evaluate the efficacy of opioid antagonists in promoting long-term smoking cessation. The drugs include naloxone and the longer-acting opioid antagonist naltrexone.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) for trials of naloxone, naltrexone and other opioid antagonists and conducted an additional search of MEDLINE using 'Narcotic antagonists' and smoking terms in June 2009. We also contacted investigators, when possible, for information on unpublished studies.

Selection criteria

We considered randomized controlled trials comparing opioid antagonists to placebo or an alternative therapeutic control for smoking cessation. We included in the meta-analysis only those trials which reported data on abstinence for a minimum of six months. We also reviewed, for descriptive purposes, results from short-term laboratory-based studies of opioid antagonists designed to evaluate psychobiological mediating variables associated with nicotine dependence.

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 cotinine- or carbon monoxide-verified abstinence from smoking after at least six months follow up in patients smoking at baseline. Where appropriate, we performed meta-analysis using a fixed-effect model (Mantel-Haenszel odds ratios).

Main results

Four trials of naltrexone met inclusion criteria for meta-analyses for long-term cessation. All four trials failed to detect a significant difference in quit rates between naltrexone and placebo. In a pooled analysis there was no significant effect of naltrexone on long-term abstinence, and confidence intervals were wide (odds ratio 1.26, 95% confidence interval 0.80 to 2.01). No trials of naloxone or buprenorphine reported long-term follow up.

Authors' conclusions

Based on limited data from four trials it is not possible to confirm or refute whether naltrexone helps people who smoke, to quit. The confidence intervals are compatible with both clinically significant benefit and possible negative effects of naltrexone in promoting abstinence. Data from larger trials of naltrexone are needed to settle the question of efficacy for smoking cessation.

PLAIN LANGUAGE SUMMARY

Do opioid antagonists such as naltrexone help people to stop smoking?

While nicotine replacement therapy and certain antidepressants help people to stop smoking, their overall effect is small because nicotine dependence involves many factors including learned behaviour, social settings and the effects of various drugs. Naltrexone is a long-acting drug (an opioid antagonist) which blunts the effects of narcotics such as heroin and morphine and might help reduce nicotine addiction by blocking some of the rewarding effects of smoking. Our review found that there is not enough evidence (with four trials covering 582 smokers) to show the effect of opioid antagonists such as naltrexone on smoking cessation. The effects of some opioid antagonists (e.g. naltrexone, naloxone: 13 trials covering 455 smokers) on withdrawal symptoms and the pleasurable effects of smoking are as yet unclear.

BACKGROUND

While nicotine replacement therapy (NRT) and certain antidepressants help people to stop smoking, the absolute effects are small, so there is continued interest in other pharmacological agents for assisting cessation. Nicotine dependence involves a complex interplay of learned or conditioned behaviours, personality, social settings, and pharmacological factors. The reinforcing properties of nicotine are theorized to be mediated, in part, through release of various neurotransmitters throughout the brain. Acute exposure to nicotine activates nicotinic cholinergic receptors resulting in the release of dopamine, norepinephrine, acetylcholine, vasopressin, serotonin, and beta endorphin. It has been suggested that release of beta endorphin may be associated with reduction of anxiety and tension (Benowitz 1999). Nicotine also activates nicotinic cholinergic receptors in the adrenal medulla leading to the release of epinephrine (adrenaline) and beta endorphin, which may contribute to the systemic effects of nicotine. In one study, smoking a cigarette increased beta-endorphin levels 30 to 300%, which was significantly correlated with plasma nicotine levels (Pomerleau 1983). In addition to evidence suggesting a possible reinforcing role for the endogenous opioid system in smoking, findings from other studies suggest that this system might be involved with mediating nicotine withdrawal. Studies by Malin and colleagues indicate that the opioid antagonist naloxone precipitates nicotine withdrawal in nicotine-maintained rats, and nicotine-induced reversal of this withdrawal syndrome is antagonized by naloxone (Malin 1993; Malin 1996).

The focus of this review and meta-analysis is on trials which provide evidence for an effect on long-term smoking cessation. A secondary focus is the effect of opioid antagonists on psycho-biological mediating variables associated with nicotine dependence and smoking cessation.

Naloxone (NarcanTM; half-life 30-100 min; Goodrich 1990), a short-acting opioid antagonist, is routinely administered to reverse the acute effects of narcotic overdose. Evidence that naloxone and related drugs may block the reinforcing properties of nicotine and affect nicotine withdrawal has led to clinical trials of naloxone to determine its effects on smoking behaviour and withdrawal symptoms.

Naltrexone (NarpanTM, ReviaTM; half-life 240 min; Meyer 1984), a long-acting opioid antagonist, is a marketed drug which blunts certain effects of narcotics such as heroin, meperidine, morphine and oxycodone. It has been shown to help in the treatment

of alcohol dependence (O'Malley 1995; Volpicelli 1992). Naltrexone occupies the μ-opioid receptors, which putatively diminishes the activation of mesolimbic dopamine and therefore may reduce craving for nicotine. Thus, it is believed that NRT and naltrexone could produce additive effects by reducing craving through different mechanisms of action. Since opioid antagonists are known to precipitate nicotine withdrawal in nicotine dependent animals (Malin 1993; Malin 1996), NRT may have the additional benefit of attenuating the increased withdrawal, dysphoria, and sedation caused by naloxone and naltrexone.

Buprenorphine, a mixed agonist-antagonist, has also been evaluated in two published studies of smoking (Mello 1985; Mutschler 2002).

OBJECTIVES

The primary objective of the review was to evaluate the efficacy of opioid antagonists (including naltrexone, naloxone, buprenorphine), alone or in combination with nicotine replacement, in promoting smoking cessation.

The secondary objectives of the review were to evaluate the efficacy of opioid antagonists in treating withdrawal symptoms, attenuating the reinforcing value of smoking, and reducing ad libitum smoking. In the analysis, specific opioid antagonists were considered separately rather than grouping these medications as a class. For example, studies evaluating naltrexone were compared only to other studies evaluating naltrexone and not grouped with naloxone.

The main hypotheses were:

1. Opioid antagonists are more effective than placebo in promoting sustained abstinence from smoking.

2. Opioid antagonists used in combination with nicotine replacement therapy are more effective than either opioid antagonists or nicotine replacement therapy alone in promoting sustained abstinence from smoking.

