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Systematic Review and Meta-Analysis of Opioid Antagonists for Smoking Cessation

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ABSTRACT

Objectives: This meta-analysis sought to evaluate the efficacy of opioid antagonists in promoting long-term smoking cessation. Post-treatment abstinence was examined as a secondary outcome and effects on withdrawal symptoms, craving, and reduced consumption were also explored.

Design: The search strategy for this meta-analysis included clinical trials (published and unpublished data) in the Cochrane Tobacco Addiction Group Specialized Register and MEDLINE.

Participants: Adult smokers.

Interventions: We included randomized trials comparing opioid antagonists to placebo or an alternative therapy for smoking cessation and reported data on abstinence for a minimum of six months.

Primary and secondary outcome measures: Outcomes included smoking abstinence at long-term follow-up (primary); abstinence at end of treatment (secondary); and effects on withdrawal, craving, and smoking consumption (exploratory).

Results: Eight trials with a total of 1213 participants were included. Half the trials examined the benefit of adding naltrexone versus placebo to nicotine replacement therapy (NRT). There was no significant difference between naltrexone and placebo alone (relative risk (RR) 1.00; (95% CI) 0.66 to 1.51) or as an adjunct to NRT (RR 0.95; (CI) 0.70 to 1.30), with an overall pooled estimate of RR 0.97; CI: 0.76 to 1.24. Findings for naltrexone effects on withdrawal, craving, and reduced smoking were equivocal.

Conclusions: The findings indicate no beneficial effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence. While further trials may narrow the confidence limits, they are unlikely to appreciably alter the conclusion.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The strengths of this study are:

• This meta-analysis compares opioid antagonists to placebo or an alternative therapy for smoking cessation and reports data on abstinence for a minimum of six months.

• The meta-analysis includes published and unpublished results from eight trials with a total of 1213 participants.

• The findings indicate no beneficial effect of naltrexone alone or as an adjunct to nicotine replacement therapy on short or long-term smoking abstinence, which suggests that further investment in clinical trials of naltrexone for this indication are unlikely to change the conclusion that this medication does not provide a clinically-significant benefit for helping smokers stop smoking.

The limitations of this study are:

• Inability to refute published claims of differential benefits of naltrexone for smoking cessation in subgroups defined by gender or secondary benefits on reduction of post-cessation weight gain.

BACKGROUND

Tobacco use is the leading preventable cause of death.[1] US clinical practice guidelines recommend the use of pharmacotherapy for quitting smoking.[2] Medications with demonstrable efficacy for cessation include nicotine replacement therapy (NRT) in the form of gum, patch, lozenge, inhaler, and nasal spray with pooled relative risk (RR) for any NRT of 1.60, 95% confidence interval (CI) 1.53 to 1.68;[3] bupropion with RR=1.69, CI 1.53 to 1.85;[4] and varenicline with RR=2.27, CI 2.02 to 2.55.[3,5] Effective second-line treatments include nortriptyline (RR 2.03; CI 1.48 to 2.78)[4]and clonidine (OR 1.89, CI 1.30 to 2.74).[6] Yet, long-term quit rates with these pharmacotherapies are relatively modest, in the range of 19.0% to 36.5%.[2] With relapse as the norm, there is continued interest in medication development and discovery of pharmacological agents for assisting tobacco cessation.

The reinforcing properties of nicotine are mediated through several neurotransmitters. Exposure to nicotine stimulates central nicotinic cholinergic receptors, which enhances synaptic release of dopamine, norepinephrine, acetylcholine, vasopressin, serotonin, glutamate, gamma-amino butyric acid (GABA), and beta-endorphin.[7] Rodent studies indicate that nicotine-induced beta-endorphin release in the brain is anxiolytic[8-10] and may reduce anxiety and tension.[11] Nicotine also evokes neuroregulatory effects when binding to nicotinic cholinergic receptors in the adrenal medulla, resulting in the release of epinephrine (adrenaline) and beta-endorphin, which may contribute to the systemic effects of nicotine.[12] Furthermore, acute and chronic exposure to nicotine alters the synthesis and release of beta-endorphin, met-enkephalin and dynorphin in the nucleus accumbens and other brain regions implicated in nicotine reinforcement (mu-opioid receptors) and aversive effects of nicotine including physical manifestations of nicotine withdrawal (delta- and kappa-opioid receptors).

Naltrexone (Narpan, Revia, Vivitrol, with half-life of 240 min[13]), a long-acting opioid antagonist, is a marketed drug that blunts the effects of narcotics such as heroin, meperidine,

morphine and oxycodone and is effective in the treatment of alcohol dependence.[14,15] Naltrexone occupies μ-opioid receptors, which putatively diminishes the activation of mesolimbic dopamine and therefore may reduce craving for nicotine. With different mechanisms of action, it has been postulated that NRT and naltrexone could produce additive effects for treating nicotine withdrawal and preventing relapse. Since opioid antagonists are known to precipitate nicotine withdrawal in nicotine dependent animals,[16-19] administering NRT in conjunction may attenuate any increased withdrawal, dysphoria, and sedation caused by naloxone and naltrexone. Naloxone (Narcan, with half-life 30-100 min[20]) is a short-acting opioid antagonist routinely administered to reverse the acute effects of narcotic overdose. Naloxone has been shown to block the reinforcing properties of nicotine and precipitate physical and affective symptoms of nicotine withdrawal in rodent studies.[16-19] Buprenorphine (Buprenex, Subutex, Suboxone [combination buprenorphine/naltrexone], Butrans, with half-life 24-60 hrs)[21] is a mixed agonist-antagonist used for the treatment of opioid dependence. Although less widely studied for this indication, naloxone and buprenorphine have also been evaluated as potential smoking cessation aids and are included in this review.

Concerns regarding potential adverse effects have led to US Food and Drug Administration black box warnings for the cessation medications bupropion and varenicline. With respect to the adverse event profile of opioid antagonists when used in the treatment of opioid dependence, serious adverse effects are uncommon but there is an FDA black box warning regarding potential hepatotoxicity for naltrexone. Nervous system side effects reported in >10% of patients during treatment for opioid dependence have included headaches, nervousness, anxiety, difficulty sleeping, and low energy; those reported in <10% of patients include loss of appetite, increased energy, irritability, and dizziness. Asthenia, agitation, hyperkinesia, nervousness, fatigue, restlessness, confusion, disorientation, and somnolence have been reported rarely. Side effects of buprenorphine are similar to those of other opioids and include nausea, vomiting, and constipation.

While opioid antagonists are typically used in the treatment of opioid dependence, the primary objective of this systematic review and meta-analysis was to evaluate the long-term efficacy of opioid antagonists (i.e., naltrexone, naloxone, buprenorphine), alone or in combination with NRT, in promoting smoking cessation. The secondary objective was to evaluate the short-term (post-treatment) abstinence effects. Specific opioid antagonists were considered separately rather than grouping the medications as a class. We tested the hypotheses that opioid antagonists: (1) are more effective than placebo in promoting early and sustained abstinence from smoking and (2) when used in combination with NRT are more effective than NRT alone in promoting early and sustained abstinence from smoking. We also summarize the literature on the effects of opioid antagonists in treating withdrawal symptoms, attenuating the reinforcing value of smoking, and reducing ad libitum smoking.

METHODS

Search Strategy and Study Selection

We included randomized controlled trials of opioid antagonists with adult smokers that reported smoking status at least six months after intervention to assess the efficacy for long-term cessation. For the secondary outcome, we also considered randomized controlled trials of opioid antagonists reporting abstinence at end-of treatment or that reported the outcomes of nicotine withdrawal, reinforcing properties of smoking, or ad libitum smoking. The medications evaluated were naltrexone, naloxone, buprenorphine or other opioid antagonists, with or without concurrent use of NRT.

To identify eligible studies, we searched the Tobacco Addiction group Specialized Register in April 2013 using the terms ‘naloxone’ or ‘naltrexone’ or ‘opioid antagonist’ or ’opiate antagonist’ or ‘narcotic antagonist’ in the title or abstract, or as keywords (see Appendix 1 for details). At the time of the search, the Register included the results of searches of the Cochrane Central Register of Controlled

trials (CENTRAL), issue 3, 2013; MEDLINE (via OVID) through March 29, 2013; EMBASE (via OVID) through March 16, 2013 and PsycINFO (via OVID) through April 1, 2013. An additional search of MEDLINE (via OVID through April 17, 2013) used the terms (explode "Narcotic-Antagonists"/ all subheadings) AND ("Smoking-Cessation"/all subheadings OR "Tobacco-Use-Disorder"/all subheadings OR "Smoking"/all subheadings). Two authors cross-checked the studies to insure they met the inclusion criteria. Discrepancies were resolved by mutual consent including a third author, as required. We noted reasons for the non-inclusion of studies. Details of the search are in Figure 1.

Data Extraction

Data extraction included: basic study characteristics (sample size, design, blinding, method of randomization, location), sample characteristics (cigarettes/day, intention to quit), tobacco measures and outcomes, reported averse effects, and attrition. The primary outcome measure of interest was abstinence at six months or longer, with preference given to the longest follow-up available. Abstinence at end of treatment was a secondary outcome. We used a sustained cessation rate in preference to point prevalence, and biochemical verification of self-reported quitting where reported (e.g., carbon monoxide, cotinine). Other outcome measures of interest included withdrawal, reinforcing or hedonic effects of smoking, mood states, and ad libitum smoking.

Data Analysis

For the abstinence outcomes, we calculated relative risks using as the denominators the numbers of patients randomized to each arm excluding any deaths and treating those who dropped out or were lost to follow up 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. Separately, we combined the results of studies evaluating short- and long-term cessation using the Mantel-Haenszel fixed-effect model for pooling risk ratios. Effect sizes were calculated for all trials together and by whether or not NRT was used. In a sensitivity analysis, we estimated the effect at end of treatment of

adding in the results from studies excluded due to lack of long-term follow-up. For assessment of risk of bias, we evaluated studies on the basis of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), and incomplete outcome data (attrition bias).[22] Procedures varied and few studies reported on measures of withdrawal, craving, and smoking reduction; hence, these outcomes were narratively summarized.

FINDINGS

Long-term Abstinence

We identified eight trials evaluating naltrexone and reporting long-term abstinence rates with a total of 1213 participants (Table 1).[23-31] Three studies examined naltrexone monotherapy relative to placebo; four studies examined naltrexone as an adjunct to NRT or placebo; and one study had 4 arms, which allowed for examination of naltrexone alone versus as an adjunct to NRT with matched placebo conditions for both arms.[30] There was no evidence of heterogeneity in subgroups with or without NRT, and the pooled estimate for the 8 trials gave no evidence of a treatment effect (RR 0.97; CI 0.76 to 1.24; Table 2). Naltrexone dose ranged from 25 mg to 150 mg daily. Five trials provided cessation counseling with the medication of either brief (15 to 20 min)[24,30] or more extended duration.[23,25,29] Four studies biochemically confirmed nonsmoking status.[24,25,28,29] Abstinence data were unpublished for two of the studies and obtained directly from the authors.[26,27] For one of the studies, part of a multi-center trial with 350 subjects enrolled at five centers in the US, the authors could only report data from the Mayo Clinic site, which enrolled 100 people. Despite our attempts to obtain unpublished data for the other 250 participants, the funder DuPont, has not disclosed further results.[32]

For the five studies that examined naltrexone alone versus placebo (n=450), the pooled estimate was RR = 1.00, CI 0.66 to 1.51 (Table 2)[23,26-28,30], and the estimate was not sensitive to

exclusion of the two studies with unpublished data lacking biochemical validation of abstinence.[26,27]. For the four studies that examined naltrexone versus placebo as an adjunct to NRT (n=768), the pooled estimate was RR = 0.95; CI 0.70 to 1.30.[24,25,29,30]

Three trials raised the possibility that there could be a difference in effect by sex, with women showing more evidence of a benefit than men for smoking cessation in two trials[23,25] and showing less of a benefit in a third.[29] In one trial naltrexone showed a greater effect in preventing weight gain for women than men.[29] The other five abstinence studies did not report quit rates for men and women separately 25, 27-29, 31, 33 and a summary estimate could not be calculated without risk of reporting bias.

