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Nicotine replacement therapy for smoking cessation (Review)

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T



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Nicotine replacement therapy for smoking cessation

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ABSTRACT

Background

The aim of nicotine replacement therapy (NRT) is to temporarily replace much of the nicotine from cigarettes to reduce motivation to smoke and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence.

Objectives

The aims of this review were:

To determine the effect of NRT compared to placebo in aiding smoking cessation, and to consider whether there is a difference in effect for the different forms of NRT (chewing gum, transdermal patches, oral and nasal sprays, inhalers and tablets/lozenges) in achieving abstinence from cigarettes.

To determine whether the effect is influenced by the dosage, form and timing of use of NRT; the intensity of additional advice and support offered to the smoker; or the clinical setting in which the smoker is recruited and treated.

To determine whether combinations of NRT are more likely to lead to successful quitting than one type alone.

To determine whether NRT is more or less likely to lead to successful quitting compared to other pharmacotherapies.

Search methods

We searched the Cochrane Tobacco Addiction Group trials register for papers mentioning 'NRT' or any type of nicotine replacement therapy in the title, abstract or keywords. Date of most recent search July 2012.

Selection criteria

Randomized trials in which NRT was compared to placebo or to no treatment, or where different doses of NRT were compared. We excluded trials which did not report cessation rates, and those with follow-up of less than six months.

Data collection and analysis

We extracted data in duplicate on the type of participants, the dose, duration and form of nicotine therapy, the outcome measures, method of randomization, and completeness of follow-up.

The main outcome measure was abstinence from smoking after at least six months of follow-up. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. We calculated the risk ratio (RR) for each study. Where appropriate, we performed meta-analysis using a Mantel-Haenszel fixed-effect model.

Main results

We identified 150 trials; 117 with over 50,000 participants contributed to the primary comparison between any type of NRT and a placebo or non-NRT control group. The risk ratio (RR) of abstinence for any form of NRT relative to control was 1.60 (95% confidence interval [CI] 1.53 to 1.68). The pooled RRs for each type were 1.49 (95% CI 1.40 to 1.60, 55 trials) for nicotine gum; 1.64 (95% CI 1.52 to 1.78, 43 trials) for nicotine patch; 1.95 (95% CI 1.61 to 2.36, 6 trials) for oral tablets/lozenges; 1.90 (95% CI 1.36 to 2.67, 4 trials) for nicotine inhaler; and 2.02 (95% CI 1.49 to 2.73, 4 trials) for nicotine nasal spray. One trial of oral spray had an RR of 2.48 (95% CI 1.24 to 4.94). The effects were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. The effect was similar in a small group of studies that aimed to assess use of NRT obtained without a prescription. In highly dependent smokers there was a significant benefit of 4 mg gum compared with 2 mg gum, but weaker evidence of a benefit from higher doses of patch. There was evidence that combining a nicotine patch with a rapid delivery form of NRT was more effective than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51, 9 trials). The RR for NRT used for a short period prior to the quit date was 1.18 (95% CI 0.98 to 1.40, 8 trials), just missing statistical significance, though the efficacy increased when we pooled only patch trials and when we removed one trial in which confounding was likely. Five studies directly compared NRT to a non-nicotine pharmacotherapy, bupropion; there was no evidence of a difference in efficacy (RR 1.01; 95% CI 0.87 to 1.18). A combination of NRT and bupropion was more effective than bupropion alone (RR 1.24; 95% CI 1.06 to 1.45, 4 trials). Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. There is no evidence that NRT increases the risk of heart attacks.

Authors' conclusions

All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50 to 70%, regardless of setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.

PLAIN LANGUAGE SUMMARY

Can nicotine replacement therapy (NRT) help people quit smoking?

NRT aims to reduce withdrawal symptoms associated with stopping smoking by replacing the nicotine from cigarettes. NRT is available as skin patches that deliver nicotine slowly, and chewing gum, nasal and oral sprays, inhalers, and lozenges/tablets, all of which deliver nicotine to the brain more quickly than from skin patches, but less rapidly than from smoking cigarettes. This review includes 150 trials of NRT, with over 50,000 people in the main analysis. We found evidence that all forms of NRT made it more likely that a person's attempt to quit smoking would succeed. The chances of stopping smoking were increased by 50 to 70%. The evidence suggests no overall difference in effectiveness between different forms of NRT, nor a benefit for using patches beyond eight weeks. NRT works with or without additional counselling, and does not need to be prescribed by a doctor. Heavier smokers may need higher doses of NRT. People who use NRT during a quit attempt are likely to further increase their chance of success by using a combination of the nicotine patch and a faster acting form or by combining the patch with the antidepressant bupropion. Data suggest that starting to use NRT patches shortly before the planned quit date may increase the chance of success. Adverse effects from using NRT are related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. There is no evidence that NRT increases the risk of heart attacks.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Nicotine replacement therapy						
Patient or population: people who smoke cigarettes Settings: clinical and non-clinical, including over the counter Intervention: nicotine replacement therapy of any form						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Nicotine replacement therapy of any form				
Smoking cessation at 6+ months follow-up Follow-up: 6 - 24 months	Study population		RR 1.6 (1.53 to 1.68)	51265 (117 studies)	⊕⊕⊕⊕ high ^{1,2}	
	100 per 1000	161 per 1000 (154 to 169)				
	Limited behavioural support					
	40 per 1000	64 per 1000 (61 to 67)				
	Intensive behavioural support					
	150 per 1000	240 per 1000 (229 to 252)				
<p>*The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).</p> <p>CI: Confidence interval; RR: Risk ratio;</p>						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Most studies judged to be at low or unclear risk of bias, and given the large number of studies it is unlikely that limitations would affect overall confidence in the effect.

² There are likely to be some unpublished trials with less favourable results that we were unable to identify, and a funnel plot showed some evidence of asymmetry. However, given the large number of trials in the review, this does not suggest the results would be altered significantly were smaller studies with lower RRs included.

BACKGROUND

Nicotine replacement therapy (NRT) aims to reduce motivation to smoke and the physiological and psychomotor withdrawal symptoms often experienced during an attempt to stop smoking, and therefore increase the likelihood of remaining abstinent (West 2001). Nicotine undergoes first pass metabolism in the liver, reducing the overall bioavailability of swallowed nicotine pills. A pill that could reliably produce high enough nicotine levels in the central nervous system would risk causing adverse gastrointestinal effects. To avoid this problem, nicotine replacement products are formulated for absorption through the oral or nasal mucosa (chewing gum, lozenges, sublingual tablets, inhaler/inhalator, spray) or through the skin (transdermal patches). Other products are also under development (Park 2002; D'Orlando 2004; Ikinici 2006; Bolliger 2007; McRobbie 2010).

Nicotine patches differ from the other products in that they deliver the nicotine dose slowly and passively. They do not replace any of the behavioural activities of smoking. In contrast the other types of NRT are faster acting, but require more effort on the part of the user. Transdermal patches are available in several different doses, and deliver between 5 mg and 52.5 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers (Fiore 1992). Some brands of patch are designed to be worn for 24 hours whilst others are to be worn for 16 hours each day. Nicotine gum is available in both 2 mg and 4 mg strengths, and nicotine lozenges are available in 1 mg, 1.5 mg, 2 mg and 4 mg strengths, though the amount of nicotine absorbed by the user is less than the original dose. None of the available products deliver such high doses of nicotine as quickly as cigarettes. An average cigarette delivers between 1 and 3 mg of nicotine and the typical pack-per-day smoker absorbs 20 to 40 mg of nicotine each day (Henningfield 2005).