METHODS

Criteria for considering studies for this review

Types of studies

This review includes two tiers of evidence. We used randomized controlled trials of opioid antagonists that report smoking status at least six months after intervention to assess the efficacy for long-term cessation. We also considered randomized controlled trials of opioid antagonists with short-term follow up that report the outcomes of withdrawal, reinforcing properties of smoking, or ad libitum smoking.

Types of participants

Adults who smoke.

Types of interventions

Naltrexone, naloxone, buprenorphine or other opioid antagonists, with or without concurrent nicotine replacement therapy.

Types of outcome measures

Six-month abstinence was the primary outcome measure. We used sustained cessation rate in preference to point prevalence, and biochemical verification of self-reported quitting was required. We regarded people lost to follow up as continuing smoking. We noted any adverse effects.
Secondary outcome measures included withdrawal, reinforcing or hedonic effects of smoking, mood states, and ad libitum smoking.

Search methods for identification of studies

Our search of the Cochrane Central Register of Controlled Trials (CENTRAL) used the terms 'naloxone' or 'naltrexone' or ' opioid antagonist*' or 'opiate antagonist*' or 'narcotic antagonist*' in the title or abstract, or as key words. An additional search of MEDLINE used the terms (explode "Narcotic-Antagonists"/ all subheadings) AND ("Smoking-Cessation"/ all subheadings OR "Tobacco-Use-Disorder"/ all subheadings OR "Smoking"/ all subheadings). Date of most recent search: June 2009

Data collection and analysis

Two authors checked the studies generated by the search strategy for relevance, according to the inclusion criteria. One author extracted data and a second author checked them. Discrepancies were resolved by mutual consent. If significant disagreement had arisen at either stage this would have been resolved with the participation of a third author, as required. We noted reasons for the non-inclusion of studies.
Evaluation of quality
We evaluated studies on the basis of the quality of the randomization procedure used, as described in the Cochrane Handbook (Handbook 2005). The following information about each trial is reported in the table 'Characteristics of Included Studies':

- Country
- Criteria for recruitment (whether current smokers only, or recent quitters) and whether selected according to willingness to make a quit attempt

- Other relevant inclusion/exclusion criteria for trial
- Method of randomization, blinding, allocation concealment
- Smoking behaviour and characteristics of participants
- Adverse events
- Support measures
- Primary outcome measures - definition of long-term abstinence used in review, use of biochemical validation
- Secondary outcomes - withdrawal symptoms, ad libitum smoking, hedonic effects

Analysis of the data

We calculated quit rates based on the numbers of patients randomized to an intervention excluding any deaths (intention-to-treat analysis). Those who dropped out or were lost to follow up were regarded as continuing to smoke. We noted any deaths and adverse events in the results tables. If necessary, we contacted authors for clarification of specific points. Interventions including nicotine replacement therapy were grouped separately to those without. We combined the results of studies evaluating long-term cessation using the Mantel-Haenszel odds ratio method, fixed-effect model. Data on short-term outcomes were tabulated and described narratively.

RESULTS

Description of studies

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

Further details of these studies are presented in the Table of Included Studies.

Studies evaluating long term abstinence

Naltrexone:

We identified four trials evaluating naltrexone and reporting long-term abstinence data (six months or more). Covey 1999 and Wong 1999 examined the effects of treatment on withdrawal symptoms and on abstinence, while O'Malley 2006 and King 2006 examined long-term abstinence and effects on weight gain and gender differences. We made several attempts to obtain unpublished data from the multi-centre trial for which only one centre's results have been published (Wong 1999), but the funder, Dupont, has not disclosed further results.

In Wong 1999, 100 volunteers were randomized to receive 12 weeks of either placebo only, naltrexone only, placebo with nicotine patches, or naltrexone with nicotine patches. The naltrexone dose was 50 mg taken once daily, and the nicotine patch dose was 21 mg/24-hour for the first eight weeks and 14 mg/24-hour for the remaining four weeks. Treatment with naltrexone and/or the nicotine patches started on the target quit date (TQD). The trial therefore tested the efficacy of four treatment combinations (1. Naltrexone with nicotine patch 2. Naltrexone alone 3. Nicotine patch alone 4. No active drug). All participants received brief (15 to 20 minutes) counselling sessions throughout the treatment phase. The investigators reported continuous abstinence to six months and point prevalence abstinence at six months (the latter outcome was not used in our meta-analysis). Brief behavioural intervention was provided at each visit. This study was part of a multi-centre, partially-blinded, 2 X 2 factorial design study of naltrexone (50 mg, active versus placebo) and nicotine patch (active versus no treatment). Three hundred and fifty subjects were enrolled at five centres in the United States. However, the authors report only data from the Mayo Clinic site.

In the second study (Covey 1999), 80 volunteers were randomized to either naltrexone or placebo daily for four weeks. All smokers began taking 25 mg naltrexone or placebo at least three days before the TQD and the dose was increased to 50 mg on the TQD. Medication was continued for four weeks and all subjects received individual counselling. The investigators reported continuous abstinence at three and six months.

O'Malley 2006 randomized 385 volunteers to four treatment conditions: placebo, 25 mg, 50 mg or 100 mg of naltrexone for six weeks. All participants also received 21 mg active nicotine patch throughout the study period, and brief weekly counselling sessions and self-help support. Abstinence, weight gain and adverse events were the main outcomes of interest. The published report gives outcomes at six weeks. Quit rates at six and 12 months were provided to us by the authors. The longer term outcome is used in the meta-analysis.

King 2006 randomized 110 smokers to either naltrexone 50 mg a day or placebo for six weeks. All participants received nicotine patch. Prolonged abstinence was assessed at eight and 24 weeks.

The remaining included studies do not report long-term abstinence and are not included in the meta-analysis. However, they fall into our second eligible category of studies that cover withdrawal, reinforcing or hedonic effects of smoking, mood states, and ad libitum smoking.

Studies evaluating effects on other outcomes

Naltrexone:

Naltrexone was also evaluated for its effects on withdrawal syndrome, ad libitum smoking, and/or the reinforcing properties of smoking in randomized, double-blind, placebo-controlled crossover or within-subjects design studies in laboratory settings (Brauer 1999; Caskey 2001; Epstein 2004; Houtsmuller 1997; Hutchison 1999; King 2000; Knott 2007; Lee 2005; Ray 2006;

Ray 2007; Rohsenow 2007; Rukstalis 2005; Sutherland 1995; Wewers 1998) and in non laboratory-based randomized controlled trials (Covey 1999; King 2006; O'Malley 1998; Rohsenow 2003; Wong 1999).