Short-term Abstinence

Similar to the analysis of long-term abstinence effects, there was no evidence of an early treatment effect and with a slightly narrower confidence interval (RR 1.03; CI 0.88 to 1.22, Table 2). Three studies in addition to the eight trials in the main analysis were found that only reported short-term outcomes.[33-35] Inclusion of the 116 participants from these trials did not greatly alter the estimate (RR 1.09, CI 0.93 to 1.27).

Risk of Bias in Included Studies

Studies included in the meta-analysis were evaluated on their attempts to control bias in randomization, allocation, assessment, and analysis. None of the eight studies were judged at high risk for selection bias due to inadequate randomization or allocation concealment procedures, but three did not report methods in sufficient detail for the possibility of allocation bias to be discounted.[22, 29, 30] Two of these studies have only been reported as abstracts with limited methodological detail. All studies were described as double blind. The long-term cessation studies confirmed abstinence with biochemical verification, with two exceptions.[26,27] Five studies reported exhaled carbon monoxide (CO) verification,[24,25,29,30,35], and one study reported plasma cotinine concentration.[23] This

study had high attrition in both groups and greater attrition earlier in the naltrexone group: ten people in the naltrexone group and two people in the placebo group were considered treatment failures because they dropped out prior to the target quit day.[23]

Withdrawal, Hedonic Effects, and Smoking Reduction

Overall, findings were mixed for effects of naltrexone, naloxone, and buprenorphine on measures of nicotine withdrawal, nicotine reward, and ad libitum smoking. Ten studies indicated no effect of naltrexone on withdrawal symptom scores.[23,25,28,30,35-41] Five studies reported reductions in withdrawal or smoking urge.[24,25,29,40,42] For one of the trials, the effect was found only at the 100mg dose compared to placebo and not at lower doses.[24] Additionally, three trials indicated diminished withdrawal symptoms following provocative smoking cues during sustained abstinence,[43-45] and one trial reported that naltrexone reduced ethanol's enhancing effect on smoking urge symptoms but naltrexone did not have a significant main effect on smoking urges.[46] For naloxone, two studies found no significant difference in withdrawal symptoms or mood states relative to placebo,[47,48] and another study showed an increased urge to smoke (craving) and tiredness at lower dosages of naloxone.[49]

Studies evaluating the reinforcing effects of smoking also were mixed. Two studies found no effect of naltrexone on self-reported satisfaction from smoking[36] or smoking reinforcement.[44,45,50] Other studies found significant reduction in self-reported satisfaction with smoking,[47,51] increased negative mood following smoking;[38] increased lightheadedness, dizziness, and head rush following a cigarette,[39] and significantly reduced post-cigarette craving.[39] For naloxone, two studies found no effect on the reinforcing properties of smoking cigarettes.[48,52]

Lastly, the results regarding ad libitum smoking were mixed. There were no significant effects of naltrexone on ad libitum smoking in three small trials.[36-38] However, six trials demonstrated statistically significant reductions in the number of cigarettes smoked ad libitum.[39,40,42,44,53,54]

Five trials designed to evaluate abstinence and other outcomes during smoking cessation reported effects of naltrexone on daily or weekly smoking during and/or after treatment with naltrexone.[24,28-30,35] Three studies did not find any association between naltrexone and number of cigarettes smoked among continuing smokers,[26,27,30] another reported cigarettes per week increased more in the placebo group compared to the naltrexone group at the 100 mg dose of naltrexone,[24] and two studies reported significantly lower weekly cigarettes smoked in the naltrexone (vs placebo) arms of the respective trials.[28,29] For naloxone, two studies reported significant reductions in number of cigarettes smoked relative to placebo[48,52] and one study did not find an effect over a wide range of dosages for any measure of cigarette smoking, including number of cigarettes, number of puffs, or expired air carbon monoxide.[55] With buprenorphine, two studies found an increase in cigarette consumption associated with buprenorphine.[56,57]

DISCUSSION

Eight double-blinded, randomized controlled trials of naltrexone with a total of 1213 adult smokers reported long-term abstinence data and 11 reported short-term outcomes. The point estimate for the risk ratio of the long-term effect of cessation pooling all studies, RR=0.97, suggests that naltrexone has no effect on abstinence. Further, there was no benefit of naltrexone relative to placebo for smoking cessation whether used alone or in combination with NRT. The 95% confidence interval of 0.76 to 1.24 indicates that the likelihood of any clinically important effect is very small. By comparison, the RR of long-term abstinence for NRT from 117 trials with over 50,000 participants was 1.60 (CI 1.53 to 1.68).[3]We also know that one industry-sponsored naltrexone trial remains unpublished, the likelihood being that it too did not detect evidence of benefit.[32] The results suggest that further research is only likely to make the confidence interval narrower around no effect. A secondary analysis of pooled short-term outcomes also showed no evidence of a treatment effect. Including three

randomized clinical trials that only reported short-term effects, with a total of 116 participants, did not alter this conclusion.

While we were unable to meta-analyze sex-specific effects including data from all 8 trials, there was no compelling or consistent evidence of robust sex differences in efficacy for naltrexone. Although not an endpoint of this systematic review, two trials reported significant benefits of naltrexone for reducing post-cessation weight gain,[23,25] while one did not.[29] A Cochrane review showed a modest benefit of naltrexone on reduced post-cessation weight gain at end of treatment (MD -0.78 kg, 95% CI -1.52, -0.05, N=2 trials), with insufficient data to assess the effects at 6 or 12-months. There were mixed results from individual trial as to whether opioid antagonists reduced nicotine withdrawal symptoms, the reinforcing effects of nicotine and tobacco, or cigarette consumption, but the heterogeneity of methods and reporting precluded use of meta-analytic techniques. Though there was no evidence of effect for any dose on the primary outcome of this review, abstinence, there was some

CONCLUSIONS

While it would seem biologically plausible that opioid antagonists may support smoking cessation vis-à-vis attenuation of positive reinforcement, the current evidence suggests that naltrexone provides no benefit for immediate or sustained smoking cessation. The neurobiology of nicotine addiction is complex and involves interactions between multiple neurotransmitter systems.[58] Unequivocal benefits have been reported for other classes of smoking cessation medications (i.e., nicotine replacement, bupropion, varenicline) with different mechanisms of action in large meta-analyses of scores of clinical trials.[3-5] However, based on data from eight trials and over 1200 individuals, there is no evidence of a therapeutic effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence rates. While further trials may narrow the confidence limits, they are unlikely to change the conclusion of lack of benefit.

COMPETING INTERESTS

All authors have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JJP has served on ad hoc scientific advisory and grant review boards for Pfizer and has a Pfizer funded investigator initiated research award. All other authors have no competing interests to declare.

CONTRIBUTIONS

All authors contributed to this work. SPD designed the study, implemented all methods, and guided interpretation of the results. SPD and IMC and participated in the drafting and editing of the paper at every stage. SPD, TL, AEE, and JJP posed the question, coordinated the research team and participated in all stages of the analysis and drafting of the manuscript. SPD, TL, LFS, and JJP assisted in study design and extraction of data and advised on the analysis methods.

TABLES

Table 1. Characteristics of included studies

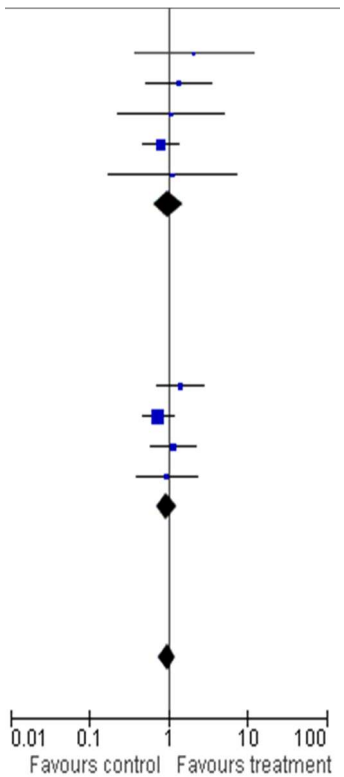
Trial Description						Risk of Bias				
Trial	**Follow up time point for abstinence**	**Region**	**Treatment**	**Number of participants at baseline**	**Number participants at longest follow up**	**Biochemical validation**	**Random sequence generation**	**Allocation concealment**	**Incomplete outcome data**	**Blinding**
Baltieri et al. 2009	12 weeks 6 months	Brazil	1) Naltrexone 50 mg/day for 12w 2) Placebo 3) Topiramate up to 300 mg/day (not used in this review)	65	28	No	Unclear	Low	Unclear	Low
Covey et al 1999	4 weeks 6 months	USA	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	80	54	Yes	Unclear	Unclear	High	Low
King et al 2006	8weeks 24 weeks	USA	1. Naltrexone 25 mg for 3 days then 50 mg for 2m, nicotine patch for 1m 2. Placebo & nicotine patch	110	89	Yes	Low	Low	Low	Low
King et al 2012	12 weeks 6 months 12 months	USA	1. Naltrexone (50 mg/day) x 12 weeks plus Nicotine Patch (21 mg/day x 2 weeks, 14 mg/day x 1 week, 7 mg/day x 1 week) 2. Placebo x 12 weeks plus 12 weeks plus Nicotine Patch (same schedule)	315	238	Yes	Low	Low	Low	Low
Meszaros et al 2010	12 weeks	USA	1. Naltrexone 3 times/week (100 mg Mon & Tue; 150 mg Fri) x 3	79	Not given	No	Unclear	Unclear	Unclear	Unclear

			months 2. Placebo (same schedule)							
O'Malley et al 2006	12 months	USA	1. Naltrexone 100 mg 2. Naltrexone 50 mg 3. Naltrexone 25 mg 4. Placebo All participants also received 21 mg NRT patch x 6 weeks, initial 45 min counseling session, weekly 15min counseling sessions for 6 weeks, plus self-help materials including dietary & exercise tips	385	295	Yes	Low	Low	Low	Low
Toll et al 2010	6 weeks 6 months	USA	1. Naltrexone (25 mg/day) x 27 weeks 2. Placebo x 27 weeks	172	58	Yes	Low	Low	Low	Low
Wong et al 1999	12 weeks 6 months	USA	1. Naltrexone 50 mg/day for 12 weeks 2. Nicotine patch (21 mg 8 weeks/14 mg 4 weeks) + placebo pill 3. Naltrexone (50 mg/day) + nicotine patch (21/14) for 12 weeks 4. Placebo pill for 12 weeks. All groups received weekly counseling. No placebo patches used	100	69	Yes	Low	Low	Unclear	Unclear

Risk of bias assessments -- biochemical validation indicates cotinine or exhaled carbon monoxide verification of abstinence evident from publication or investigator correspondence ('yes'/'no'). Risk of reporting bias and risk of bias was assessed for lack of random sequence generation (selection bias), allocation concealment (selection bias), incompletely-reported outcome data (attrition bias) or lack of or incomplete blinding (performance bias and detection bias), ('high,/'low'/'unclear') respectively.