The availability of NRT products on prescription or for over-the-counter purchase varies from country to country. Table 1 summarises the products currently licensed in the United Kingdom.

In earlier versions, this review focused on the effect of nicotine replacement therapy in comparison to placebo for helping people stop smoking. The evidence that NRT helps some people to stop smoking is now well accepted, and many clinical guidelines recommend NRT as a first line treatment for people seeking pharmacological help to stop smoking (West 2000; NZ MoH 2007; Woolacott 2002; Italy ISS 2004; Le Foll 2005; Fiore 2008; Zwar 2011). This review still provides an estimate of the expected effect of using NRT, using meta-analysis. We also address questions about when and how to use NRT most effectively. This includes consideration of the effect of the type of NRT used, including the use of combinations of different types of NRT, the effect of the setting in which it is used (including purchasing over the counter versus prescription use), the effect of dosing according to characteristics of the individual quitter and whether the effect of NRT

is altered by different levels of behavioural support. NRT is now one of several forms of pharmacotherapy available to support quit attempts, including some antidepressants and the nicotine receptor partial agonist varenicline. These pharmacotherapies are evaluated in separate Cochrane reviews (Hughes 2007; Cahill 2007). This review includes in its scope evaluations of randomized trials directly comparing NRT to these treatments, or combining NRT with them.

OBJECTIVES

To determine the effectiveness of nicotine replacement therapy (NRT), including gum, transdermal patch, intranasal spray and inhaled and oral preparations, in achieving long-term smoking cessation.

We addressed the following questions:

- Is NRT more effective than a placebo or 'no NRT' intervention in promoting smoking cessation?
- Is NRT relatively more effective when given with higher levels of behavioural support?
- Is NRT relatively more effective for people who are highly motivated to quit smoking?
- Is 4 mg nicotine gum more effective than 2 mg nicotine gum?
- Are fixed dosing schedules for nicotine gum more effective than ad lib use?
- Is higher dose nicotine patch therapy more effective than standard dose (~1 mg/hour) therapy?
- Are nicotine patches worn for 24 hours more effective than 16-hour patches?
- Is a longer duration of nicotine patch use more effective than shorter treatment?
- Is weaning from nicotine patch use more effective than an abrupt end of therapy?
- Are combinations of different forms of NRT more effective than the usual dose of a single type?
- Does NRT assist cessation among people who have relapsed after recent use of NRT?
- Is initiating NRT use before making a quit attempt more effective than starting on the quit day?
- Is NRT more or less effective than bupropion for smoking cessation?
- Is NRT combined with bupropion more effective than NRT alone?

- Are there harms associated with using NRT?

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. Trials where allocation to treatment was by a quasi-randomized method were also included, but appropriate sensitivity analysis was used to determine whether their inclusion altered the results.

Types of participants

Men or women who smoked and were motivated to quit were included irrespective of the setting from which they were recruited and/or their initial level of nicotine dependence. We included studies that randomized therapists, rather than smokers, to offer NRT or a control, provided that the specific aim of the study was to examine the effect of NRT on smoking cessation. Trials that randomized physicians or other therapists to receive an educational intervention, which included encouraging their patients to use NRT, were not included, but have been reviewed separately (Carson 2012).

Types of interventions

Comparisons of NRT (including chewing gum, transdermal patches, nasal and oral spray, inhalers and tablets or lozenges) versus placebo or no NRT control. The terms 'inhaler' and 'inhalator' (an oral device which delivers nicotine to the buccal mucosa by sucking) are used interchangeably in the literature. We have used the term 'inhaler' throughout the rest of this review.

We also included trials comparing different doses of NRT, comparing more than one type of NRT to a single type, comparing NRT with bupropion and combinations of the two, and comparing use of NRT prior to quit date as opposed to from quit date only.

In some analyses we categorized the trials into groups depending on the level of additional support provided (low or high). The definition of the low intensity category was intended to identify a level of support that could be offered as part of the provision of routine medical care. If the duration of time spent with the smoker (including assessment for the trial) exceeded 30 minutes at the initial consultation or the number of further assessment and reinforcement visits exceeded two, the level of additional support was categorized as high. The high intensity category included trials where there were a large number of visits to the clinic or trial centre, but these were often brief, spread over an extended period

during treatment and follow-up, and did not include a specific counselling component. To provide a more fine-grained analysis and to distinguish between high intensity group-based support and other trials within the high intensity category, we have therefore specified where the support included multi-session group-based counselling with frequent sessions around the quit date.

Types of outcome measures

The review evaluates the effects of NRT versus control on smoking cessation, rather than on withdrawal symptoms. We excluded trials that followed up participants for less than six months, except for trials amongst pregnant women, where the interval between enrolment and delivery may have been shorter. For each study we chose the strictest available criteria to define abstinence. For example, in studies where biochemical validation of cessation was available, only those participants who met the criteria for biochemically confirmed abstinence were regarded as being abstinent. Wherever possible we chose a measure of sustained cessation rather than point prevalence. People who were lost to follow-up were regarded as being continuing smokers.

For the current update we collected data on adverse events in both the included and excluded studies, where they were reported. We have not attempted to pool these findings, apart from one meta-analysis of reports of palpitations, tachycardia or chest pains.

Trials that evaluated the effect of NRT for individuals who were attempting to reduce the number of cigarettes smoked rather than to quit are no longer included in this review. They are covered by a separate review on harm reduction approaches (Stead 2007).

Search methods for identification of studies

We searched the specialized register of the Cochrane Tobacco Addiction Group in July 2012 for any reports of trials making reference to the use of nicotine replacement therapy of any type, by searching for 'NRT', or 'nicotine' near to terms for nicotine replacement products in the title, abstract or keywords. The most recent issues of the databases included in the register as searched for the current update of this review were: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, Issue 7, 2012), MEDLINE (Ovid) to update code 20120622, EMBASE (Ovid) to week 27 2012, PsycINFO (Ovid) to update 20120625. The search strategy for the Register is given in Appendix 1. For details of the searches used to create the specialized register see the [Tobacco Addiction Group Module](#) in the *The Cochrane Library*. The trials register also includes trials identified by handsearching of abstract books from meetings of the Society for Research on Nicotine & Tobacco. For earlier versions of this review we performed searches of additional databases: Cancerlit, Health Planning and Administration, Social Scisearch, Smoking & Health and Dissertation Abstracts. Since the searches did not produce any additional trials we did not search these databases af-

ter December 1996. During preparation of the first version of this review, we also sent letters to manufacturers of NRT preparations. Since this did not result in additional data we have not repeat the exercise for subsequent updates.

Data collection and analysis

Selection of studies

One author (LS) screened records retrieved by searches, to exclude papers that were not reports of potentially relevant studies. Reports that linked to potentially relevant studies but did not report the outcomes of interest are listed along with the main study report in the References to Studies section. The primary reference to the study is indicated, and for most studies the first author and year used as the study identifier corresponds the primary reference. Where data for a study were extracted from more than one report this is noted in the [Characteristics of included studies](#) table.