Naloxone:

The studies of naloxone and buprenorphine were designed to evaluate effects on withdrawal syndrome, ad libitum smoking, and/or the reinforcing properties of smoking. Five studies of naloxone were small sample, placebo-controlled, crossover or within-subjects designed studies carried out in controlled laboratory environments (Boureau 1978; Gorelick 1988; Karras 1980; Krishnan-Sarin 1999; Nemeth-Coslett 1986).

Buprenorphine:

The effect of buprenorphine on amount smoked was assessed in two studies. Mello 1985 administered buprenorphine to seven heroin addicts, and Mutschler 2002 randomized 23 opioid- and cocaine-dependent detoxification inpatients to 4 or 8 mg of buprenorphine for 12 days.

Risk of bias in included studies

The studies were judged on their attempts to control bias in randomization, allocation, assessment and analysis. All four of the long-term cessation studies confirmed abstinence with biochemical verification. Wong 1999, O'Malley 2006 and King 2006 reported exhaled carbon monoxide (CO) verification and did not report plasma or urine cotinine (although O'Malley 2006 tested serum cotinine at baseline). Covey 1999 reported plasma cotinine concentration. All four studies were randomized and double-blind. In Wong 1999 and O'Malley 2006, randomization was performed using computer-generated random numbers, while the other two abstinence trials did not report randomization methods in sufficient detail for the possibility of allocation bias to be discounted. Many of the other included studies were published only as abstracts, and provided limited information on methodological issues in general, with randomization methods not reported in sufficient detail to discount allocation bias. Many of the trials evaluating withdrawal symptoms, ad libitum smoking, and hedonic effects either did not use identical rating scales or did not report dichotomous outcomes for these variables. We did not perform meta-analyses for these outcomes.

Effects of interventions

Studies evaluating long term abstinence

Only four published studies of opioid antagonists (Covey 1999; King 2006; O'Malley 2006; Wong 1999) reported long-term abstinence data and are included in the primary outcome meta-analysis. All of these trials evaluated the efficacy of naltrexone for smoking cessation. We summarize the results of studies of opioid antagonists evaluating other outcomes (withdrawal symptoms, ad libitum smoking, hedonic effects) below as a review of extant data with potential utility for clinical practice pending further and more generalizable studies.

Naltrexone versus placebo without NRT

Covey and colleagues (Covey 1999) reported quit rates favouring naltrexone at three months, and at six months (26.7% for naltrexone; 15.2% for placebo, odds ratio (OR) 1.9, P non-significant). These rates exclude ten people in the naltrexone and two in the placebo group who dropped out prior to the target quit day, for reasons including drug-related side effects. We have included these people as treatment failures, leading to a smaller odds ratio contributing to the meta-analysis (OR 1.42, 95% confidence interval (CI) 0.44 to 4.53). Wong 1999 failed to detect an effect on smoking abstinence at six months when naltrexone was used as the only pharmacotherapy. The continuous abstinence for these arms were 9% for naltrexone and 8% for placebo (OR 1.05, 95% CI 0.38 to 2.91). The pooled results from the relevant arms of these two studies did not detect a significant benefit for naltrexone over placebo (OR 0.39, 95% CI 0.49 to 3.69).

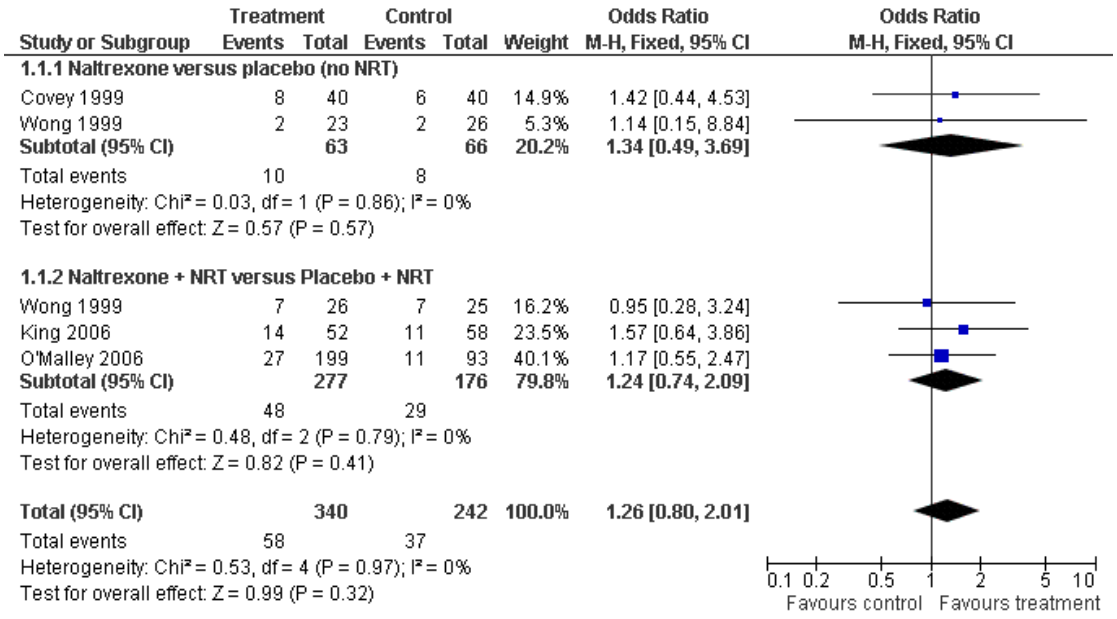
Naltrexone versus placebo as an adjunct to NRT

Both Wong 1999 and O'Malley 2006 also failed to detect an effect of naltrexone on long-term smoking abstinence in the trial arms where naltrexone or placebo was used in addition to the nicotine patch. The six-month continuous abstinence rates in Wong 1999 were 27% for naltrexone plus nicotine patch and 28% for placebo and nicotine patch (OR 0.95, 95% CI 0.28 to 3.24). Twelve-month point prevalence abstinence rates in O'Malley 1995 were 13.6% for the combined 50 mg and 100 mg arms of naltrexone plus nicotine patch and 11.8% for placebo plus nicotine patch (OR 1.17, 95% CI 0.55 to 2.47). Separate comparisons of the 50 mg and 100 mg arms with the placebo arm similarly failed to detect significant differences, so we have combined both of these naltrexone arms in the meta-analysis. King 2006 reported non-significant trends towards higher rates of continuous abstinence at end of treatment (eight weeks) and at 24 weeks. Long-term quit rates were 27% for the naltrexone plus patch group versus 19% for the patch only group (OR 1.57, 95% CI 0.64 to 3.86). The pooled results from the relevant arms in these three studies did not show a significant benefit of naltrexone as an adjunct to the nicotine patch (OR 1.24, 95% CI 0.74 to 2.09).