Table 2: Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), abstinence at longest follow up.

Study or Subgroup	Treatment # Abstinent	Treatment Total	Control # Abstinent	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Naltrexone vs placebo (no NRT)							
Baltieri et al. 2009	3	27	2	38	1.6%	2.11 (0.38, 11.79)	
Covey et al 1999	8	40	6	40	5.8%	1.33 (0.51, 3.49)	
Meszaros et al 2010	3	38	3	41	2.8%	1.08 (0.23, 5.02)	
Toll et al 2010	19	87	23	85	22.4%	0.81 (0.48, 1.37)	
Wong et al 1999	2	23	2	26	1.8%	1.13 (0.17, 7.39)	
Subtotal (95% CI)		**215**		**230**	**34.3%**	**1.00 (0.66, 1.51)**	
Heterogeneity: Chi^2 = 1.72, df=4 (P=0.79); I^2= 0%							
Test for overall effect: Z= 0.02 (P = 0.98)							
Naltrexone vs placebo with NRT?							
King et al 2006	14	52	11	58	10.0%	1.42 (0.71, 2.85)	
King et al 2012	27	161	35	154	34.4%	0.74 (0.47, 1.16)	
O'Malley et al 2006	27	199	11	93	14.4%	1.15 (0.60, 2.21)	
Wong et al 1999	7	26	7	25	6.9%	0.96 (0.39, 2.35)	
Subtotal (95% CI)		**438**		**330**	**65.7%**	**0.95 (0.70, 1.30)**	
Total events	75		64				
Heterogeneity: Chi^2 = 2.81, df=3 (P=0.42); I^2= 0%							
Test for overall effect: Z= 0.30 (P = 0.77)							
Subtotal (95% CI)		**653**		**560**	**100%**	**0.97 (0.76, 1.24)**	
Total events	110		100				
Heterogeneity: Chi^2 = 4.53, df=8 (P=0.81); I^2= 0%							
Test for overall effect: Z= 0.25 (P = 0.80)							
Test for subgroup differences: Chi^2 = 0.02, df=1 (P=0.88); I^2= 0%							



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COMPETING INTERESTS

The Lead Author, Sean P David, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. Discrepancies from the study as planned have been explained.

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DATA SHARING STATEMENT

Unreported data from clinical trials that were either not published or for which results were not provided upon request to meta-analysis authors.

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FIGURE LEGENDS

Figure 1: PRISMA diagram of literature search and data extraction

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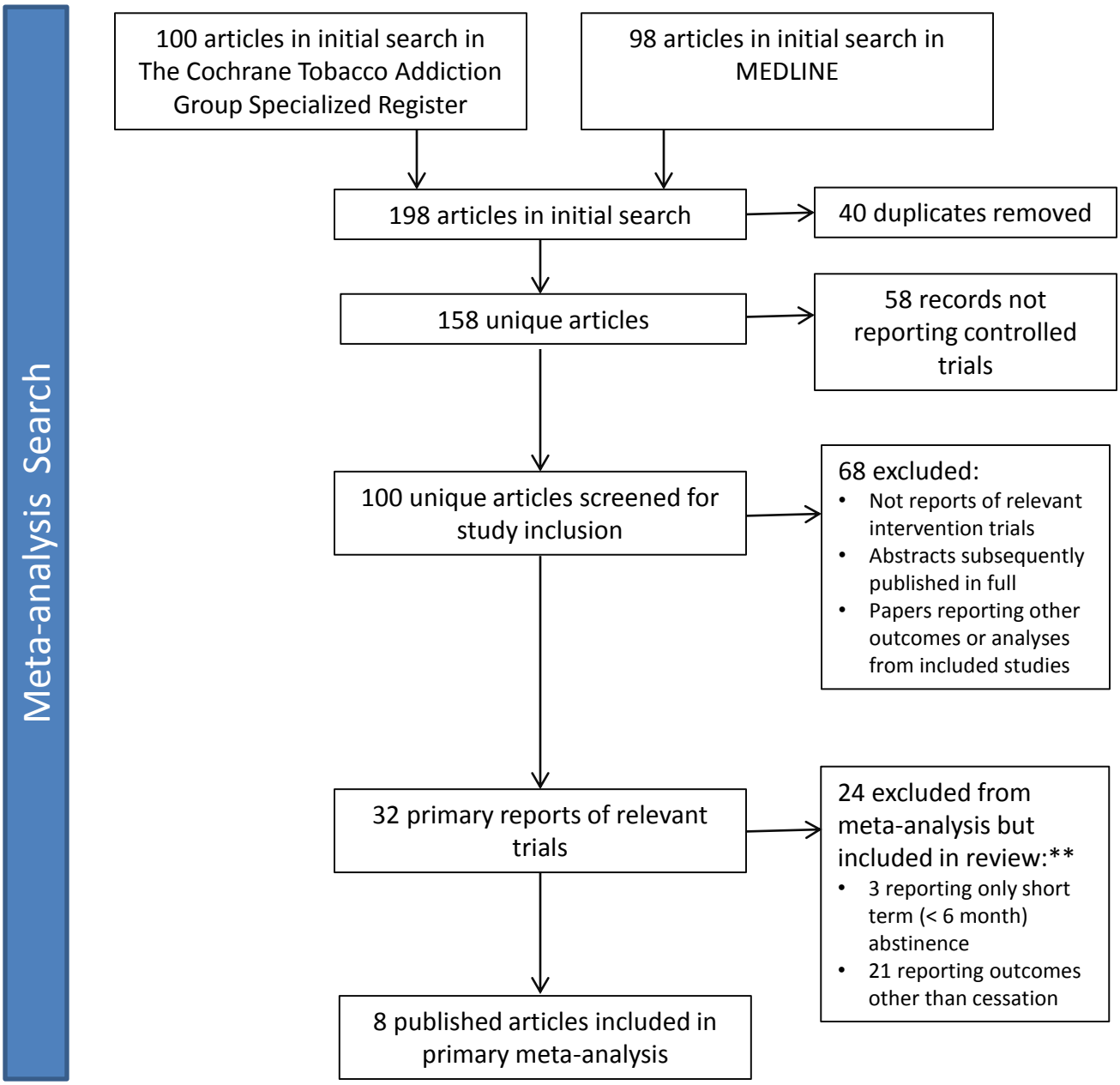

•Register holds reports of controlled trials on smoking cessation identified from searches of CENTRAL, MEDLINE, EMBASE and other sources including conference abstracts. See Specialized Register http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/frame.html

**24 studies excluded from meta-analyses were included in review for sensitivity analyses of short-term outcomes (k=3) and reporting outcomes other than abstinence.

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Both. Cover sheet, abstract and page 4.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2. Per BMJ instructions.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	This review was originally conducted using the Cochrane method.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5

PRISMA Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Pages 5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5 and 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 7 and 9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1 is mentioned on page 6 and attached as a separate file.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pages 7 and 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Pages 5 and 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 8 and 9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 8 and 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 10

PRISMA Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

Systematic Review and Meta-Analysis of Opioid Antagonists for Smoking Cessation

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Systematic Review and Meta-Analysis of Opioid Antagonists for Smoking Cessation

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ABSTRACT

Objectives: This meta-analysis sought to evaluate the efficacy of opioid antagonists in promoting long-term smoking cessation. Post-treatment abstinence was examined as a secondary outcome and effects on withdrawal symptoms, craving, and reduced consumption were also explored.

Design: The search strategy for this meta-analysis included clinical trials (published and unpublished data) in the Cochrane Tobacco Addiction Group Specialized Register and MEDLINE.

Participants: Adult smokers.

Interventions: We included randomized trials comparing opioid antagonists to placebo or an alternative therapy for smoking cessation and reported data on abstinence for a minimum of six months.

Primary and secondary outcome measures: Outcomes included smoking abstinence at long-term follow-up (primary); abstinence at end of treatment (secondary); and effects on withdrawal, craving, and smoking consumption (exploratory).

Results: Eight trials with a total of 1213 participants were included. Half the trials examined the benefit of adding naltrexone versus placebo to nicotine replacement therapy (NRT). There was no significant difference between naltrexone and placebo alone (relative risk (RR) 1.00; (95% CI) 0.66 to 1.51) or as an adjunct to NRT (RR 0.95; (CI) 0.70 to 1.30), with an overall pooled estimate of RR 0.97; CI: 0.76 to 1.24. Findings for naltrexone effects on withdrawal, craving, and reduced smoking were equivocal.

Conclusions: The findings indicate no beneficial effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence. While further trials may narrow the confidence limits, they are unlikely to appreciably alter the conclusion.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The strengths of this study are:

• This meta-analysis compares opioid antagonists to placebo or an alternative therapy for smoking cessation and reports data on abstinence for a minimum of six months.

• The meta-analysis includes published and unpublished results from eight trials with a total of 1213 participants.

• The findings indicate no beneficial effect of naltrexone alone or as an adjunct to nicotine replacement therapy on short or long-term smoking abstinence, which suggests that further investment in clinical trials of naltrexone for this indication are unlikely to change the conclusion that this medication does not provide a clinically-significant benefit for helping smokers stop smoking.

The limitations of this study are:

• Inability to refute published claims of differential benefits of naltrexone for smoking cessation in subgroups defined by gender or secondary benefits on reduction of post-cessation weight gain.

BACKGROUND

Tobacco use is the leading preventable cause of death.[1] US clinical practice guidelines recommend the use of pharmacotherapy for quitting smoking.[2] Medications with demonstrable efficacy for cessation include nicotine replacement therapy (NRT) in the form of gum, patch, lozenge, inhaler, and nasal spray with pooled relative risk (RR) for any NRT of 1.60, 95% confidence interval (CI) 1.53 to 1.68;[3] bupropion with RR=1.69, CI 1.53 to 1.85;[4] and varenicline with RR=2.27, CI 2.02 to 2.55.[3 5] Effective second-line treatments include nortriptyline (RR 2.03; CI 1.48 to 2.78)[4] and clonidine (OR 1.89, CI 1.30 to 2.74).[6] Yet, long-term quit rates with these pharmacotherapies are relatively modest, in the range of 19.0% to 36.5%.[2] With relapse as the norm, there is continued interest in medication development and discovery of pharmacological agents for assisting tobacco cessation.