Data extraction and management

Two individuals independently extracted data from the published reports and abstracts. We resolved disagreements by discussion or referral to a third party. We made no attempt to blind these individuals either to the results of the primary studies or to which treatment participants received. We examined reports published only in non-English language journals with the assistance of translators.

Assessment of risk of bias in included studies

We assessed included studies for risks of selection bias, (methods of randomized sequence generation, and allocation concealment), performance and detection bias (the presence or absence of blinding), attrition bias (levels and reporting of loss to follow-up), and any other threats to study quality.

Measures of treatment effect

We extracted smoking cessation rates in the intervention and control groups from the reports at six or 12 months. Since not all studies reported cessation rates at exactly these intervals, we allowed a window period of six weeks at each follow-up point. For trials without 12-month follow-up we used six-month data. For trials which also reported follow-up for more than a year we used 12-month outcomes in most cases. (We note exceptions in the included study table.) For trials of NRT in pregnant women, we extracted smoking cessation outcomes at the closest follow-up to end of pregnancy, and also at longest follow-up postpartum if reported. Following the Cochrane Tobacco Addiction Group's recommended method of data analysis, we use the risk ratio for summarizing individual trial outcomes and for estimates of pooled

effect. Whilst there are circumstances in which odds ratios may be preferable, there is a danger that they will be interpreted as if they are risk ratios, making the treatment effect seem larger ([Deeks 2005](#)).

Dealing with missing data

We treated participants who dropped out or who were lost to follow-up after randomization as being continuing smokers. We noted in the risk of bias table the proportion of participants for whom the outcome was imputed in this way, and whether there was either high or differential loss to follow-up. The assumption that 'missing = smoking' will give conservative absolute quit rates, and will make little difference to the risk ratio unless drop-out rates differ substantially between groups.

Assessment of heterogeneity

To assess heterogeneity we use the I^2 statistic, given by the formula $[(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom ([Higgins 2003](#)). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to indicate substantial heterogeneity. When there are large numbers of trials as in this review, the χ^2 test for heterogeneity will be unduly powerful and may identify statistically significant but clinically unimportant heterogeneity.

Data synthesis

We estimated a pooled weighted average of risk ratios using a Mantel-Haenszel method, with 95% confidence intervals.

Subgroup analysis and investigation of heterogeneity

In comparing NRT to placebo or control, we performed subgroup analysis for each form of NRT. We did additional subgroup analyses within type of NRT (gum, patch, etc) to investigate whether the relative treatment effect differed according to the way in which smoking cessation was defined, and the intensity of behavioural support. We also used subgroup analyses to compare effect sizes across nicotine patch trials using different lengths of treatment, durations of daily use and tapering of dose at the end of treatment and to compare effect sizes across nicotine gum trials by dose and schedule. Additionally, we conducted subgroup analysis based on clinical setting of treatment. Where the estimates of effect clearly differed across subgroups we used meta-regression to test for significance.

For descriptive purposes we calculated an average quit rate for the control groups in some subgroup analyses, weighting by the inverse variance. Quit rates will vary between studies depending on many factors, including the period in which the study was done and the definition of abstinence used by the study. To provide a clinical perspective in the Discussion we estimated the number

of people who would need to be treated to benefit (NNTB) with NRT in order to produce one successful quitter at 12 months beyond that which would be achieved from a quit attempt without NRT. To do this we specified baseline quit rates and used the risk ratio derived from meta-analysis to calculate the quit rate likely with treatment; we then calculated the NNTB as the inverse of the difference between the treated and untreated quit rates (Altman 2002).

The Cochrane Tobacco Addiction Group's Glossary of smoking-related terms is included in this review (Appendix 2).

RESULTS

Description of studies

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

Included studies

The review includes 150 studies, 18 of which are new in the 2012 update (Bullen 2010; Coleman 2012; Cooney 2009; Etter 2009; Gariti 2009; Hughes 2010; Oncken 2008; Ortega 2011; Piper 2009; Pollak 2007; Rose 2009; Rose 2010; Schnoll 2010a; Schnoll 2010b; Shiffman 2009 (2mg); Shiffman 2009 (4mg); Smith 2009; Tønnesen 2012; Wittchen 2011). Trials were conducted in North America (77 studies), Europe (60 studies), Australasia (5 studies), Japan (2 studies), South America (2 studies), South Africa, Taiwan, Thailand, and in multiple regions (1 study each). The median sample size was around 240 but ranged from fewer than 50 to over 3500 participants.

Participants

Participants were typically adult cigarette smokers with an average age of 40 to 50. One trial recruited adolescents (Moolchan 2005). Most trials had approximately similar numbers of men and women. Kornitzer 1987 recruited only men in a workplace setting. Four trials recruited only pregnant women (Coleman 2012; Oncken 2008; Pollak 2007; Wisborg 2000) and a further four recruited only women (Cooper 2005; Oncken 2007; Pirie 1992; Prapavessis 2007). Two trials recruited African-American smokers (Ahluwalia 1998; Ahluwalia 2006).

Trials typically recruited people who smoked at least 15 cigarettes a day. Although some trials included lighter smokers as well, the average number smoked was over 20 per day in most studies. Ahluwalia 2006 recruited only people who smoked 10 or fewer cigarettes per day and Gariti 2009 recruited only people who smoked six to 15 cigarettes per day. Killen 1999 recruited people

smoking 25 or more per day and two trials recruited only people smoking 30 or more per day (Hughes 1990; Hughes 2003). Cooney 2009 recruited participants who were alcohol-dependent at the time of the study and two trials recruited people with a history of alcohol dependence (Hughes 2003; Kalman 2006). Joseph 1996 recruited people with a history of cardiac disease, and Gourlay 1995 recruited relapsed smokers.

Type and dose of nicotine replacement therapy

One hundred and seventeen studies (119 comparisons) contributed to the primary analysis of the efficacy of one or more types of NRT compared to a placebo or other control group not receiving any type of NRT. In this group of studies there were 55 trials of nicotine gum, 43 of transdermal nicotine patch, six of an oral nicotine tablet or lozenge, five offering a choice of products, four of intranasal nicotine spray, four of nicotine inhaler, one of oral spray (Tønnesen 2012), one providing patch and inhaler (Hand 2002) and one providing patch and lozenge (Piper 2009).

Trials that did not contribute to the primary analysis addressed a range of other questions including treatment duration, dose, combinations of different types of NRT compared to a single type, NRT compared to the smoking cessation pharmacotherapy bupropion, and use of NRT for a short period before the target quit day.

Most trials comparing nicotine gum to control provided the 2 mg dose. A few provided 4 mg gum to more highly addicted smokers, and two used only the 4mg dose (Blondal 1989; Puska 1979). Five trials included a comparison of 2 mg and 4 mg doses (Garvey 2000; Herrera 1995; Hughes 1990; Kornitzer 1987; Tønnesen 1988). In three trials the physician offered nicotine gum but participants did not necessarily accept or use it (Ockene 1991; Page 1986; Russell 1983). In one trial participants self selected 2 mg or 4 mg doses; the two groups are treated as separate trials in the meta-analysis (Shiffman 2009 (2mg); Shiffman 2009 (4mg)). Two trials compared a fixed dosage regimen with an ad lib regimen (Goldstein 1989; Killen 1990). The treatment period was typically two to three months, but ranged from 3 weeks to 12 months. Some trials did not specify how long the gum was available. Many of the trials included a variable period of dose tapering, but most encouraged participants to be gum-free by six to 12 months.