We also considered whether pooling all four studies with long-term abstinence outcomes would detect a benefit of naltrexone

irrespective of the use of NRT. The confidence intervals still failed to support a significant effect (OR 1.26, 95% CI 0.80 to 2.01, Figure 1). There was no evidence of heterogeneity in any of the pooled estimates.

Figure 1. Forest plot of comparison: 1 Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), outcome: 1.1 Abstinence at longest follow up.



Studies evaluating effects on withdrawal symptoms

Naltrexone:

Houtsmuller 1997 did not find a difference between the naltrexone and placebo condition for the total score on the withdrawal symptoms questionnaire. However, in this study the individual withdrawal symptoms (craving, urges to smoke, restlessness and increased eating) were all reduced by naltrexone (P values between 0.058 and 0.078). Brauer 1999 and King 2000 found no effect on withdrawal symptoms. Sutherland 1995 did not find a significant reduction in withdrawal symptoms. Covey 1999 found that naltrexone appeared to increase difficulty in concentrating ($P < 0.03$) but otherwise had no effect on withdrawal symptoms. Hutchison 1999 (naltrexone plus nicotine patch) and Epstein 2004 (naltrexone only) both found that subjects using naltrexone demonstrated diminished withdrawal symptoms when given provocative smoking cues during sustained abstinence. Knott 2007 demonstrated that naltrexone did not affect the ameliorating effects of nicotine on withdrawal symptoms. Rohsenow 2007 observed that naltrexone reduced cue-elicited withdrawal symptoms but did not reduce smoking urges or abstinence-induced withdrawal prior to cue exposure. Ray 2007 demonstrated that naltrexone reduced the enhancing effect of ethanol challenge on urge to smoke. Similar to these cue reactivity studies, Houtsmuller 1997, Caskey 2001, King 2006, Lee 2005 and O'Malley 2006 all found that naltrexone decreased unelicited withdrawal symptoms. Wong 1999 found that naltrexone used in combination with the nicotine patch reduced withdrawal symptoms but there was no significant main effect for naltrexone alone; it did not reduce withdrawal symptoms and there was no significant difference in any measures of withdrawal between the naltrexone plus patch and placebo plus patch groups.

Naloxone:

Wewers 1998 found no significant difference in withdrawal symptoms or mood states between the naloxone and control groups. Gorelick 1988 did not find any impact of naloxone on withdrawal. Krishnan-Sarin 1999 found that naloxone apparently increased urge to smoke (craving) and tiredness at lower dosages.

Studies evaluating ad libitum smoking

Naltrexone:

The results regarding ad libitum smoking were mixed. There were no significant effects of naltrexone on ad libitum smoking in three of the laboratory-based trials (Brauer 1999; Houtsmuller 1997; Sutherland 1995). However, six trials (Caskey 2001; Epstein 2004; King 2000, Lee 2005; Olmstead 2002; Rohsenow 2003) demonstrated statistically significant reductions in the number of cigarettes smoked ad libitum. Wong 1999, designed to evaluate abstinence, did not find any association between naltrexone and number of cigarettes smoked among continuing smokers. Data on ad libitum smoking from other centres involved in this multicentre trial were not reported or released upon request of the investigators.

Naloxone:

The results on naloxone are mixed. Karras 1980 and Gorelick 1988 found significant reductions in number of cigarettes smoked in the naloxone group when compared with placebo. However, Nemeth-Coslett 1986 did not find an effect of naloxone over a wide range of dosages for any measure of cigarette smoking, including number of cigarettes, number of puffs, or expired air carbon monoxide.

Buprenorphine:

Mello 1985 found that cigarette consumption by seven heroin addicts increased compared to the pre-buprenorphine baseline. Mutschler 2002 detected a significant increase among detoxified opioid- and cocaine-dependent inpatients in the rate of ad libitum smoking with buprenorphine administration.

Studies evaluating reinforcing effects of smoking

Naltrexone:

Studies have reported mixed results for the effect of naltrexone on hedonic effects. Sutherland 1995 did not find any significant effect of naltrexone on self-reported satisfaction from smoking. Wewers 1998 found a significant reduction in self-reported satisfaction with smoking for subjects treated with naltrexone compared to placebo. Brauer 1999 found that naltrexone increased negative mood following smoking. King 2000 found that naltrexone significantly reduced post-cigarette craving and increased lightheadedness, dizziness, and head rush following a cigarette. Ray 2006 did not observe any effect of naltrexone on smoking reinforcement. However, Rohsenow 2007 found that naltrexone did not affect reinforcing or aversive measures of smoking.

Naloxone:

Neither Karras 1980 nor Gorelick 1988 found an effect of naloxone on the reinforcing properties of smoking cigarettes.

DISCUSSION

Only four trials of naltrexone with a total of 582 smokers randomized to naltrexone and placebo tablets reported long-term abstinence data. Given the wide confidence intervals (odds ratio (OR) 1.26, 95% confidence interval (CI) 0.80 to 2.01 for all studies, with and without NRT), we cannot exclude either a positive or negative effect of naltrexone on smoking cessation, whether used alone or in combination with nicotine replacement therapy (NRT). Larger trials would be needed to exclude these possibilities. By comparison, the pooled odds ratio of continuous abstinence rates for bupropion from 21 trials (7171 participants) was 1.99 (95% CI 1.73 to 2.30) (Hughes 2004) and bupropion clearly appears to reduce withdrawal symptoms (Shiffman 2000).