Naltrexone (Narpan, Revia, Vivitrol, with half-life of 240 min[7]), a long-acting opioid antagonist, is a marketed drug that blunts the effects of narcotics such as heroin, meperidine, morphine and oxycodone and is effective in the treatment of alcohol dependence.[8 9] Naltrexone occupies μ-opioid receptors, which putatively diminishes the activation of mesolimbic dopamine and therefore may reduce craving for nicotine. With different mechanisms of action, it has been postulated that NRT and naltrexone could produce additive effects for treating nicotine withdrawal and preventing relapse. Since opioid antagonists are known to precipitate nicotine withdrawal in nicotine dependent animals,[10-13] administering NRT in conjunction may attenuate any increased withdrawal, dysphoria, and sedation caused by naloxone and naltrexone. Naloxone (Narcan, with half-life 30-100 min[14]) is a short-acting opioid antagonist routinely administered to reverse the acute effects of narcotic overdose. Naloxone has been shown to block the reinforcing properties of nicotine and precipitate physical and affective symptoms of nicotine withdrawal in rodent studies.[10-13] Buprenorphine (Buprenex, Subutex, Suboxone [combination buprenorphine/naltrexone], Butrans, with half-life 24-60 hrs)[15] is a mixed agonist-antagonist used for the treatment of opioid dependence. Although less widely studied for this

indication, naloxone and buprenorphine have also been evaluated as potential smoking cessation aids and are included in this review.

Concerns regarding potential adverse effects have led to US Food and Drug Administration black box warnings for the cessation medications bupropion and varenicline. With respect to the adverse event profile of opioid antagonists when used in the treatment of opioid dependence, serious adverse effects are uncommon but there is an FDA black box warning regarding potential hepatotoxicity for naltrexone. Nervous system side effects reported in >10% of patients during treatment for opioid dependence have included headaches, nervousness, anxiety, difficulty sleeping, and low energy; those reported in <10% of patients include loss of appetite, increased energy, irritability, and dizziness. Asthenia, agitation, hyperkinesia, nervousness, fatigue, restlessness, confusion, disorientation, and somnolence have been reported rarely. Side effects of buprenorphine are similar to those of other opioids and include nausea, vomiting, and constipation.

While opioid antagonists are typically used in the treatment of opioid dependence, the primary objective of this systematic review and meta-analysis was to evaluate the long-term efficacy of opioid antagonists (i.e., naltrexone, naloxone, buprenorphine), alone or in combination with NRT, in promoting smoking cessation. The secondary objective was to evaluate the short-term (post-treatment) abstinence effects. Specific opioid antagonists were considered separately rather than grouping the medications as a class. We tested the hypotheses that opioid antagonists: (1) are more effective than placebo in promoting early and sustained abstinence from smoking and (2) when used in combination with NRT are more effective than NRT alone in promoting early and sustained abstinence from smoking. We also summarize the literature on the effects of opioid antagonists in treating withdrawal symptoms, attenuating the reinforcing value of smoking, and reducing ad libitum smoking. The results of this systematic review and meta-analyses have been published in a recent Cochrane Review.[16]

METHODS

Search Strategy and Study Selection

We included randomized controlled trials of opioid antagonists with adult smokers that reported smoking status at least six months after intervention to assess the efficacy for long-term cessation. For the secondary outcome, we also considered randomized controlled trials of opioid antagonists reporting abstinence at end-of treatment or that reported the outcomes of nicotine withdrawal, reinforcing properties of smoking, or ad libitum smoking. The medications evaluated were naltrexone, naloxone, buprenorphine or other opioid antagonists, with or without concurrent use of NRT.

To identify eligible studies, we searched the Tobacco Addiction group Specialized Register in April 2013 using the terms 'naloxone' or 'naltrexone' or 'buprenorphine' or 'opioid antagonist' or 'opiate antagonist' or 'narcotic antagonist' in the title or abstract, or as keywords. At the time of the search, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 3, 2013; MEDLINE (via OVID) through March 29, 2013; EMBASE (via OVID) through March 16, 2013 and PsycINFO (via OVID) through April 1, 2013. An additional search of MEDLINE (via OVID through April 17, 2013) used the terms (explode "Narcotic-Antagonists"/ all subheadings) AND ("Smoking-Cessation"/all subheadings OR "Tobacco-Use-Disorder"/all subheadings OR "Smoking"/all subheadings). Two authors cross-checked the studies to insure they met the inclusion criteria. Discrepancies were resolved by mutual consent including a third author, as required. We noted reasons for the non-inclusion of studies. Details of the search are in the PRISMA Diagram (Figure 1).

Data Extraction

Data extraction included: basic study characteristics (sample size, design, blinding, method of randomization, location), sample characteristics (cigarettes/day, intention to quit), tobacco measures

and outcomes, reported averse effects, and attrition. The primary outcome measure of interest was abstinence at six months or longer, with preference given to the longest follow-up available. Abstinence at end of treatment was a secondary outcome. We used a sustained cessation rate in preference to point prevalence, and biochemical verification of self-reported quitting where reported (e.g., carbon monoxide, cotinine). Other outcome measures of interest included withdrawal, reinforcing or hedonic effects of smoking, mood states, and ad libitum smoking.

Data Analysis

For the abstinence outcomes, we calculated relative risks of abstinence at longest follow-up using as the denominators the numbers of patients randomized to each arm excluding any deaths and treating those who dropped out or were lost to follow up 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. Separately, we combined the results of studies evaluating short- and long-term cessation using the Mantel-Haenszel fixed-effect model for pooling risk ratios. Effect sizes were calculated for all trials together and by whether or not NRT was used. In a sensitivity analysis, we estimated the effect at end of treatment of adding in the results from studies excluded due to lack of long-term follow-up. For assessment of risk of bias, we evaluated studies on the basis of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), and incomplete outcome data (attrition bias).[17] None of the trials of buprenorphine or naloxone were eligible for inclusion in meta-analyses of abstinence because of lack of sufficient follow-up or available abstinence outcomes. Therefore, we report abstinence results only for naltrexone. Procedures varied and few studies reported on measures of withdrawal, craving, and smoking reduction for buprenorphine, naloxone and naltresone; hence, these outcomes were narratively summarized. Characteristics of all included and excluded studies are published in the Cochrane Review.[16]

FINDINGS

Long-term Abstinence

We identified eight trials evaluating naltrexone and reporting long-term abstinence rates with a total of 1213 participants (Table 1).[18-26] Three studies examined naltrexone monotherapy relative to placebo; four studies examined naltrexone as an adjunct to NRT or placebo; and one study had 4 arms, which allowed for examination of naltrexone alone versus as an adjunct to NRT with matched placebo conditions for both arms.[25] There was no evidence of heterogeneity in subgroups with or without NRT. Naltrexone dose ranged from 25 mg to 150 mg daily. Five trials provided cessation counseling with the medication of either brief (15 to 20 min)[19 25] or more extended duration.[18 20 24] Four studies biochemically confirmed nonsmoking status.[19 20 23 24] Abstinence data were unpublished for two of the studies and obtained directly from the authors.[21 22] For one of the studies, part of a multi-center trial with 350 subjects enrolled at five centers in the US, the authors only published the results from the Mayo Clinic site, which enrolled 100 people but would not provide unpublished data for the other study sites upon repeated requests.[27] Despite our attempts to obtain unpublished data for the other 250 participants, the funder DuPont, has not disclosed further results.[16] In one study,[19] there were three different treatment arms of 25 mg, 50 mg, and 100 mg naltrexone. The 50 mg and 100 mg groups were combined and included in the meta-analysis, however, we conducted a sensitivity analysis and including the 25 mg arm did not significantly change the results – as previously reported.[16]

The pooled estimate for the 8 trials gave no evidence of a treatment effect (RR 0.97; CI 0.76 to 1.24; Table 2). For the five studies that examined naltrexone alone versus placebo (n=450), the pooled estimate was RR = 1.00, CI 0.66 to 1.51 (Table 2),[18 21-23 25] and the estimate was not sensitive to exclusion of the two studies with unpublished data lacking biochemical validation of abstinence.[21 22] For the four studies that examined naltrexone versus placebo as an adjunct to NRT (n=768), the pooled estimate was RR = 0.95; CI 0.70 to 1.30.[19 20 24 25]

Three trials raised the possibility that there could be a difference in effect by sex, with women showing more evidence of a benefit than men for smoking cessation in two trials[18 20] and showing less of a benefit in a third.[24] In one trial, naltrexone showed a greater effect in preventing weight gain for women than men.[24] The other five abstinence studies did not report quit rates for men and women separately[20 22 24 26 28] and a summary estimate could not be calculated without risk of reporting bias.

Short-term Abstinence

Similar to the analysis of long-term abstinence effects, there was no evidence of an early treatment effect and with a slightly narrower confidence interval (RR 1.03; CI 0.88 to 1.22, Table 3). Three studies in addition to the eight trials in the main analysis were found that only reported short-term outcomes.[28-30] Inclusion of the 116 participants from these trials did not greatly alter the estimate (RR 1.09, CI 0.93 to 1.27).

Risk of Bias in Included Studies

Studies included in the meta-analysis were evaluated on their attempts to control bias in randomization, allocation, assessment, and analysis. None of the eight studies were judged at high risk for selection bias due to inadequate randomization or allocation concealment procedures, but three did not report methods in sufficient detail for the possibility of allocation bias to be discounted.[18 21 22] Two of these studies have only been reported as abstracts with limited methodological detail. All studies were described as double blind. The long-term cessation studies confirmed abstinence with biochemical verification, with two exceptions.[21 22] Five studies reported exhaled carbon monoxide (CO) verification,[19 20 24 25 30], and one study reported plasma cotinine concentration.[18] This study had high attrition in both groups and greater attrition earlier in the naltrexone group: ten people in the naltrexone group and two people in the placebo group were considered treatment failures because they dropped out prior to the target quit day.[18]

Withdrawal, Hedonic Effects, and Smoking Reduction

Overall, findings were mixed for effects of naltrexone, naloxone, and buprenorphine on measures of nicotine withdrawal, nicotine reward, and ad libitum smoking. Ten studies indicated no effect of naltrexone on withdrawal symptom scores.[18 20 23 25 30-36] Five studies reported reductions in withdrawal or smoking urge.[19 20 24 35 37] For one of the trials, the effect was found only at the 100mg dose compared to placebo and not at lower doses.[19] Additionally, three trials indicated diminished withdrawal symptoms following provocative smoking cues during sustained abstinence,[38-40] and one trial reported that naltrexone reduced ethanol's enhancing effect on smoking urge symptoms but naltrexone did not have a significant main effect on smoking urges.[41] For naloxone, two studies found no significant difference in withdrawal symptoms or mood states relative to placebo,[42 43] and another study showed an increased urge to smoke (craving) and tiredness at lower dosages of naloxone.[44]

Studies evaluating the reinforcing effects of smoking also were mixed. Two studies found no effect of naltrexone on self-reported satisfaction from smoking[31] or smoking reinforcement.[39 40 45] Other studies found significant reduction in self-reported satisfaction with smoking,[42 46] increased negative mood following smoking;[33] increased lightheadedness, dizziness, and head rush following a cigarette,[34] and significantly reduced post-cigarette craving.[34] For naloxone, two studies found no effect on the reinforcing properties of smoking cigarettes.[43 47]

Lastly, the results regarding ad libitum smoking were mixed. There were no significant effects of naltrexone on ad libitum smoking in three small trials.[31-33] However, six trials demonstrated statistically significant reductions in the number of cigarettes smoked ad libitum.[34 35 37 39 48 49] Five trials designed to evaluate abstinence and other outcomes during smoking cessation reported effects of naltrexone on daily or weekly smoking during and/or after treatment with naltrexone.[19 23-25 30] Three studies did not find any association between naltrexone and number of cigarettes smoked among continuing smokers,[21 22 25] another reported cigarettes per week increased more in the placebo group compared to the naltrexone group at the 100 mg dose of naltrexone,[19] and two studies reported

significantly lower weekly cigarettes smoked in the naltrexone (vs placebo) arms of the respective trials.[23 24] For naloxone, two studies reported significant reductions in number of cigarettes smoked relative to placebo[43 47] and one study did not find an effect over a wide range of dosages for any measure of cigarette smoking, including number of cigarettes, number of puffs, or expired air carbon monoxide.[50] With buprenorphine, two studies found an increase in cigarette consumption associated with buprenorphine.[51 52]

DISCUSSION

Eight double-blinded, randomized controlled trials of naltrexone with a total of 1213 adult smokers reported long-term abstinence data and 11 reported short-term outcomes. The point estimate for the risk ratio of the long-term effect of cessation pooling all studies, RR=0.97, suggests that naltrexone has no effect on abstinence. Further, there was no benefit of naltrexone relative to placebo for smoking cessation whether used alone or in combination with NRT. The 95% confidence interval of 0.76 to 1.24 indicates that the likelihood of any clinically important effect is very small. By comparison, the RR of long-term abstinence for NRT from 117 trials with over 50,000 participants was 1.60 (CI 1.53 to 1.68).[3] We also know that one industry-sponsored naltrexone trial remains unpublished, the likelihood being that it too did not detect evidence of benefit.[27] The results suggest that further research is only likely to make the confidence interval narrower around no effect. A secondary analysis of pooled short-term outcomes also showed no evidence of a treatment effect. Including three randomized clinical trials that only reported short-term effects, with a total of 116 participants, did not alter this conclusion.