In nicotine patch trials the usual maximum daily dose was 15 mg for a 16-hour patch, or 21 mg for a 24-hour patch. Forty-two studies used a 24-hour formulation and 11 a 16-hour product. One study offered, among other dosage options, a 52.5 mg/24 hour patch (Wittchen 2011). If studies tested more than one dose we combined all active arms in the comparison to placebo. For one study we included an arm with a lower maximum dose of 14 mg but excluded a 7 mg dose arm (TNSG 1991). One trial (Daughton 1991) included a direct comparison between groups wearing 16-hour or 24-hour patches in addition to a placebo control. Eight trials directly compared a higher dose patch to a standard dose; in seven patch use was initiated on the quit date (CEASE 1999;

Dale 1995; Hughes 1999; Jorenby 1995; Kalman 2006; Killen 1999; Paoletti 1996) and in one patch use was initiated two weeks before the target quit date (Rose 2010). The minimum duration of therapy ranged from three weeks (Glavas 2003a, half the participants of Glavas 2003b) to three months, with a tapering period, if required, in 38 of the trials. Five trials directly compared two durations of therapy (Bolin 1999; CEASE 1999; Glavas 2003b; Hilleman 1994; Schnoll 2010a).

There are six studies of nicotine sublingual tablets or lozenges. Three used 2 mg sublingual tablets (Glover 2002; Tonnesen 2006; Wallstrom 2000). One used a 1 mg nicotine lozenge (Dautzenberg 2001). One used 2 mg or 4 mg lozenges according to dependence level based on manufacturers' instructions (Piper 2009) and one used 2 mg or 4 mg based on participants' time to first cigarette of the day (TTFC); smokers whose TTFC was more than 30 minutes were randomized to 2 mg lozenges or placebo (Shiffman 2002 (2mg)), whilst smokers with a TTFC less than 30 minutes had higher dose 4 mg lozenges or placebo (Shiffman 2002 (4mg)). The two groups are treated in the meta-analysis as separate trials making seven in total. There are four trials of intranasal nicotine spray (Blondal 1997; Hjalmarsen 1994; Schneider 1995; Sutherland 1992), one trial of oral nicotine spray (Tonnesen 2012) and four trials of nicotine inhaler (Hjalmarsen 1997; Leischow 1996; Schneider 1996; Tonnesen 1993). One trial of a nicotine inhaler was excluded as follow-up was for only three months (Glover 1992). Leischow refers to another unpublished study by different investigators that did not demonstrate any benefit of a nicotine inhaler. One trial compared four different types of NRT (patch, gum, inhaler and nasal spray) but only followed patients for 12 weeks and was excluded (Hajek 1999).

Nine trials compared combinations of two forms of nicotine therapy with only one form: patch with gum to patch alone (Cooney 2009; Kornitzer 1995); patch with gum to gum alone (Puska 1995); patch with nasal spray to patch alone (Blondal 1999); patch with inhaler to inhaler alone (Bohadana 2000); patch with lozenge to either one alone (Piper 2009; Smith 2009); patch with inhaler to either one alone (Tonnesen 2000); and patch with nasal spray to either one alone (Croghan 2003). In addition to these last four trials allowing a direct comparison between two single types, Lerman 2004 compared patch to nasal spray. Two unpublished trials of combination therapies with only three-month follow-up are excluded but contribute to a sensitivity analysis in the results (Finland unpublished; Sutherland 1999).

Five trials directly compared nicotine and bupropion (Gariti 2009; Jorenby 1999; Piper 2009; Smith 2009; Wittchen 2011).

Treatment setting

Eighteen trials in the main comparison (12 gum, five patch and one offering a choice of NRT products) were conducted in a primary care setting where smokers were usually recruited in response to a specific invitation from their doctor during a consultation. A further two gum trials were undertaken in workplace

clinics (Fagerstrom 1984; Roto 1987), and one in a university clinic (Harackiewicz 1988). One trial recruited via community physicians (Niaura 1994). Since participants in these trials were recruited in a similar way to primary care, we have aggregated them in the subgroup analysis by setting. One patch trial conducted in Veterans Affairs Medical Centers and recruiting patients with cardiac diseases (Joseph 1996) was also included in the primary care category. Four trials recruiting pregnant women in antenatal clinics (Coleman 2012; Oncken 2008; Piper 2009; Wisborg 2000) were kept in a separate category. Six of the gum trials, two of the nasal spray trials, and two of the inhaler/inhalator trials were carried out in specialized smoking cessation clinics to which participants had usually been referred. Ten trials (four patch, three gum, two giving a choice of products and one giving a combination of products) were undertaken with hospital in- or outpatients, some of who were recruited because they had a coexisting smoking-related illness. Three patch trials (Davidson 1998; Hays 1999; Sonderskov 1997) and one gum trial (split into Shiffman 2009 (2mg) and Shiffman 2009 (4mg)) were undertaken in settings intended to resemble 'over-the-counter' (OTC) use of NRT. One of these also allowed a comparison between purchased and free patches with minimal support (Hays 1999). Two trials compared purchased NRT without behavioural support (simulating an OTC setting) to purchased NRT with brief physician support (using patch, Leischow 1999; using inhaler, Leischow 2004). These two trials did not have a non-NRT control so do not contribute to the primary comparison. One trial of pre-cessation NRT (Bullen 2010) recruited participants who were all callers to a national quit line. One trial in a primary care setting evaluated the effect of cost on the use and efficacy of nicotine gum (Hughes 1991). The remaining trials were undertaken in participants from the community, most of whom had volunteered in response to media advertisements, but who were treated in clinical settings.

Pre-cessation use of NRT

Eight trials tested the use of NRT compared to placebo or control prior to quit date: five initiated patch use two weeks before the quit date (Rose 1994; Rose 1998; Rose 2006; Rose 2009; Schuurmans 2004); one initiated patch or gum use two weeks before the quit date (Bullen 2010); one initiated lozenge use three weeks prior to the quit date (Hughes 2010); and one initiated gum use four weeks prior to the quit date (Etter 2009). Following the quit date all study arms received active NRT. Three of the studies included other factorial arms testing mecamlamine. We combined the arms with the same pre-quit NRT conditions in our analysis. Rose 2010 compared two different doses of nicotine patch, both started two weeks before the target quit date and Shiffman 2009 (2mg)/Shiffman 2009 (4mg) was a placebo controlled trial in which participants were instructed to reduce cigarette consumption and increase gum use before quitting; neither of these trials were relevant to the pre-cessation analysis.