Two study reports (Covey 1999; King 2006) raised the possibility that there could be a difference in effect by gender, with women showing more evidence of a benefit than men. The other two abstinence studies (O'Malley 2006; Wong 1999) did not report quit rates for men and women separately, so we could not conduct a meta-analysis without risk of reporting bias.

There are mixed results with regard to whether or not naltrexone reduces withdrawal symptoms or diminishes the reinforcing effects of nicotine and tobacco. However, because of heterogeneity of methods and data reporting we are unable to examine withdrawal symptoms and reinforcing effects using meta-analytic techniques. Also, we do not have enough data to examine whether or not the use of combination naltrexone and nicotine replacement has a significant effect on withdrawal symptoms compared to nicotine replacement plus placebo.

There were no clear trends suggesting positive or negative effects of naloxone on withdrawal, ad libitum smoking or hedonic effects. In any case, the very short half-life, and route of administration of naloxone (intravenous, intramuscular or subcutaneous) precludes its use as an agent for smoking cessation in clinical settings.

Given the purported role of opioid pathways in nicotine dependence, it would seem biologically plausible that opioid antagonists

would blunt the rewarding effects of smoking. Moreover, we would expect, if opioid antagonists diminished reinforcing properties of smoking, that this would translate to decreased tobacco consumption or ad libitum smoking. However, we found no such trends. This lack of observed effects of opioid antagonists on smoking rates and aversive or reinforcing properties of nicotine is consistent with a study in rats that showed no effect on nicotine self-administration (Corrigall 1991).

A large body of converging evidence suggests that the release of dopamine in the mesocorticolimbic system plays an important role in the reinforcing properties of smoking. Blum 1995 and others have suggested that individuals may be at higher risk for dependence on nicotine and other substances because of deficiencies in dopamine transmission in the mesocorticolimbic system. The dopamine re-uptake inhibitor bupropion appears to diminish the rewarding effects of smoking and also appears to decrease withdrawal (Shiffman 2000). While we cannot draw any firm conclusions on the effect of opioid antagonists on the reinforcing properties of smoking or withdrawal, the literature to date suggests that dopaminergic pathways play a more important role in nicotine dependence.

AUTHORS' CONCLUSIONS

Implications for practice

The current evidence does not support the clinical use of naltrexone or other opioid antagonists for smoking cessation.

Implications for research

More research is needed with larger sample sizes to determine whether naltrexone is efficacious for smoking cessation.

Longer-term smoking cessation outcomes data (six months or more), if collected by investigators in past, present, or future studies, should be made available to the public domain, if not to the Cochrane database, to improve the reliability and generalizability of meta-analyses for smoking cessation medications such as opioid antagonists and other classes of pharmacological agents.

With a more comprehensive analysis of existing data, we would be able to make a compelling case for advising clinicians either to consider naltrexone as a second-line medication for smoking cessation or to exclude naltrexone from our current armamentarium of smoking cessation medications. Research is also needed to investigate the efficacy of combining naltrexone with other smoking cessation medications that appear to diminish withdrawal symptoms and negative affect (e.g., bupropion, nortriptyline, clonidine).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Boureau 1978

Methods	NALOXONE Country: France Recruitment: Not clear, abstract only Design: Laboratory-based, double-blind, placebo-controlled, crossover study
Participants	20 smokers, 35% F
Interventions	Naloxone 0.4mg or placebo
Outcomes	Number of cigarettes smoked per day
Notes	Not long-term abstinence

Brauer 1999

Methods	NALTREXONE Country: USA Recruitment: Newspaper adverts Design: Laboratory, double-blind, double dummy, within-subjects trial
Participants	19 smokers aged 18-55, smoked >=20 cpd for at least 2 yrs, in good health
Interventions	1. Naltrexone 50 mg plus placebo patch 2. Placebo tablet plus nicotine patch 3. Naltrexone plus nicotine patch 4. Placebo tablet plus placebo patch 1 week on each condition, day 7 smoked normal and denicotinized cigarettes in laboratory Abstinence not attempted
Outcomes	Cigarette satisfaction, depression, withdrawal symptoms, mood, smoking behaviour, cardiovascular measures, and cognitive and psychomotor performance
Notes	No attempt at ascertaining abstinence

Caskey 2001

Methods	NALTREXONE Country: USA Recruitment: Not clear, abstract only
Participants	16 smokers

Caskey 2001 (*Continued*)

Interventions	1. Naltrexone 100 mg 2. Naltrexone 50 mg 3. Placebo
Outcomes	Smoking topography, urge to smoke, serum nicotine and cotinine
Notes	No abstinence data reported

Covey 1999

Methods	NALTREXONE Country: USA Recruitment: By notices at University and newspaper adverts Randomization: no details Design: Randomized double-blind, placebo controlled
Participants	80 smokers, >= 20 cpd, age 18-65, smoked before leaving house in morning, made at least 1 quit attempt, and experienced withdrawal symptoms during quit attempt
Interventions	1. Naltrexone 25 mg/day at least 3 days before QD, increased to 50-75 mg/day on quit date and continued for 4 weeks 2. Placebo Both groups received weekly individual behavioural counselling
Outcomes	Self-reported continuous abstinence verified at all visits up to 6m by plasma cotinine <=15 ng/mL Mood
Notes	Subject drop out high and differential. 32.5% (n=13) dropped out in naltrexone group; 32.5% (n=13) also dropped out in placebo group. However 10/13 drop outs in naltrexone group occurred before quit date for wide range of side effects or excuses

Epstein 2004

Methods	NALTREXONE Country: USA Recruitment: Flyers and newspaper adverts
Participants	44 regular smokers, 48% F
Interventions	Naltrexone 50mg/day and placebo in random sequence
Outcomes	Ad lib smoking, smoking urges, positive and negative affect, withdrawal symptoms, exhaled CO
Notes	No abstinence data reported

Risk of bias

Epstein 2004 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Gorelick 1988

Methods	NALOXONE Country: USA Recruitment: Hospital employees and outpatients Design: Laboratory, double-blind, placebo-controlled, crossover trial
Participants	10 male chronic smokers with severe nicotine dependence (mean FTQ score of 7.4 and past failure to quit smoking)
Interventions	Each subject evaluated in 2 laboratory sessions receiving either naloxone 10 mg sc or placebo (drug vehicle)
Outcomes	Number of cigarettes smoked, CO content of expired air, subjective aspects of smoking and withdrawal, physiologic data
Notes	No abstinence data reported