While we were unable to meta-analyze sex-specific effects including data from all 8 trials, there was no compelling or consistent evidence of robust sex differences in efficacy for naltrexone. Although not an endpoint of this systematic review, two trials reported significant benefits of naltrexone for

reducing post-cessation weight gain,[18 20] while one did not.[24] A Cochrane review showed a modest benefit of naltrexone on reduced post-cessation weight gain at end of treatment (MD -0.78 kg, 95% CI -1.52, -0.05, N=2 trials), with insufficient data to assess the effects at 6 or 12-months. There were mixed results from individual trial as to whether opioid antagonists reduced nicotine withdrawal symptoms, the reinforcing effects of nicotine and tobacco, or cigarette consumption, but the heterogeneity of methods and reporting precluded use of meta-analytic techniques.

CONCLUSIONS

While it would seem biologically plausible that opioid antagonists may support smoking cessation vis-à-vis attenuation of positive reinforcement, the current evidence suggests that naltrexone provides no benefit for immediate or sustained smoking cessation. The neurobiology of nicotine addiction is complex and involves interactions between multiple neurotransmitter systems.[53] Unequivocal benefits have been reported for other classes of smoking cessation medications (i.e., nicotine replacement, bupropion, varenicline) with different mechanisms of action in large meta-analyses of scores of clinical trials.[3-5] However, based on data from eight trials and over 1200 individuals, there is no evidence of a therapeutic effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence rates. While further trials may narrow the confidence limits, they are unlikely to change the conclusion of lack of benefit.

COMPETING INTERESTS

All authors have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JJP has served on ad hoc scientific advisory and grant review boards for Pfizer and has a Pfizer funded investigator initiated research award. All other authors have no competing interests to declare.

CONTRIBUTIONS

All authors contributed to this work. SPD designed the study, implemented all methods, and guided interpretation of the results. SPD and IMC and participated in the drafting and editing of the paper at every stage. SPD, TL, AEE, and JJP posed the question, coordinated the research team and participated in all stages of the analysis and drafting of the manuscript. SPD, TL, LFS, and JJP assisted in study design and extraction of data and advised on the analysis methods.

COMPETING INTERESTS

None declared.

DATA SHARING

Unreported data from clinical trials that were either not published or for which results were not provided upon request to meta-analysis authors.

TABLES

Table 1. Characteristics of included studies.

Trial Description						Risk of Bias				
Trial	**Follow up time point for abstinence**	**Region**	**Treatment**	**Number of participants at baseline**	**Number participants at longest follow up**	**Biochemical validation**	**Random sequence generation**	**Allocation concealment**	**Incomplete outcome data**	**Blinding**
Baltieri et al. 2009[21]	12 weeks 6 months	Brazil	1) Naltrexone 50 mg/day for 12w 2) Placebo 3) Topiramate up to 300 mg/day (not used in this review)	65	28	No	Unclear	Low	Unclear	Low
Covey et al 1999[18]	4 weeks 6 months	USA	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	80	54	Yes	Unclear	Unclear	High	Low
King et al 2006[20]	8weeks 24 weeks	USA	1. Naltrexone 25 mg for 3 days then 50 mg for 2m, nicotine patch for 1m 2. Placebo & nicotine patch	110	89	Yes	Low	Low	Low	Low
King et al 2012[24]	12 weeks 6 months 12 months	USA	1. Naltrexone (50 mg/day) x 12 weeks plus Nicotine Patch (21 mg/day x 2 weeks, 14 mg/day x 1 week, 7 mg/day x 1 week) 2. Placebo x 12 weeks plus 12 weeks plus Nicotine Patch (same schedule)	315	238	Yes	Low	Low	Low	Low
Meszaros et al 2010[22]	12 weeks	USA	1. Naltrexone 3 times/week (100 mg Mon & Tue; 150 mg Fri) x 3 months 2. Placebo (same schedule)	79	Not given	No	Unclear	Unclear	Unclear	Unclear
O'Malley et al 2006[19]	12 months	USA	1. Naltrexone 100 mg 2. Naltrexone 50 mg 3. Naltrexone 25 mg	385	295	Yes	Low	Low	Low	Low

			4. Placebo All participants also received 21 mg NRT patch x 6 weeks, initial 45 min counseling session, weekly 15min counseling sessions for 6 weeks, plus self-help materials including dietary & exercise tips							
Toll et al 2010[26]	6 weeks 6 months	USA	1. Naltrexone (25 mg/day) x 27 weeks 2. Placebo x 27 weeks	172	58	Yes	Low	Low	Low	Low
Wong et al 1999[25]	12 weeks 6 months	USA	1. Naltrexone 50 mg/day for 12 weeks 2. Nicotine patch (21 mg 8 weeks/14 mg 4 weeks) + placebo pill 3. Naltrexone (50 mg/day) + nicotine patch (21/14) for 12 weeks 4. Placebo pill for 12 weeks. All groups received weekly counseling. No placebo patches used	100	69	Yes	Low	Low	Unclear	Unclear

Risk of bias assessments -- biochemical validation indicates cotinine or exhaled carbon monoxide verification of abstinence evident from publication or investigator correspondence ('yes'/'no'). Risk of reporting bias and risk of bias was assessed for lack of random sequence generation (selection bias), allocation concealment (selection bias), incompletely-reported outcome data (attrition bias) or lack of or incomplete blinding (performance bias and detection bias), ('high,/'low'/'unclear') respectively.

Table 2: Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), abstinence at longest follow up.

Study or Subgroup	Treatment # Abstinent	Treatment Total	Control # Abstinent	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Naltrexone vs placebo (no NRT)							
Baltieri et al. 2009[21]	3	27	2	38	1.6%	2.11 (0.38, 11.79)	
Covey et al 1999[18]	8	40	6	40	5.8%	1.33 (0.51, 3.49)	
Meszaros et al 2010[22]	3	38	3	41	2.8%	1.08 (0.23, 5.02)	
Toll et al 2010[26]	19	87	23	85	22.4%	0.81 (0.48, 1.37)	
Wong et al 1999[25]	2	23	2	26	1.8%	1.13 (0.17, 7.39)	
Subtotal (95% CI)		**215**		**230**	**34.3%**	**1.00 (0.66, 1.51)**	
Heterogeneity: Chi^2 = 1.72, df=4 (P=0.79); I^2= 0%							
Test for overall effect: Z= 0.02 (P = 0.98)							
Naltrexone vs placebo (with NRT)							
King et al 2006[20]	14	52	11	58	10.0%	1.42 (0.71, 2.85)	
King et al 2012[24]	27	161	35	154	34.4%	0.74 (0.47, 1.16)	
O'Malley et al 2006[19]	27	199	11	93	14.4%	1.15 (0.60, 2.21)	
Wong et al 1999[25]	7	26	7	25	6.9%	0.96 (0.39, 2.35)	
Subtotal (95% CI)		**438**		**330**	**65.7%**	**0.95 (0.70, 1.30)**	
Total events	75		64				
Heterogeneity: Chi^2 = 2.81, df=3 (P=0.42); I^2= 0%							
Test for overall effect: Z= 0.30 (P = 0.77)							
Subtotal (95% CI)		**653**		**560**	**100%**	**0.97 (0.76, 1.24)**	
Total events	110		100				
Heterogeneity: Chi^2 = 4.53, df=8 (P=0.81); I^2= 0%							
Test for overall effect: Z= 0.25 (P = 0.80)							
Test for subgroup differences: Chi^2 = 0.02, df=1 (P=0.88); I^2= 0%							

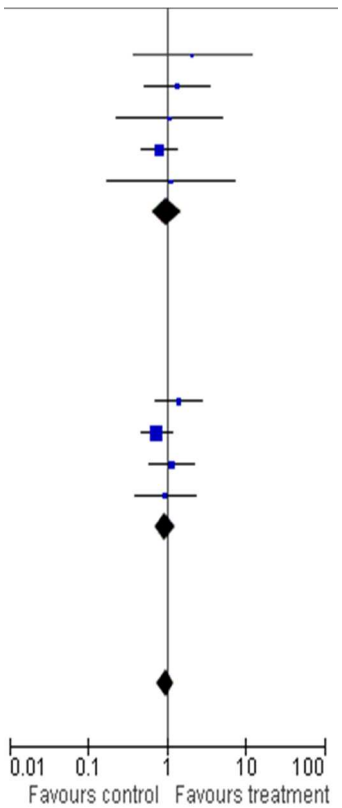
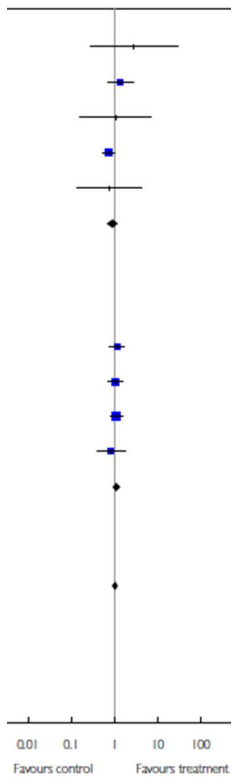


Table 3: Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), abstinence at end of treatment (short term outcomes).