Excluded studies

Studies that were potentially relevant but excluded are listed with reasons in the [Characteristics of excluded studies](#) table. Some studies were excluded due to short follow-up. Some of these had as their primary outcome withdrawal symptoms rather than cessation. Studies that provided NRT or placebo to people trying to cut down their smoking but not make an immediate quit attempt are now excluded and are considered in detail in a separate review of interventions for reduction ([Stead 2007](#)). We excluded two trials in which NRT was provided to encourage a quit attempt but participants did not need to be planning to quit: [Velicer 2006](#) proactively recruited people by telephone, with those in one intervention group being mailed a six-week course of nicotine patches if they were judged to be in the preparation stage or in contemplation and had more pros than cons for quitting; [Carpenter 2011](#) encouraged all participants to make a practice quit attempt, and gave the intervention group trial samples of nicotine lozenges. We excluded one trial ([Ferguson 2012](#)) in which callers to the NHS Quitline were randomized to be offered free NRT or not to receive the offer; the control group had access to and used free NRT and other stop smoking medication at high levels. We excluded [Walker 2011](#) in which callers to a quitline were randomized either to receive a sample box of NRT products to try out before their quit date and to choose one of two to use, or to receive usual care, in which patch, gum or a combination was provided based on discussion with the adviser.

Risk of bias in included studies

Four trials are included based on data available from abstracts or conference presentations ([Dautzenberg 2001](#); [Kralikova 2002](#); [Mori 1992](#); [Nakamura 1990](#)), so had limited methodological details.

Thirty-eight studies (25%) reported allocation procedures in sufficient detail to be rated as being at low risk for their attempts to control selection bias, by using a system of treatment allocation which could not be known or predicted until a participant is enrolled and assigned to a study condition. Thirty-one of these low-risk trials (82%) also reported adequate sequence generation procedures. The majority of studies either did not report how randomization was performed and allocation concealed, or reported them in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made (rated as being at unclear risk). A small number of nicotine gum trials randomized to treatment according to day or week of clinic attendance ([Page 1986](#); [Richmond 1993](#); [Russell 1983](#)), or to birth date ([Fagerstrom 1984](#)), and were consequently rated as being at high risk of bias. One study ([Nebot 1992](#)) randomized by physician and there was no information about avoidance of selection bias in enrolment of smokers, so this was also rated as being at high risk. The main findings were not sensitive to the exclusion from the meta-analysis of trials at unclear risk, or of trials at unclear and at high risk of bias. A summary illustration of the risk of bias profile for each trial is shown in [Figure 1](#).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Sixteen gum trials (Gilbert 1989; Gross 1995; Hall 1985; Harackiewicz 1988; Killen 1984; Jensen 1991; McGovern 1992; Nakamura 1990; Nebor 1992; Niaura 1994; Niaura 1999; Richmond 1993; Roto 1987; Segnan 1991; Villa 1999; Zelman 1992), four patch trials (Cinciripini 1996; Otero 2006; Velicer 2006; Wong 1999) and three trials with choice of NRT product (Ortega 2011; Pollak 2007; Wittchen 2011) did not have a matched placebo control. A further two had both a placebo and a non-placebo control which were combined for the meta-analysis control group (Buchkremer 1988; Russell 1983). The main findings were not sensitive to the exclusion of studies and arms without a placebo.

Definitions of abstinence varied considerably. One hundred and five trials (70%) reported some measure of sustained abstinence, which included continuous abstinence with not even a slip since quit day, repeated point prevalence abstinence (with or without biochemical validation) at multiple follow-ups, or self reported abstinence for a prolonged period. Forty (27%) reported only the point prevalence of abstinence at the longest follow-up. In five studies it was unclear exactly how abstinence was defined. In four trials, participants who smoked two or three cigarettes per week were still classified as abstinent (Abelin 1989; Ehrensam 1991; Glavas 2003a; Glavas 2003b). Sensitivity analyses excluding these four trials made no difference to the overall findings. Most studies reported follow-up at least 12 months from start of treatment. Eighteen gum trials, 13 patch trials, one patch and lozenge trial, and one lozenge trial in the primary analysis had only six months follow-up. We report the findings of a subgroup analysis by type of abstinence and length of follow-up in the results section. Four trials in pregnant women reported abstinence close to the time of delivery. Three of these also reported outcomes postpartum (Wisborg 2000; Pollak 2007; Oncken 2008), at between six weeks and three months after delivery. In Analysis 1.1 we used the results at longest follow-up, but in a separate analysis we pooled peripartum and postpartum results separately (Analysis 15.1).

Biochemical validation of self reported smoking cessation at longest follow-up was used in 129 (86%) of the trials. Validation of abstinence was carried out by measurement of nicotine metabolites in saliva, urine or blood in 32 trials. The most common form of validation was measurement of carbon monoxide (CO) in expired air. The 'cut-off' level of CO used to define abstinence varied from less than 4 to 11 parts per million. Some of the 21 trials that did not validate all self report at longest follow-up did

use biochemical confirmation at earlier points, or validated some self reports. The main findings were not sensitive to the exclusion of 17 studies contributing to that analysis that did not attempt to validate all reported abstinence (Ahluwalia 1998; Buchkremer 1988; Daughton 1991; Davidson 1998; Fagerstrom 1984; Huber 1988; Hughes 1990; Ockene 1991; Ortega 2011; Otero 2006; Page 1986; Perng 1998; Roto 1987; Russell 1983; Sonderskov 1997; Villa 1999; Zelman 1992).

Some of the studies examine NRT versus usual care, and are inevitably not double-blind in design. One third of the trials reported some measure of blinding, but we did not assess whether the integrity of the procedure was tested, in line with the CONSORT guidelines (CONSORT 2001). Where they are done, assessments of blinding integrity should always be carried out before the clinical outcome has been determined, and the findings reported (Altman 2004). Mooney 2004 notes that few published trials report this information. While those that do provide some evidence that participants are likely to assess their treatment assignment correctly, it is insufficient to assess whether this is associated with differences in treatment effects. Further, there may be an apparent breaking of the blinding in trials where the treatment effect is marked, for either an intended outcome or an adverse effect, but participants who successfully decipher assignment may disguise their unblinding actions (Altman 2004). It is also possible that those who believe that they are receiving a placebo may be more likely to stop trying to quit.

Effects of interventions

See: [Summary of findings for the main comparison](#) Nicotine replacement therapy

Any type of NRT versus placebo or no NRT control

Analysis 1.1 included 117 trials, with over 50,000 participants ([Summary of findings for the main comparison](#)). A small number of trials contributed to more than one sub group and two trials were treated as two separate studies in the analyses. Each of the six forms of nicotine replacement therapy (NRT) significantly increased the rate of cessation compared to placebo or no NRT, as did a choice of product. The pooled risk ratio for abstinence for any form of NRT relative to control was 1.60 (95% CI 1.53 to 1.68). The risk ratio and 95% CI for each type are tabulated below. The inclusion of two small trials that compared a combination of types to no NRT did not affect the overall estimate.