Houtsmuller 1997

Methods	NALTREXONE Country: USA Recruitment: No data given in abstract on recruitment Design: Laboratory, double-blind, placebo-controlled, within-subjects trial
Participants	14 smokers. No data given in abstract on gender, age, inclusion or exclusion criteria
Interventions	Naltrexone 50 mg/d and placebo for 4 days each, with 10-day washout period between
Outcomes	Withdrawal symptoms, ad lib smoking using smoking topography measures
Notes	Did not report hedonic effects or ad lib smoking

Hutchison 1999

Methods	NALTREXONE Country: USA Recruitment: Newspaper adverts and flyers Design: Laboratory, randomized, double-blind, placebo-controlled trial
Participants	20 smokers, >= 20 cpd
Interventions	Naltrexone 50 plus nicotine patch vs. placebo pill plus nicotine patch. Cue reactivity evaluate after 9hr abstinence

Hutchison 1999 (*Continued*)

Outcomes	Nicotine dependence severity, (FTQ), positive and negative affect, withdrawal symptoms
Notes	No abstinence data reported

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Karras 1980

Methods	NALOXONE Country: USA Recruitment: Unclear from manuscript Design: laboratory-based double-blind, drug-placebo, crossover trial
Participants	7 smokers, employees at medical centre, >= 20 cpd
Interventions	Naloxone 10 mg/ml or 1ml or placebo sc
Outcomes	Number of puffs smoked, weight of smoked portion, desire for cigarette, satisfaction, mood, side effects
Notes	No abstinence data reported

King 2000

Methods	NALTREXONE Country: USA Recruitment: adverts Design: Laboratory-based, randomized, double-blind, placebo controlled within-subjects trial
Participants	22 regular cigarette smokers aged 19-50. Excluded if history of major psychiatric illnesses or positive blood or urine toxicology for cocaine, opiates, benzodiazepines, amphetamine, barbiturates, and phencyclidine
Interventions	Each subject participated in 2 identical testing sessions in double-blind study. Sessions spaced 8 days apart. Each subject received pre-administration of either 50 mg naltrexone or identical placebo in random order, after overnight abstinence. Offered up to 4 cigs over 2hrs
Outcomes	Withdrawal symptoms and ad lib smoking
Notes	No long-term abstinence data

Risk of bias

Item	Authors' judgement	Description

King 2000 (*Continued*)

Allocation concealment?	Yes	

King 2006

Methods	NALTREXONE AS ADJUNCT TO NICOTINE PATCH Country: USA Recruitment: Newspaper adverts, flyers, word of mouth	
Participants	110 smokers (15-40 cpd), 51% F, av age 44	
Interventions	1. Naltrexone 25 mg for 3 days then 50 mg for 2m, nicotine patch for 1m 2. Placebo & nicotine patch All participants received 6 individual 45-60 mins behavioural therapy sessions	
Outcomes	Continuous abstinence at 24 weeks, validated by CO <=10 ppm Smoking urges, withdrawal, side effects, body weight changes	
Notes	Preliminary results presented in King 2002, King 2003. Gender difference noted in outcomes	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	

Knott 2007

Methods	NALTREXONE Country: Canada Recruitment: Not described	
Participants	18 smokers, >=10 cpd, 40% F, av age 23	
Interventions	Lab-based, randomized (via counterbalanced Latin Square design), double-blind, 4-session, study: 1. 2-sessions active naltrexone 50 mg; 2. 2-sessions placebo tablets; 3. 2-session nicotine gum 4 mg; 4. 2-session placebo gum	
Outcomes	Change in withdrawal symptoms or hedonic effects of nicotine	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	

Krishnan-Sarin 1999

Methods	NALOXONE Country: USA Recruitment: Newspaper adverts in community Design: Laboratory-based, single group, within-subjects design
Participants	9 smokers (smoked 1-1½ packs per day) and 11 non-smoking volunteers
Interventions	Naloxone in dosages of 0, 0.8, and 1.6 mg iv
Outcomes	Narcotic withdrawal scale, smoking urges, blood cortisol levels
Notes	Did not report ad lib smoking or hedonic effects

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	

Lee 2005

Methods	NALTREXONE Country: South Korea Recruitment: Not clear, apparently recruited from clinical setting
Participants	25 male smokers
Interventions	Naltrexone 25 mg/d x 7 days, then 50 mg/d x 7 days vs. placebo
Outcomes	Daily cigarette consumption, exhaled CO, nicotine dependence severity, ACTH, cortisol, prolactin, beta-endorphin, dynorphin
Notes	No abstinence data reported

Mello 1985

Methods	BUPRENORPHINE Country: USA Recruitment: From drug rehabilitation clinic Design: Laboratory-based, single group, within-subjects design
Participants	7 heroin addicts
Interventions	Buprenorphine ascending dosages (0.5-8mg/d)
Outcomes	Number of cigarettes smoked

Mello 1985 (*Continued*)

Notes	Did not report hedonic effects or withdrawal symptoms

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	

Mutschler 2002

Methods	BUPRENORPHINE Country: USA Recruitment: Patients admitted to a clinical research ward for concurrent opioid and cocaine dependence Design: randomized trial with randomization to 4mg or 8mg of buprenorphine
Participants	23 adult men with DSM III-R diagnosis of concurrent opioid and cocaine dependence
Interventions	Buprenorphine with randomization to 4 or 8 mg/day with ascending dosages following 6 days of detoxification on methadone
Outcomes	Smoking topography, urge to smoke, serum nicotine and cotinine
Notes	Did not report hedonic effects or withdrawal symptoms

Nemeth-Coslett 1986

Methods	NALOXONE Country: USA Recruitment: From clinical setting
Participants	7 smokers
Interventions	Injection of naloxone HCl (0.0625, 0.25, 1.0, or 4.0 mg/kg) or placebo. Each subject received each treatment 3 times in a mixed order across days
Outcomes	Number of cigarettes smoked, number of puffs, exhaled CO
Notes	Did not report abstinence outcomes