Study or Subgroup	Treatment # Abstinent	Treatment Total	Control # Abstinent	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Naltrexone vs placebo (no NRT)							
Baltieri et al. 2009[21]	2	27	1	38	0.5%	2.81 (0.27, 29.49)	
Covey et al 1999[18]	14	40	10	40	5.7%	1.40 (0.71, 2.77)	
Meszaros et al 2010[22]	2	38	2	41	1.1%	1.08 (0.16, 7.28)	
Toll et al 2010[26]	33	87	43	85	24.7%	0.75 (0.53, 1.05)	
Wong et al 1999[25]	2	23	3	26	1.6%	0.75 (0.14, 4.12)	
Subtotal (95% CI)		**215**		**230**	**33.6%**	**0.90 (0.67, 1.21)**	
Heterogeneity: Chi^2 = 3.69, df=4 (P=0.45); I^2= 0%							
Test for overall effect: Z= 0.70 (P = 0.48)							
Naltrexone vs placebo (with NRT)							
King et al 2006[20]	25	52	24	58	12.9%	1.16 (0.77, 1.76)	
King et al 2012[24]	40	161	35	154	20.4%	1.09 (0.74, 1.62)	
O'Malley et al 2006[19]	87	199	36	93	27.9%	1.13 (0.84, 1.53)	
Wong et al 1999[25]	8	26	9	25	5.2%	0.85 (0.39, 1.86)	
Subtotal (95% CI)		**438**		**330**	**66.4%**	**1.10 (0.90, 1.35)**	
Total events	75		64				
Heterogeneity: Chi^2 = 0.50, df=3 (P=0.92); I^2= 0%							
Test for overall effect: Z= 0.95 (P = 0.34)							
Subtotal (95% CI)		**653**		**560**	**100%**	**1.03 (0.88, 1.22)**	
Total events	110		100				
Heterogeneity: Chi^2 = 5.94, df=8 (P=0.65); I^2= 0%							
Test for overall effect: Z= 0.40 (P = 0.69)							
Test for subgroup differences: Chi^2 = 1.25, df=1 (P=0.26); I^2= 20%							



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COMPETING INTERESTS

The Lead Author, Sean P David, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. Discrepancies from the study as planned have been explained.

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DATA SHARING STATEMENT

Unreported data from clinical trials that were either not published or for which results were not provided upon request to meta-analysis authors.

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CONTRIBUTORSHIP

All authors contributed to this work. SPD designed the study, implemented all methods, and guided interpretation of the results. SPD and IMC and participated in the drafting and editing of the paper at every stage. SPD, TL, AEE, and JJP posed the question, coordinated the research team and participated in all stages of the analysis and drafting of the manuscript. SPD, TL, LFS, and JJP assisted in study design and extraction of data and advised on the analysis methods.

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FIGURE LEGENDS

Figure 1: PRISMA diagram of literature search and data extraction

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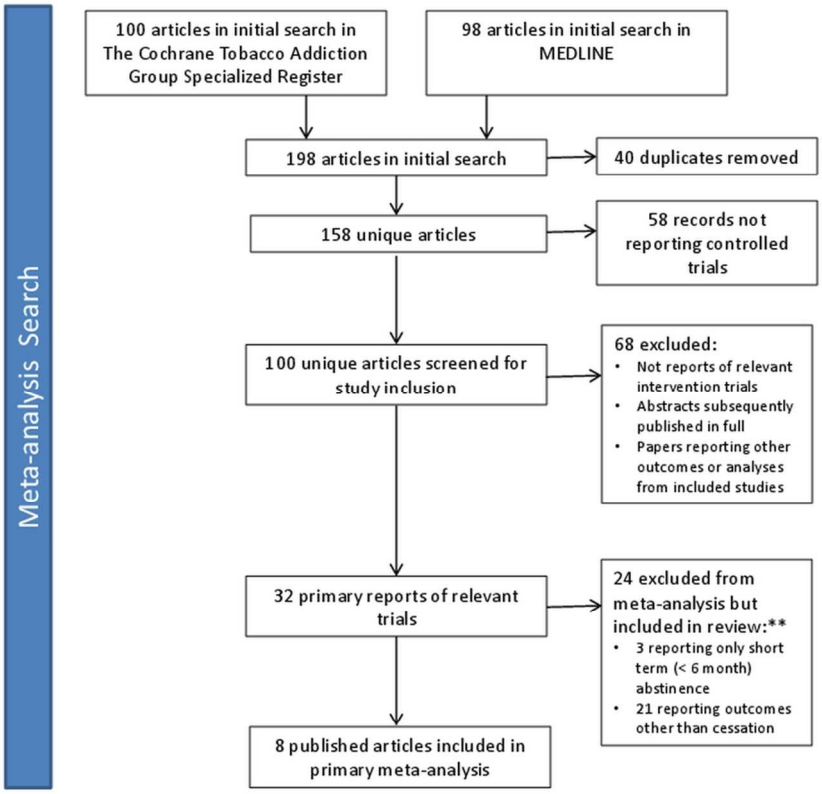

•Register holds reports of controlled trials on smoking cessation identified from searches of CENTRAL, MEDLINE, EMBASE and other sources including conference abstracts. See Specialized Register http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/frame.html

**24 studies excluded from meta-analyses were included in review for sensitivity analyses of short-term outcomes (k=3) and reporting outcomes other than abstinence.

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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Both. Cover sheet, abstract and page 4.
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2. Per BMJ instructions.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	This review was originally conducted using the Cochrane method.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5

PRISMA Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Pages 5-6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 5 and 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 7 and 9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1 is mentioned on page 6 and attached as a separate file.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Pages 6-8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Pages 7 and 9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Pages 5 and 7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Pages 8 and 9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 8 and 9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 9
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 10

PRISMA Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: www.prisma-statement.org.

Systematic Review and Meta-Analysis of Opioid Antagonists for Smoking Cessation

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ABSTRACT

Objectives: This meta-analysis sought to evaluate the efficacy of opioid antagonists in promoting long-term smoking cessation. Post-treatment abstinence was examined as a secondary outcome and effects on withdrawal symptoms, craving, and reduced consumption were also explored.

Design: The search strategy for this meta-analysis included clinical trials (published and unpublished data) in the Cochrane Tobacco Addiction Group Specialized Register and MEDLINE.

Participants: Adult smokers.

Interventions: We included randomized trials comparing opioid antagonists to placebo or an alternative therapy for smoking cessation and reported data on abstinence for a minimum of six months.

Primary and secondary outcome measures: Outcomes included smoking abstinence at long-term follow-up (primary); abstinence at end of treatment (secondary); and effects on withdrawal, craving, and smoking consumption (exploratory).

Results: Eight trials with a total of 1213 participants were included. Half the trials examined the benefit of adding naltrexone versus placebo to nicotine replacement therapy (NRT). There was no significant difference between naltrexone and placebo alone (relative risk (RR) 1.00; (95% CI) 0.66 to 1.51) or as an adjunct to NRT (RR 0.95; (CI) 0.70 to 1.30), with an overall pooled estimate of RR 0.97; CI: 0.76 to 1.24. Findings for naltrexone effects on withdrawal, craving, and reduced smoking were equivocal.

Conclusions: The findings indicate no beneficial effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence. While further trials may narrow the confidence limits, they are unlikely to appreciably alter the conclusion.

STRENGTHS AND LIMITATIONS OF THIS STUDY

The strengths of this study are:

• This meta-analysis compares opioid antagonists to placebo or an alternative therapy for smoking cessation and reports data on abstinence for a minimum of six months.

• The meta-analysis includes published and unpublished results from eight trials with a total of 1213 participants.

• The findings indicate no beneficial effect of naltrexone alone or as an adjunct to nicotine replacement therapy on short or long-term smoking abstinence, which suggests that further investment in clinical trials of naltrexone for this indication are unlikely to change the conclusion that this medication does not provide a clinically-significant benefit for helping smokers stop smoking.

The limitations of this study are:

• Inability to refute published claims of differential benefits of naltrexone for smoking cessation in subgroups defined by gender or secondary benefits on reduction of post-cessation weight gain.

BACKGROUND

Tobacco use is the leading preventable cause of death.[1] US clinical practice guidelines recommend the use of pharmacotherapy for quitting smoking.[2] Medications with demonstrable efficacy for cessation include nicotine replacement therapy (NRT) in the form of gum, patch, lozenge, inhaler, and nasal spray with pooled relative risk (RR) for any NRT of 1.60, 95% confidence interval (CI) 1.53 to 1.68;[3] bupropion with RR=1.69, CI 1.53 to 1.85;[4] and varenicline with RR=2.27, CI 2.02 to 2.55.[3 5] Effective second-line treatments include nortriptyline (RR 2.03; CI 1.48 to 2.78)[4] and clonidine (OR 1.89, CI 1.30 to 2.74).[6] Yet, long-term quit rates with these pharmacotherapies are relatively modest, in the range of 19.0% to 36.5%.[2] With relapse as the norm, there is continued interest in medication development and discovery of pharmacological agents for assisting tobacco cessation.

~~The reinforcing properties of nicotine are mediated through several neurotransmitters. Exposure to nicotine stimulates central nicotinic cholinergic receptors, which enhances synaptic release of dopamine, norepinephrine, acetylcholine, vasopressin, serotonin, glutamate, gamma-amino butyric acid (GABA), and beta-endorphin.[7] Rodent studies indicate that nicotine-induced beta-endorphin release in the brain is anxiolytic[8-10] and may reduce anxiety and tension.[11] Nicotine also evokes neuroregulatory effects when binding to nicotinic cholinergic receptors in the adrenal medulla, resulting in the release of epinephrine (adrenaline) and beta-endorphin, which may contribute to the systemic effects of nicotine.[12] Furthermore, acute and chronic exposure to nicotine alters the synthesis and release of beta-endorphin, met-enkephalin and dynorphin in the nucleus accumbens and other brain regions implicated in nicotine reinforcement (mu-opioid receptors) and aversive effects of nicotine including physical manifestations of nicotine withdrawal (delta- and kappa-opioid receptors).~~

Naltrexone (Narpan, Revia, Vivitrol, with half-life of 240 min[7]), a long-acting opioid antagonist, is a marketed drug that blunts the effects of narcotics such as heroin, meperidine, morphine and oxycodone and is effective in the treatment of alcohol dependence.[8 9] Naltrexone occupies μ-opioid

receptors, which putatively diminishes the activation of mesolimbic dopamine and therefore may reduce craving for nicotine. With different mechanisms of action, it has been postulated that NRT and naltrexone could produce additive effects for treating nicotine withdrawal and preventing relapse. Since opioid antagonists are known to precipitate nicotine withdrawal in nicotine dependent animals,[10-13] administering NRT in conjunction may attenuate any increased withdrawal, dysphoria, and sedation caused by naloxone and naltrexone. Naloxone (Narcan, with half-life 30-100 min[14]) is a short-acting opioid antagonist routinely administered to reverse the acute effects of narcotic overdose. Naloxone has been shown to block the reinforcing properties of nicotine and precipitate physical and affective symptoms of nicotine withdrawal in rodent studies.[10-13] Buprenorphine (Buprenex, Subutex, Suboxone [combination buprenorphine/naltrexone], Butrans, with half-life 24-60 hrs)[15] is a mixed agonist-antagonist used for the treatment of opioid dependence. Although less widely studied for this indication, naloxone and buprenorphine have also been evaluated as potential smoking cessation aids and are included in this review.

Concerns regarding potential adverse effects have led to US Food and Drug Administration black box warnings for the cessation medications bupropion and varenicline. With respect to the adverse event profile of opioid antagonists when used in the treatment of opioid dependence, serious adverse effects are uncommon but there is an FDA black box warning regarding potential hepatotoxicity for naltrexone. Nervous system side effects reported in >10% of patients during treatment for opioid dependence have included headaches, nervousness, anxiety, difficulty sleeping, and low energy; those reported in <10% of patients include loss of appetite, increased energy, irritability, and dizziness. Asthenia, agitation, hyperkinesia, nervousness, fatigue, restlessness, confusion, disorientation, and somnolence have been reported rarely. Side effects of buprenorphine are similar to those of other opioids and include nausea, vomiting, and constipation.