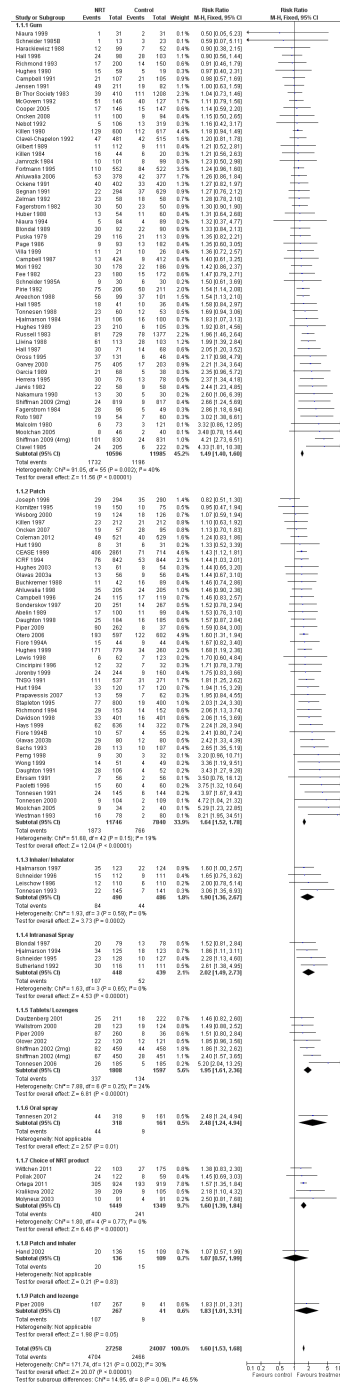
Type of NRT	RR	95% CI	I ²	N of studies	N of participants Intervention/ Control
Gum	1.49	1.40 to 1.60	40%	56*	10,596/ 11,985
Patch	1.64	1.52 to 1.78	19%	43	11,746/ 7,840
Inhaler/inhalator	1.90	1.36 to 2.67	0%	4	490/ 486
Intranasal spray	2.02	1.49 to 2.73	0%	4	448/ 439
Tablets/lozenges	1.95	1.61 to 2.36	24%	7*	1808/ 1597
Oral spray	2.48	1.24 to 4.94	NA	1	318/ 161
Choice of product	1.60	1.39 to 1.84	NA	5	1449/ 1349
Patch and inhaler	1.07	0.57 to 1.99	NA	1	136/ 109
Patch and lozenge	1.83	1.01 to 3.31	NA	1	267/ 41
* includes 1 study treated as 2 for analysis					

Although the estimated effect sizes varied across the different products, confidence intervals were wide for the products with higher estimates which had small numbers of trials. In a meta-regression with gum as baseline, no significant difference between the products was detected. The I^2 statistic was 41%, indicating that little of the variability was attributable to between-trial differences. Seven nicotine gum and two patch trials had lower quit rates in the treatment than control groups at the end of follow-up, and in a further 64 (55%) of trials the 95% confidence interval for the risk ratio included 1 (i.e. the trials did not detect a significant treatment

effect). Many of these trials had small numbers of smokers, and hence insufficient power to detect a modest treatment effect with reasonable certainty. One large trial of nicotine patches for people with cardiovascular disease had lower quit rates in the intervention than in the control group (Joseph 1996); at six months the quit rates were 14% for active patch and 11% for placebo, but after 48 weeks there had been greater relapse in the active group and rates were 10% and 12% respectively.

[Figure 2](#)

Figure 2. Forest plot of comparison: I Any type of NRT versus placebo/ no NRT control, outcome: I.I Smoking cessation at 6+ months follow up.



Sensitivity to definition of abstinence

For the nicotine gum and patch we assessed whether trials that reported sustained abstinence at 12 months had different treatment effects from those that only reported a point prevalence outcome, or had shorter follow-up (Analysis 2.1; Analysis 2.2). Subgroup categories were sustained abstinence at 12 months or more, sustained abstinence at six months, point prevalence or unclear definition at 12 months, and point prevalence/unclear at six months. For nicotine gum 32/55 studies (58%) reported sustained 12-month abstinence and the estimate was similar to that for all 55 studies (sustained 12-month RR 1.43, 95% CI 1.31 to 1.56 compared with RR 1.49, 95% CI 1.40 to 1.60). The highest estimate was for the subgroup of six studies reporting sustained abstinence at six months, which was significantly higher in a meta-regression (RR 2.77, 95% CI 2.14 to 3.59). This seems to be attributable to one new study (Shiffman 2009 (2mg); Shiffman 2009 (4mg)) and is unlikely to be of methodological or clinical significance. For nicotine patch, 21/43 studies (49%) reported sustained 12-month abstinence, and the relative risk estimate was also similar to that for all 43 studies (sustained 12-month RR 1.51, 95% CI 1.35 to 1.70, compared with RR 1.64, 95% CI 1.52 to 1.78 overall). For patch studies there was no evidence that the risk ratios differed significantly between subgroups.

Sensitivity to intensity of behavioural support

Almost all trials provided the same behavioural support in terms of advice, counselling, and number of follow-up visits to the active pharmacotherapy and control groups, but different trials provided different amounts of support. One pre-cessation trial gave both arms the same amount of counselling but sessions were offered at different time points relative to quit date and gave different advice depending on study arm (Hughes 2010). We conducted subgroup analyses by intensity of support for gum and patch trials separately (Analysis 3.1; Analysis 3.2). For nicotine gum the relative risk estimate was similar across all three subgroups. The control group quit rates varied as expected, averaging 3.5% with low intensity support, 9% with high intensity individual support and 11.7% with group-based support. Nicotine patch trials showed the same pattern; the relative risk estimates were similar for each subgroup and the average control group quit rates were 6.3% with low intensity support, 6.8% with high intensity individual support and 14.8% with group-based support. Using meta-regression we confirmed that there was no evidence that the relative effect differed by type of support.

Two small studies in primary care directly compared the effect of providing high versus low intensity follow-up to participants receiving nicotine gum (Fagerstrom 1984; Marshall 1985). The pooled results favoured intensive follow-up but the result was not

statistically significant. In the one patch trial that compared minimal counselling with two forms of more intensive counselling in patients receiving one of two nicotine doses, the intensive intervention did not lead to improved outcomes (Jorenby 1995). Pooling all three studies showed no effect of increased behavioural support (Analysis 3.3, RR 1.14, 95% CI 0.88 to 1.47). It should be emphasised that these three studies do not address the efficacy of NRT and that only a factorial placebo-controlled trial with different intensities of support can adequately investigate whether pharmacotherapy and behavioural interventions have interactive effects.

Sensitivity to treatment settings

We conducted further subgroup analyses for each type of setting in which smokers were recruited or treated (with type of NRT as a subgroup beneath setting). The pooled RR for trials in community volunteers where care was provided in a medical setting was 1.60 (95% CI 1.51 to 1.70, 66 trials, Analysis 4.1) and was similar to that of trials conducted in smoking clinics (RR 1.73, 95% CI 1.48 to 2.03, 10 trials, Analysis 4.2), trials conducted in primary care settings (RR 1.52, 95% CI 1.34 to 1.71, 23 trials, Analysis 4.3) and trials conducted in hospitals (RR 1.44, 95% CI 1.28 to 1.62, 10 trials, Analysis 4.4). Pooled results from four trials in antenatal clinics were lower than in other settings (RR 1.22, 95% CI 0.92 to 1.62, Analysis 4.5); this was the only setting in which results did not show a statistically significant effect of the intervention. Pooled results from the five trials in community volunteers in which treatment was provided in an 'over-the-counter' (OTC) setting were significantly higher than in other settings (RR 2.71, 95% CI 2.11 to 3.49, Analysis 4.6), though heterogeneity was present ($I^2 = 51\%$). In a meta-regression we checked whether there was any evidence of interaction between the treatment setting and type of NRT used. The effect of nicotine gum was highest in the OTC setting and this seems to be attributable to the same study that contributed heterogeneity in the abstinence subgroup analysis above (Shiffman 2009 (2mg); Shiffman 2009 (4mg)).