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	

O'Malley 1998

Methods	NALTREXONE Country: USA Recruitment: No information given in abstract regarding recruitment. Design: Randomized, double-blind, placebo-controlled, factorial design
Participants	60 smokers who were not alcohol-dependent. No other data provided in abstract
Interventions	Naltrexone 50 mg/d orally or similar dose placebo pill and assignment to 1 of 3 nicotine patch conditions: (1) 21mg for 4 weeks; (2) 21mg for 2 weeks followed by 14 mg and 7 mg for 1 week each; (3) no patch
Outcomes	Withdrawal symptoms, ad lib smoking, self-reported abstinence at 4 weeks
Notes	No specific data on number randomized to each group or number abstinent at 4 weeks given

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	

O'Malley 2006

Methods	NALTREXONE AS ADJUNCT TO NICOTINE PATCH Country: USA Recruitment: Patients at a Connecticut mental health centre and a VA healthcare centre, recruited through press, advertisements and mailings to physicians . Design: Double-blind randomized controlled trial, to test effects of naltrexone, with and without NRT, on smoking cessation and on weight gain. Block randomization stratified by sex after 150 enrolments. Allocation by random sequence provided to pharmacist
Participants	385 smokers (from 400 eligible), age >=18, =>20 cpd, CO>10 ppm. 46% F, av cpd 28, av age 46
Interventions	1. Naltrexone 100 mg 2. Naltrexone 50 mg 3. Naltrexone 25mg 4. Placebo All participants also received 21mg NRT patch x 6 weeks, initial 45 min counselling session, weekly 15 min counselling sessions for 6 weeks, plus self-help materials including dietary & exercise tips
Outcomes	PPA at 12m (also 6m, & 6wk continuous abstinence) validated by expired CO <10ppm. Adverse events
Notes	Analyses were ITT and per protocol (completers); weight change was a secondary outcome. 50mg & 100mg dose groups combined in main analysis. Sensitivity analysis using individual groups, and 6 month outcomes did no alter conclusions

Risk of bias

O'Malley 2006 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Olmstead 2002

Methods	NALTREXONE Country: USA Recruitment: Not described
Participants	29 smokers: >15 cpd (N=19) or <6 cpd (N=-10).
Interventions	Repeated measures, 12 hour sessions x 3 randomized by sequence to naltrexone 100 mg/d, 50 mg/d, and placebo
Outcomes	Smoking topography, smoking urges, serum cotinine and nicotine, exhaled CO
Notes	No abstinence data reported.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	

Ray 2006

Methods	NALTREXONE Country: USA Recruitment: Not described
Participants	30 smokers, >=10 cpd, 37% F, av age 43, av cpd 22
Interventions	Lab-based, counterbalanced design randomized within-subjects comparison of necrotomized (0.6 mg) vs. denicotinized (0.05 mg) cigarettes
Outcomes	Withdrawal symptoms, craving
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

Ray 2007

Methods	NALTREXONE Country: USA Recruitment: Not described
Participants	10 smokers (heavy drinkers), 20% F, av age 22, av cpd 5
Interventions	Lab-based, quasi-experimental, repeated-measures study with 2 counterbalanced sessions of 1. naltrexone 50 mg; 2. placebo tablet; + iv etoh (alcohol) challenge
Outcomes	Alcohol and cigarette craving
Notes	

Rohsenow 2003

Methods	NALTREXONE Country: USA Recruitment: From subjects enrolled in a trial of naltrexone for alcohol use outcomes
Participants	73 alcoholic smokers, abstinent from alcohol and/or drugs
Interventions	Naltrexone 50 mg/d or placebo pill for 12 weeks + counselling
Outcomes	Cigarettes per day, stage of change
Notes	Abstinence data not reported

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	

Rohsenow 2007

Methods	NALTREXONE Country: USA Recruitment: Not described
Participants	134 smokers, 54% F, >=15 cpd, av age 49
Interventions	3 x 3 randomized, between-subjects, parallel-groups, crossed-medication (naltrexone 50 mg vs. placebo) + nicotine replacement patch (42 mg vs. 21 mg); cigarette cue exposure + smoking challenge
Outcomes	Cue reactivity: smoking urges + withdrawal, hedonic + aversive effects of smoking
Notes	

Rohsenow 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	

Rukstalis 2005

Methods	NALTREXONE Country: USA Recruitment: Local adverts
Participants	Smokers, >= 10 cpd, >= 18, 42% F
Interventions	Lab-based, double-blind, within-subjects, counterbalanced, 3-session study: 1. naltrexone 50 mg; 2. bupropion 300 mg; 3. placebo; with cigarette choice (nicotinized 0.6 mg vs. denicotinized 0.05 mg cigarettes) smoking challenge
Outcomes	Smoking urges, smoking satisfaction
Notes	

Sutherland 1995

Methods	NALTREXONE Country: UK Recruitment: By newspaper adverts Design: Laboratory-based, double-blind, placebo-controlled, crossover trial
Participants	12 heavy smokers (4 men, 8 women), =>20 cpd,CO=>30
Interventions	Subjects seen on 6 occasions. Sessions grouped in 2 blocks of 3 sessions. First block evaluated at baseline, during acute nicotine administration and then given naltrexone 50 mg orally or a placebo pill with trace amounts of nicotine and asked to abstain from smoking until next session 24 hours later. Then followed for 48-hour ad lib smoking period
Outcomes	Withdrawal symptoms, mood, satisfaction and other subjective measures, ad lib smoking
Notes	No long-term abstinence data reported

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	

Wewers 1998

Methods	NALTREXONE Country: USA Recruitment: adverts Design: Laboratory-based, randomized, double-blind, repeated measures experimental design
Participants	43 smokers, >10/d, age >19, admitted to Clinical Research Centre for 6 days
Interventions	Naltrexone 50 mg or placebo pill. 22 received naltrexone and 21 received placebo for 3 days Abstinence not attempted
Outcomes	Measures: Plasma nicotine, expired air CO, number of cigarettes smoked, self-reported satisfaction with smoking, mood and withdrawal
Notes	

Wong 1999

Methods	NALTREXONE +/- NRT patch Country: USA Recruitment: adverts and press releases Randomization: by subject after stratification by gender
Participants	100 smokers, =>10 cpd at least 1yr, age 18-65, baseline CO =>15ppm without history of depression or alcohol/drug dependence
Interventions	1. Naltrexone 50mg/day for 12 weeks 2. Nicotine patch (21 mg 8 weeks/14 mg 4 weeks) + placebo pill 3. Naltrexone (50mg/day) + nicotine patch (21/14) for 12 weeks 4. Placebo pill for 12 weeks. All groups received weekly counselling. No placebo patches used
Outcomes	Self-reported abstinence to 6m verified with expired air CO, cigarettes smoked per day Self-reported ratings of urges and craving
Notes	Data reported from only 1 of 4 centres involved in study