While opioid antagonists are typically used in the treatment of opioid dependence, the primary

objective of this systematic review and meta-analysis was to evaluate the long-term efficacy of opioid antagonists (i.e., naltrexone, naloxone, buprenorphine), alone or in combination with NRT, in promoting smoking cessation. The secondary objective was to evaluate the short-term (post-treatment) abstinence effects. Specific opioid antagonists were considered separately rather than grouping the medications as a class. We tested the hypotheses that opioid antagonists: (1) are more effective than placebo in promoting early and sustained abstinence from smoking and (2) when used in combination with NRT are more effective than NRT alone in promoting early and sustained abstinence from smoking. We also summarize the literature on the effects of opioid antagonists in treating withdrawal symptoms, attenuating the reinforcing value of smoking, and reducing ad libitum smoking. The results of this systematic review and meta-analyses have been published in a recent Cochrane Review.[16]

METHODS

Search Strategy and Study Selection

We included randomized controlled trials of opioid antagonists with adult smokers that reported smoking status at least six months after intervention to assess the efficacy for long-term cessation. For the secondary outcome, we also considered randomized controlled trials of opioid antagonists reporting abstinence at end-of treatment or that reported the outcomes of nicotine withdrawal, reinforcing properties of smoking, or ad libitum smoking. The medications evaluated were naltrexone, naloxone, buprenorphine or other opioid antagonists, with or without concurrent use of NRT.

To identify eligible studies, we searched the Tobacco Addiction group Specialized Register in April 2013 using the terms 'naloxone' or 'naltrexone' or 'buprenorphine' or 'opioid antagonist' or 'opiate antagonist' or 'narcotic antagonist' in the title or abstract, or as keywords. At the time of the

search, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 3, 2013; MEDLINE (via OVID) through March 29, 2013; EMBASE (via OVID) through March 16, 2013 and PsycINFO (via OVID) through April 1, 2013. An additional search of MEDLINE (via OVID through April 17, 2013) used the terms (explode "Narcotic-Antagonists"/ all subheadings) AND ("Smoking-Cessation"/all subheadings OR "Tobacco-Use-Disorder"/all subheadings OR "Smoking"/all subheadings). Two authors cross-checked the studies to insure they met the inclusion criteria. Discrepancies were resolved by mutual consent including a third author, as required. We noted reasons for the non-inclusion of studies. Details of the search are in the PRISMA Diagram (Figure 1).

Data Extraction

Data extraction included: basic study characteristics (sample size, design, blinding, method of randomization, location), sample characteristics (cigarettes/day, intention to quit), tobacco measures and outcomes, reported averse effects, and attrition. The primary outcome measure of interest was abstinence at six months or longer, with preference given to the longest follow-up available. Abstinence at end of treatment was a secondary outcome. We used a sustained cessation rate in preference to point prevalence, and biochemical verification of self-reported quitting where reported (e.g., carbon monoxide, cotinine). Other outcome measures of interest included withdrawal, reinforcing or hedonic effects of smoking, mood states, and ad libitum smoking.

Data Analysis

For the abstinence outcomes, we calculated relative risks of abstinence at longest follow-up using as the denominators the numbers of patients randomized to each arm excluding any deaths and treating those who dropped out or were lost to follow up 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. Separately, we combined the results of studies evaluating short- and long-term cessation using the Mantel-Haenszel fixed-effect model for pooling risk ratios. Effect sizes were calculated for all trials

together and by whether or not NRT was used. In a sensitivity analysis, we estimated the effect at end of treatment of adding in the results from studies excluded due to lack of long-term follow-up. For assessment of risk of bias, we evaluated studies on the basis of random sequence generation (selection bias), allocation concealment (selection bias), blinding (performance bias and detection bias), and incomplete outcome data (attrition bias).[17] None of the trials of buprenorphine or naloxone were eligible for inclusion in meta-analyses of abstinence because of lack of sufficient follow-up or available abstinence outcomes. Therefore, we report abstinence results only for naltrexone. Procedures varied and few studies reported on measures of withdrawal, craving, and smoking reduction for buprenorphine, naloxone and naltresone; hence, these outcomes were narratively summarized. Characteristics of all included and excluded studies are published in the Cochrane Review.[16]

FINDINGS

Long-term Abstinence

We identified eight trials evaluating naltrexone and reporting long-term abstinence rates with a total of 1213 participants (Table 1).[18-26] Three studies examined naltrexone monotherapy relative to placebo; four studies examined naltrexone as an adjunct to NRT or placebo; and one study had 4 arms, which allowed for examination of naltrexone alone versus as an adjunct to NRT with matched placebo conditions for both arms.[25] There was no evidence of heterogeneity in subgroups with or without NRT. Naltrexone dose ranged from 25 mg to 150 mg daily. Five trials provided cessation counseling with the medication of either brief (15 to 20 min)[19 25] or more extended duration.[18 20 24] Four studies biochemically confirmed nonsmoking status.[19 20 23 24] Abstinence data were unpublished for two of the studies and obtained directly from the authors.[21 22] For one of the studies, part of a multi-center trial with 350 subjects enrolled at five centers in the US, the authors only published the results from the Mayo Clinic site, which enrolled 100 people but would not provide unpublished data for the other

study sites upon repeated requests.[27] Despite our attempts to obtain unpublished data for the other 250 participants, the funder DuPont, has not disclosed further results.[16] In one study,[19] there were three different treatment arms of 25 mg, 50 mg, and 100 mg naltrexone. The 50 mg and 100 mg groups were combined and included in the meta-analysis, however, we conducted a sensitivity analysis and including the 25 mg arm did not significantly change the results – as previously reported.[16]

The pooled estimate for the 8 trials gave no evidence of a treatment effect (RR 0.97; CI 0.76 to 1.24; Table 2). For the five studies that examined naltrexone alone versus placebo (n=450), the pooled estimate was RR = 1.00, CI 0.66 to 1.51 (Table 2),[18 21-23 25] and the estimate was not sensitive to exclusion of the two studies with unpublished data lacking biochemical validation of abstinence.[21 22] For the four studies that examined naltrexone versus placebo as an adjunct to NRT (n=768), the pooled estimate was RR = 0.95; CI 0.70 to 1.30.[19 20 24 25]

Three trials raised the possibility that there could be a difference in effect by sex, with women showing more evidence of a benefit than men for smoking cessation in two trials[18 20] and showing less of a benefit in a third.[24] In one trial, naltrexone showed a greater effect in preventing weight gain for women than men.[24] The other five abstinence studies did not report quit rates for men and women separately[20 22 24 26 28] and a summary estimate could not be calculated without risk of reporting bias.

Short-term Abstinence

Similar to the analysis of long-term abstinence effects, there was no evidence of an early treatment effect and with a slightly narrower confidence interval (RR 1.03; CI 0.88 to 1.22, Table 3). Three studies in addition to the eight trials in the main analysis were found that only reported short-term outcomes.[28-30] Inclusion of the 116 participants from these trials did not greatly alter the estimate (RR 1.09, CI 0.93 to 1.27).

Risk of Bias in Included Studies

Studies included in the meta-analysis were evaluated on their attempts to control bias in

randomization, allocation, assessment, and analysis. None of the eight studies were judged at high risk for selection bias due to inadequate randomization or allocation concealment procedures, but three did not report methods in sufficient detail for the possibility of allocation bias to be discounted.[18 21 22] Two of these studies have only been reported as abstracts with limited methodological detail. All studies were described as double blind. The long-term cessation studies confirmed abstinence with biochemical verification, with two exceptions.[21 22] Five studies reported exhaled carbon monoxide (CO) verification,[19 20 24 25 30], and one study reported plasma cotinine concentration.[18] This study had high attrition in both groups and greater attrition earlier in the naltrexone group: ten people in the naltrexone group and two people in the placebo group were considered treatment failures because they dropped out prior to the target quit day.[18]

Withdrawal, Hedonic Effects, and Smoking Reduction

Overall, findings were mixed for effects of naltrexone, naloxone, and buprenorphine on measures of nicotine withdrawal, nicotine reward, and ad libitum smoking. Ten studies indicated no effect of naltrexone on withdrawal symptom scores.[18 20 23 25 30-36] Five studies reported reductions in withdrawal or smoking urge.[19 20 24 35 37] For one of the trials, the effect was found only at the 100mg dose compared to placebo and not at lower doses.[19] Additionally, three trials indicated diminished withdrawal symptoms following provocative smoking cues during sustained abstinence,[38-40] and one trial reported that naltrexone reduced ethanol's enhancing effect on smoking urge symptoms but naltrexone did not have a significant main effect on smoking urges.[41] For naloxone, two studies found no significant difference in withdrawal symptoms or mood states relative to placebo,[42 43] and another study showed an increased urge to smoke (craving) and tiredness at lower dosages of naloxone.[44]

Studies evaluating the reinforcing effects of smoking also were mixed. Two studies found no effect of naltrexone on self-reported satisfaction from smoking[31] or smoking reinforcement.[39 40 45] Other studies found significant reduction in self-reported satisfaction with smoking,[42 46] increased

negative mood following smoking;[33] increased lightheadedness, dizziness, and head rush following a cigarette,[34] and significantly reduced post-cigarette craving.[34] For naloxone, two studies found no effect on the reinforcing properties of smoking cigarettes.[43 47]

Lastly, the results regarding ad libitum smoking were mixed. There were no significant effects of naltrexone on ad libitum smoking in three small trials.[31-33] However, six trials demonstrated statistically significant reductions in the number of cigarettes smoked ad libitum.[34 35 37 39 48 49] Five trials designed to evaluate abstinence and other outcomes during smoking cessation reported effects of naltrexone on daily or weekly smoking during and/or after treatment with naltrexone.[19 23-25 30] Three studies did not find any association between naltrexone and number of cigarettes smoked among continuing smokers,[21 22 25] another reported cigarettes per week increased more in the placebo group compared to the naltrexone group at the 100 mg dose of naltrexone,[19] and two studies reported significantly lower weekly cigarettes smoked in the naltrexone (vs placebo) arms of the respective trials.[23 24] For naloxone, two studies reported significant reductions in number of cigarettes smoked relative to placebo[43 47] and one study did not find an effect over a wide range of dosages for any measure of cigarette smoking, including number of cigarettes, number of puffs, or expired air carbon monoxide.[50] With buprenorphine, two studies found an increase in cigarette consumption associated with buprenorphine.[51 52]

DISCUSSION

Eight double-blinded, randomized controlled trials of naltrexone with a total of 1213 adult smokers reported long-term abstinence data and 11 reported short-term outcomes. The point estimate for the risk ratio of the long-term effect of cessation pooling all studies, RR=0.97, suggests that naltrexone has no effect on abstinence. Further, there was no benefit of naltrexone relative to placebo for smoking cessation whether used alone or in combination with NRT. The 95% confidence interval of

0.76 to 1.24 indicates that the likelihood of any clinically important effect is very small. By comparison, the RR of long-term abstinence for NRT from 117 trials with over 50,000 participants was 1.60 (CI 1.53 to 1.68).[3] We also know that one industry-sponsored naltrexone trial remains unpublished, the likelihood being that it too did not detect evidence of benefit.[27] The results suggest that further research is only likely to make the confidence interval narrower around no effect. A secondary analysis of pooled short-term outcomes also showed no evidence of a treatment effect. Including three randomized clinical trials that only reported short-term effects, with a total of 116 participants, did not alter this conclusion.