Control group quit rates varied by setting; as expected, the lowest rate was found in OTC studies (2.1%) and the highest rate in smoking clinics (12.1%). Falling within this range, control group rates were 5.7% in primary care settings, 8.8% in antenatal clinics, 9.5% in community volunteers where treatment was provided in a medical setting, and 10% in hospitals. Though the RR in OTC settings was significantly higher than in other settings, it should be noted that the control group quit rate was lowest in this group, meaning the difference between absolute numbers quit in this setting when compared with other settings would not be as marked as the RR suggests.

Two trials compared patch (Leischow 1999) or inhaler (Leischow

2004) with minimal physician support and patch/inhaler with no support in a simulated OTC setting. Abstinence rates were low in both conditions and confidence intervals wide, but when pooled there was a significant advantage for physician support compared with no support (RR 4.58, 95% CI 1.18 to 17.88, Analysis 13.1).

Nicotine gum - effects of dose and scheduling

Most trials used the 2 mg dose so we did not conduct a subgroup analysis for indirect comparison. Four trials directly compared 4 mg and 2 mg gum for treating highly dependent smokers, with a pooled estimate suggesting a significant benefit of the higher dose (RR 1.85, 95% CI 1.36 to 2.50, Garvey 2000; Herrera 1995; Kornitzer 1987; Tonnesen 1988, Analysis 5.1.1). In low dependence or unselected smokers there was no evidence for an effect (RR 0.77, 95% CI 0.49 to 1.21, Garvey 2000; Hughes 1990; Kornitzer 1987, Analysis 5.1.2).

Two trials compared a fixed dose regimen of 2 mg nicotine gum against use of an ad lib regimen (Goldstein 1989; Killen 1990). The fixed dose regimen had higher quit rates but the difference was non-significant (RR 1.22, 95% CI 0.92 to 1.61, Analysis 6.1).

Nicotine patch - effects of dose and scheduling

Eight trials have compared a high dose patch to standard dose (Analysis 7.1). Four used 24-hour patches and compared 42/44 mg doses to standard 21/22 mg doses (Dale 1995; Hughes 1999; Jorenby 1995; Kalman 2006). Three used 16-hour patches and compared a 25 mg high dose to 15 mg standard dose (CEASE 1999; Killen 1999; Paoletti 1996). Rose 2010 used 16-hour patches started two weeks before the target quit date and compared at 42 mg high dose to a 21 mg standard dose. Three studies (Hughes 1999; Killen 1999; Kalman 2006) specifically recruited heavy smokers, and one selected smokers with baseline cotinine levels of over 250 mg/ml (Paoletti 1996). One study was in heavy smokers with a history of alcohol dependence (Kalman 2006). Pooling all eight studies gives an estimated RR 1.14 (95% CI 1.01 to 1.29, Analysis 7.1), providing only marginal evidence of a small benefit from higher doses. Three studies had point estimates favouring the lower dose group, with no evidence of significant heterogeneity in the results ($I^2 = 25\%$). Only one study showed a significantly higher quit rate with the higher dose (CEASE 1999). Indirect comparison failed to detect evidence of a difference in effect between 16-hour and 24-hour patch, with similar point estimates and overlapping confidence intervals in the two subgroups. There was some evidence of heterogeneity in the results of the 11 trials that used a 16-hour patch ($I^2 = 53\%$, Analysis 8.1). One trial directly compared the effect of 16-hour and 24-hour patch use (Daughton 1991). The study did not detect a significant difference, but with just 106 participants had low power (24-hour patch versus 16-hour patch: RR 0.70, 95% CI 0.36 to 1.34).

Nicotine patch - effect of treatment duration and dose tapering

Indirect comparisons did not suggest a significant difference in treatment effect between 17 trials providing up to eight weeks of pharmacotherapy and 26 offering a longer period (Analysis 9.1). One large trial that compared a 28- to a 12-week course of treatment did not detect evidence of benefit from longer treatment (CEASE 1999, Analysis 9.2). Smaller trials comparing a three-week to a 12-week course (Bolin 1999), a three-week to a six-week course (Glavas 2003b), and an eight-week to a 24-week course (Schnoll 2010a) also found no evidence of a difference; Schnoll 2010a reported a benefit at the end of treatment but the difference was lost over the following six months.

Indirect comparison did not detect a significant difference between rates of success in nine trials where end of treatment was abrupt versus 32 trials where participants were weaned from patch use by tapering the dose (RR 1.89, 95% CI 1.50 to 2.37 and RR 1.58, 95% CI 1.44 to 1.72, respectively; Analysis 10.1). A subgroup comparison indicated significant variability in effect estimates due to genuine subgroup differences ($I^2 = 52.2\%$). This could, however, be attributable to confounding factors between the two groups. No difference was detected in the two trials that directly compared weaning with abrupt withdrawal (Hilleman 1994; Stapleton 1995, Analysis 10.2).

Combinations of different forms of nicotine therapy

Nine trials compared the use of two types of NRT with the use of a single type only. When pooled, the trials suggest a statistically significant benefit (RR 1.34, 95% CI 1.18 to 1.51, Analysis 11.1), with little statistical heterogeneity ($I^2 = 34\%$), but the trials are relatively clinically heterogeneous in the combinations and comparison therapies used. Only two of the trials, one comparing nasal spray and patch with patch alone (Blondal 1999) and one comparing patch plus lozenge versus either one alone (Smith 2009), showed a significantly higher rate of sustained abstinence at one year with the combined therapy. We are aware of two unpublished studies that failed to detect significant short-term effects and did not have long-term follow-up (Finland unpublished; Sutherland 1999, brief details in Characteristics of excluded studies). In case their exclusion biased the outcome we tested the sensitivity of the meta-analysis to including their results for cessation at three months. The meta-analysis maintained a significant, though slightly smaller, effect. We also tested the sensitivity to including only comparisons between a combination therapy and a nicotine patch only control. The effect remained significant, with or without the relevant unpublished study. Two trials also compared two types to no NRT (Hand 2002; Piper 2009); these data are included in the primary analysis but not in Analysis 11.1, which now includes only data comparing a combination of NRT products to a single type of NRT product.

Direct comparison between different types of NRT

Six trials have directly compared types of NRT (Analysis 12.1). None detected significant differences. Pooling the two that compared nasal spray with patch (RR 0.90, 95% CI 0.64 to 1.27) and pooling the three that compared lozenge with patch (RR 0.94, 95% CI 0.79 to 1.12) also failed to find significant effect. Whilst confidence intervals are wide, the direct comparison is consistent with indirect comparisons reported above in the primary analysis, suggesting that the different types have similar effects. In one open label study in which success rates were higher for patch than lozenge, more participants had expressed a preference for patch, and use of lozenge was lower than the recommended dose (Schnoll 2010b).