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	

CO: carbon monoxide
cpd: cigarettes per day
FTQ: Fagerstrom Tolerance Questionnaire
iv: intravenous

ITT: intention to treat (includes all randomized)
m: month(s)
PPA: point prevalence abstinence
ppm: parts per million
sc: subcutaneous
wks: weeks

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

Study	Reason for exclusion
Ahmadi 2003	No placebo control group, and high drop-out rates (63-95%)
Byars 2005	RCT with follow up of 12 wks
Krishnan-Sarin 2003	Follow up only 4 wks
O'Malley 1995	Designed to evaluate effect on alcohol consumption and did not provide any data on tobacco consumption
Roozen 2006	Follow up only 3 months, no placebo group, so did not contribute data on withdrawal or other outcomes
Toll 2008	Follow up only 6 wks

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

Croop 2000

Trial name or title	Naltrexone for smoking cessation
Methods	
Participants	350 volunteers at 5 different sites across the U.S. recruited through advertisements and press releases, 18-65 years old, smoking at least 10 cigarettes a day for at least one year
Interventions	Group 1: Placebo pill Group 2: Placebo pill/Nicotine patch Group3: Naltrexone alone Group 4: Naltrexone/Nicotine patch. Naltrexone dose was 50 mg daily for 12 weeks 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

Croop 2000 (*Continued*)

	nicotine/mecamylamine for 6 weeks
Outcomes	6 month, carbon monoxide verified continuous abstinence
Starting date	
Contact information	
Notes	Completed but results from 4/5 sites remain unpublished

DATA AND ANALYSES

Comparison 1. Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abstinence at longest follow up	4	582	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.80, 2.01]
1.1 Naltrexone versus placebo (no NRT)	2	129	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.49, 3.69]
1.2 Naltrexone + NRT versus Placebo + NRT	3	453	Odds Ratio (M-H, Fixed, 95% CI)	1.24 [0.74, 2.09]

Analysis 1.1. Comparison 1 Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), Outcome 1 Abstinence at longest follow up.

Review: Opioid antagonists for smoking cessation

Comparison: 1 Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT)

Outcome: 1 Abstinence at longest follow up

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Naltrexone versus placebo (no NRT)					
Covey 1999	8/40	6/40		14.9 %	1.42 [0.44, 4.53]
Wong 1999	2/23	2/26		5.3 %	1.14 [0.15, 8.84]
Subtotal (95% CI)	**63**	**66**		**20.2 %**	**1.34 [0.49, 3.69]**
Total events: 10 (Treatment), 8 (Control)					
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² =0.0%					
Test for overall effect: Z = 0.57 (P = 0.57)					
2 Naltrexone + NRT versus Placebo + NRT					
Wong 1999	7/26	7/25		16.2 %	0.95 [0.28, 3.24]
King 2006	14/52	11/58		23.5 %	1.57 [0.64, 3.86]
O'Malley 2006	27/199	11/93		40.1 %	1.17 [0.55, 2.47]
Subtotal (95% CI)	**277**	**176**		**79.8 %**	**1.24 [0.74, 2.09]**
Total events: 48 (Treatment), 29 (Control)					
Heterogeneity: Chi² = 0.48, df = 2 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					
Total (95% CI)	**340**	**242**		**100.0 %**	**1.26 [0.80, 2.01]**

(*Continued* . . .)

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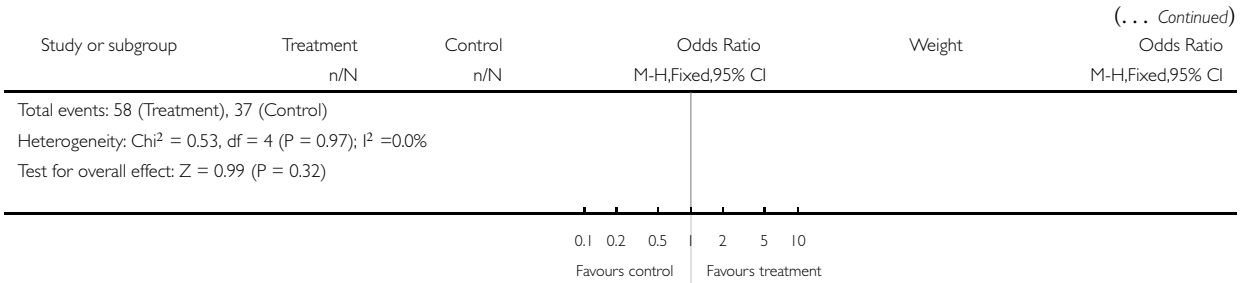

WHAT'S NEW

Last assessed as up-to-date: 11 June 2009.

Date	Event	Description
12 June 2009	New search has been performed	Updated for issue 4, 2009. No new long term cessation studies, four laboratory/ short term studies

HISTORY

Protocol first published: Issue 2, 2001

Review first published: Issue 3, 2001

Date	Event	Description
29 October 2008	Amended	Converted to new review format.
9 August 2006	New citation required but conclusions have not changed	Updated for issue 4, 2006. Two new studies with long term cessation data. Dr Eden Evins became a co-author
24 October 2002	New citation required and minor changes	Updated for issue 1, 2003. One new study of effect of buprenorphine on ad libitum smoking, not relevant to clinical intervention

CONTRIBUTIONS OF AUTHORS

SD initiated the review, drafted the protocol, checked relevant studies, extracted data and drafted the review. LS extracted data. LS and TL assisted in finalising the review. LS and TL assisted in finalising the review. SD, LS, TL, and EE reviewed and approved the update for issue 4, 2006.

DECLARATIONS OF INTEREST

Nil.

SOURCES OF SUPPORT

Internal sources

- Brown University/Memorial Hospital of Rhode Island, USA.

External sources

- Cancer Research UK General Practice Research Group, UK.
- NHS Research & Development Programme, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Buprenorphine [therapeutic use]; Naloxone [therapeutic use]; Naltrexone [therapeutic use]; Narcotic Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic; Smoking [*drug therapy]; Smoking Cessation [*methods]

MeSH check words

Humans