While we were unable to meta-analyze sex-specific effects including data from all 8 trials, there was no compelling or consistent evidence of robust sex differences in efficacy for naltrexone. Although not an endpoint of this systematic review, two trials reported significant benefits of naltrexone for reducing post-cessation weight gain,[18 20] while one did not.[24] A Cochrane review showed a modest benefit of naltrexone on reduced post-cessation weight gain at end of treatment (MD -0.78 kg, 95% CI -1.52, -0.05, N=2 trials), with insufficient data to assess the effects at 6 or 12-months. There were mixed results from individual trial as to whether opioid antagonists reduced nicotine withdrawal symptoms, the reinforcing effects of nicotine and tobacco, or cigarette consumption, but the heterogeneity of methods and reporting precluded use of meta-analytic techniques.

CONCLUSIONS

While it would seem biologically plausible that opioid antagonists may support smoking cessation vis-à-vis attenuation of positive reinforcement, the current evidence suggests that naltrexone provides no benefit for immediate or sustained smoking cessation. The neurobiology of nicotine addiction is complex and involves interactions between multiple neurotransmitter systems.[53] Unequivocal benefits have been reported for other classes of smoking cessation medications (i.e.,

nicotine replacement, bupropion, varenicline) with different mechanisms of action in large meta-analyses of scores of clinical trials.[3-5] However, based on data from eight trials and over 1200 individuals, there is no evidence of a therapeutic effect of naltrexone alone or as an adjunct to NRT on short or long-term smoking abstinence rates. While further trials may narrow the confidence limits, they are unlikely to change the conclusion of lack of benefit.

COMPETING INTERESTS

All authors have read and understood the BMJ Group policy on declaration of interests and declare the following interests: JJP has served on ad hoc scientific advisory and grant review boards for Pfizer and has a Pfizer funded investigator initiated research award. All other authors have no competing interests to declare.

CONTRIBUTIONS

All authors contributed to this work. SPD designed the study, implemented all methods, and guided interpretation of the results. SPD and IMC and participated in the drafting and editing of the paper at every stage. SPD, TL, AEE, and JJP posed the question, coordinated the research team and participated in all stages of the analysis and drafting of the manuscript. SPD, TL, LFS, and JJP assisted in study design and extraction of data and advised on the analysis methods.

COMPETING INTERESTS

None declared.

TABLES

Table 1. Characteristics of included studies.

Trial Description						Risk of Bias				
Trial	**Follow up time point for abstinence**	**Region**	**Treatment**	**Number of participants at baseline**	**Number participants at longest follow up**	**Biochemical validation**	**Random sequence generation**	**Allocation concealment**	**Incomplete outcome data**	**Blinding**
Baltieri et al. 2009[21]	12 weeks 6 months	Brazil	1) Naltrexone 50 mg/day for 12w 2) Placebo 3) Topiramate up to 300 mg/day (not used in this review)	65	28	No	Unclear	Low	Unclear	Low
Covey et al 1999[18]	4 weeks 6 months	USA	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	80	54	Yes	Unclear	Unclear	High	Low
King et al 2006[20]	8weeks 24 weeks	USA	1. Naltrexone 25 mg for 3 days then 50 mg for 2m, nicotine patch for 1m 2. Placebo & nicotine patch	110	89	Yes	Low	Low	Low	Low
King et al 2012[24]	12 weeks 6 months 12 months	USA	1. Naltrexone (50 mg/day) x 12 weeks plus Nicotine Patch (21 mg/day x 2 weeks, 14 mg/day x 1 week, 7 mg/day x 1 week) 2. Placebo x 12 weeks plus 12 weeks plus Nicotine Patch (same schedule)	315	238	Yes	Low	Low	Low	Low
Meszaros et al 2010[22]	12 weeks	USA	1. Naltrexone 3 times/week (100 mg Mon & Tue; 150 mg Fri) x 3 months 2. Placebo (same schedule)	79	Not given	No	Unclear	Unclear	Unclear	Unclear
O'Malley et al 2006[19]	12 months	USA	1. Naltrexone 100 mg 2. Naltrexone 50 mg 3. Naltrexone 25 mg	385	295	Yes	Low	Low	Low	Low

			4. Placebo All participants also received 21 mg NRT patch x 6 weeks, initial 45 min counseling session, weekly 15min counseling sessions for 6 weeks, plus self-help materials including dietary & exercise tips							
Toll et al 2010[26]	6 weeks 6 months	USA	1. Naltrexone (25 mg/day) x 27 weeks 2. Placebo x 27 weeks	172	58	Yes	Low	Low	Low	Low
Wong et al 1999[25]	12 weeks 6 months	USA	1. Naltrexone 50 mg/day for 12 weeks 2. Nicotine patch (21 mg 8 weeks/14 mg 4 weeks) + placebo pill 3. Naltrexone (50 mg/day) + nicotine patch (21/14) for 12 weeks 4. Placebo pill for 12 weeks. All groups received weekly counseling. No placebo patches used	100	69	Yes	Low	Low	Unclear	Unclear

Risk of bias assessments -- biochemical validation indicates cotinine or exhaled carbon monoxide verification of abstinence evident from publication or investigator correspondence ('yes'/'no'). Risk of reporting bias and risk of bias was assessed for lack of random sequence generation (selection bias), allocation concealment (selection bias), incompletely-reported outcome data (attrition bias) or lack of or incomplete blinding (performance bias and detection bias), ('high,/'low'/'unclear') respectively.

Table 2: Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), abstinence at longest follow up.

Study or Subgroup	Treatment # Abstinent	Treatment Total	Control # Abstinent	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Naltrexone vs placebo (no NRT)						
Baltieri et al. 2009[21]	3	27	2	38	1.6%	2.11 (0.38, 11.79)
Covey et al 1999[18]	8	40	6	40	5.8%	1.33 (0.51, 3.49)
Meszaros et al 2010[22]	3	38	3	41	2.8%	1.08 (0.23, 5.02)
Toll et al 2010[26]	19	87	23	85	22.4%	0.81 (0.48, 1.37)
Wong et al 1999[25]	2	23	2	26	1.8%	1.13 (0.17, 7.39)
Subtotal (95% CI)		**215**		**230**	**34.3%**	**1.00 (0.66, 1.51)**
Heterogeneity: Chi^2 = 1.72, df=4 (P=0.79); I^2= 0%						
Test for overall effect: Z= 0.02 (P = 0.98)						
Naltrexone vs placebo (with NRT)						
King et al 2006[20]	14	52	11	58	10.0%	1.42 (0.71, 2.85)
King et al 2012[24]	27	161	35	154	34.4%	0.74 (0.47, 1.16)
O'Malley et al 2006[19]	27	199	11	93	14.4%	1.15 (0.60, 2.21)
Wong et al 1999[25]	7	26	7	25	6.9%	0.96 (0.39, 2.35)
Subtotal (95% CI)		**438**		**330**	**65.7%**	**0.95 (0.70, 1.30)**
Total events	75		64			
Heterogeneity: Chi^2 = 2.81, df=3 (P=0.42); I^2= 0%						
Test for overall effect: Z= 0.30 (P = 0.77)						
Subtotal (95% CI)		**653**		**560**	**100%**	**0.97 (0.76, 1.24)**
Total events	110		100			
Heterogeneity: Chi^2 = 4.53, df=8 (P=0.81); I^2= 0%						
Test for overall effect: Z= 0.25 (P = 0.80)						
Test for subgroup differences: Chi^2 = 0.02, df=1 (P=0.88); I^2= 0%						

Risk Ratio M-H, Fixed, 95% CI

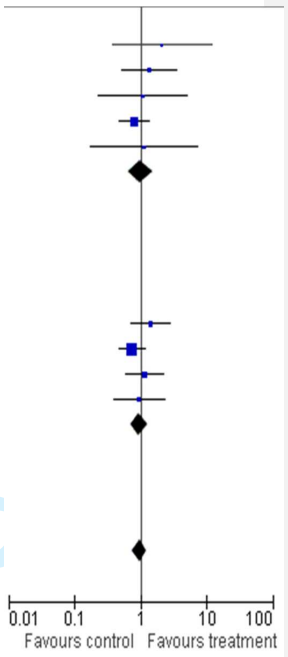

Table 3: Naltrexone versus placebo (single pharmacotherapy or adjunct to NRT), abstinence at end of treatment (short term outcomes).

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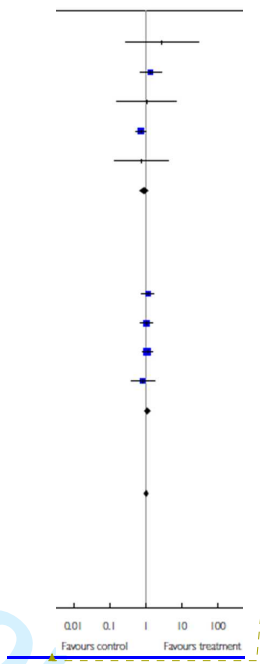
Study or Subgroup	Treatment # Abstinent	Treatment Total	Control # Abstinent	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Naltrexone vs placebo (no NRT)							
Baltieri et al. 2009[21]	2	27	1	38	0.5%	2.81 (0.27, 29.49)	
Covey et al 1999[18]	14	40	10	40	5.7%	1.40 (0.71, 2.77)	
Meszaros et al 2010[22]	2	38	2	41	1.1%	1.08 (0.16, 7.28)	
Toll et al 2010[26]	33	87	43	85	24.7%	0.75 (0.53, 1.05)	
Wong et al 1999[25]	2	23	3	26	1.6%	0.75 (0.14, 4.12)	
Subtotal (95% CI)		**215**		**230**	**33.6%**	**0.90 (0.67, 1.21)**	
Heterogeneity: Chi^2 = 3.69, df=4 (P=0.45); I^2= 0%							
Test for overall effect: Z= 0.70 (P = 0.48)							
Naltrexone vs placebo (with NRT)							
King et al 2006[20]	25	52	24	58	12.9%	1.16 (0.77, 1.76)	
King et al 2012[24]	40	161	35	154	20.4%	1.09 (0.74, 1.62)	
O'Malley et al 2006[19]	87	199	36	93	27.9%	1.13 (0.84, 1.53)	
Wong et al 1999[25]	8	26	9	25	5.2%	0.85 (0.39, 1.86)	
Subtotal (95% CI)		**438**		**330**	**66.4%**	**1.10 (0.90, 1.35)**	
Total events	75		64				
Heterogeneity: Chi^2 = 0.50, df=3 (P=0.92); I^2= 0%							
Test for overall effect: Z= 0.95 (P = 0.34)							
Subtotal (95% CI)		**653**		**560**	**100%**	**1.03 (0.88, 1.22)**	
Total events	110		100				
Heterogeneity: Chi^2 = 5.94, df=8 (P=0.65); I^2= 0%							
Test for overall effect: Z= 0.40 (P = 0.69)							
Test for subgroup differences: Chi^2 = 1.25, df=1 (P=0.26); I^2= 20%							



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COMPETING INTERESTS

The Lead Author, Sean P David, affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted. Discrepancies from the study as planned have been explained.

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DATA SHARING STATEMENT

Unreported data from clinical trials that were either not published or for which results were not provided upon request to meta-analysis authors.

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FIGURE LEGENDS

Figure 1: PRISMA diagram of literature search and data extraction