Pre-cessation use of NRT

The pooled estimate from seven trials shows a moderate but non significant increase in quit rates from using NRT for a brief period before the target quit day compared with initiating active NRT use on the quit day (RR 1.18, 95% CI 0.98 to 1.41, Analysis 14.1). The effect is slightly more pronounced when pooling together only the patch trials (RR 1.34, 95% CI 1.08 to 1.65, 6 trials), though only one of the patch trials independently detected a significant effect (Rose 2009). No significant effects were detected in the trials of pre-cessation NRT other than patch (Bullen 2010; Etter 2009; Hughes 2010). Hughes 2010 was a study of gradual cessation versus abrupt cessation using nicotine lozenges and results may have been confounded by the differences in counselling and instructions on cigarette reduction prior to quit date between the two arms. When we excluded this study from pooled results of any type of pre-cessation NRT, the results became significant (RR 1.25, 95% CI 1.03 to 1.50, *analysis not shown*). A further trial which included groups who began using nicotine gum or placebo gum a week before quit day (Herrera 1995) found that pre-cessation use did not significantly increase quitting at six weeks, but long-term outcomes were not reported. One other trial asked smokers to gradually cut down cigarette use and increase gum use before making a quit attempt; this was included in the main analysis and not here because participants continued to use nicotine or placebo gum throughout the treatment phase (Shiffman 2009 (2mg); Shiffman 2009 (4mg)). We also excluded a study in which callers to a quitline were sent a sample of NRT products to try and then choose one or more, compared with being provided with patch or gum after discussion with the quitline adviser (Walker 2011). Since only one of each product was provided we did not regard this as pre-cessation use.

Pregnant women

Four trials evaluated the effectiveness of NRT use in pregnant women. Cessation outcomes at longest follow-up (delivery in Coleman 2012 and postpartum in Oncken 2008, Pollak 2007,

and Wisborg 2000) are used in Analysis 1.1. In a separate analysis (Analysis 15.1) we pooled peri-partum and postpartum effects separately. For abstinence close to the time of delivery the benefit of NRT was of borderline statistical significance (RR 1.30, 95% CI 1.00 to 1.68). The largest trial (Coleman 2012) did not detect a significant effect and the pooled estimate is sensitive to the inclusion of Pollak 2007, which showed a larger and statistically significant benefit. Pooling the postpartum outcomes from three trials did not demonstrate a significant difference between NRT and control groups (RR 1.20, 95% CI 0.80 to 1.80).

Relapsed smokers

Although many of the trials reported here did not specifically exclude people who had previously tried and failed to quit with NRT, one trial recruited people who had relapsed after patch and behavioural support in an earlier phase of the study but were motivated to make a second attempt (Gourlay 1995). This study did not detect an effect on continuous abstinence (RR 1.25, 95% CI 0.34 to 4.60, *analysis not shown*), although it did detect a significant increase in 28-day point prevalence abstinence (RR 2.49, 95% CI 1.11 to 5.57). Quit rates were low in both groups with either definition of abstinence.

Cost of therapy

One study comparing the effectiveness of free and purchased patch in an OTC model setting found no significant difference in quit rates between the two conditions; 8.7% (28/321) quit with free patch, 11% (34/315) with purchased patch, RR 0.81, 95% CI 0.50 to 1.30 (Hays 1999). Those receiving free NRT were part of a placebo-controlled substudy. One small study of the cost of nicotine gum for patients receiving brief physician advice found non-significantly higher quit rates for participants who could obtain free gum compared to those paying close to full price; 6/32 (22%) versus 3/38 (12%). People who could get free gum were much more likely to obtain it (Hughes 1991).

Comparison and combination with bupropion

Pooled together, the five studies directly comparing three different types of NRT with bupropion found no difference between the two (RR 1.01, CI 95% 0.87 to 1.18, Analysis 16.1). There was heterogeneity, especially in the subgroup of four trials that used nicotine patch, attributable to one study in which the cessation rate was significantly lower for nicotine patch plus placebo tablet than for bupropion plus placebo patch (Jorenby 1999); no other studies directly comparing patch, gum or lozenge versus bupropion detected a significant difference.

The combination of NRT and bupropion had a modest but significant effect when compared with bupropion alone (RR 1.24, CI 95% 1.06 to 1.45, 4 studies, Analysis 16.2). The combination

of bupropion and NRT significantly increased the rate of cessation over placebo alone (RR 2.61, CI 95% 1.65 to 4.12, Analysis 16.3), but there was heterogeneity between the two studies, with [Piper 2009](#) not detecting a significant benefit, although with wide confidence intervals, so whilst the combination would be expected to be effective, the size of effect is uncertain.

Adverse Effects

We have made no systematic attempt in this review to synthesize quantitatively the incidence of the various side effects reported with the different NRT preparations. This was because of the extensive variation in reporting the nature, timing and duration of symptoms. The major side effects usually reported with nicotine gum include hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems ([Fiore 1992](#); [Palmer 1992](#)). The only side effect that appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use ([Fiore 1992](#)). The major side effects reported with the nicotine inhaler and nasal and oral sprays are related to local irritation at the site of administration (mouth and nose respectively). For example, symptoms such as throat irritation, coughing, and oral burning were reported significantly more frequently with subjects allocated to the nicotine inhaler than to placebo control ([Schneider 1996](#)); none of the experiences, however, were reported as severe. With the nasal spray, nasal irritation and runny nose are the most commonly reported side effects. In the study of oral spray, hiccoughs and throat irritation were the most commonly reported adverse events ([Tønnesen 2012](#)). Nicotine sublingual tablets have been reported to cause hiccoughs, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers ([Wallstrom 1999](#)). A review of adverse effects based on 35 trials with over 9,000 participants did not find evidence of excess adverse cardiovascular events amongst those assigned to nicotine patch, and the total number of such events was low ([Greenland 1998](#)). When first licensed there was concern about the safety of NRT in smokers with cardiac disease ([TNWG 1994](#)). A trial of nicotine patch ([Joseph 1996](#)) that recruited smokers aged over 45 with at least one diagnosis of cardiovascular disease found no evidence that serious adverse events were more common in smokers in the nicotine patch group. Events related to cardiovascular disease such as an increase in angina severity occurred in approximately 16% of patients, but did not differ according to whether or not patients were receiving NRT. A review of safety in patients with cardiovascular disease found no evidence of an increased risk of cardiac events ([Joseph 2003](#)). This included data from two randomized trials with short-term follow-up that are excluded from the present review ([Tzivoni 1998](#); [Working Group 1994](#)) and a case-control study in a population-based sample. An analysis of 187 smokers admitted to hospital with acute coronary syndromes who received nicotine patches showed no evidence of difference in short- or long-term mortality

compared to a propensity-matched sample of smokers in the same database who did not receive NRT ([Meine 2005](#)).

A recent meta-analysis of adverse events associated with NRT ([Mills 2010](#)) across 92 RCTs and 28 observational studies addressed a possible excess of chest pains and heart palpitations among users of NRT compared with placebo groups. The authors report an OR of 2.06 (95% CI 1.51 to 2.82) across 12 studies. We replicated this data collection exercise and analysis where data were available across the 260 RCTs (included and excluded) in this review, and detected a similar but slightly lower estimate, OR 1.88 (95% CI 1.37 to 2.57; Analysis 17.1; OR rather than RR calculated for comparison) across 15 studies. This is potentially the only clinically significant serious adverse event to emerge from the trials, and constitutes an extremely rare event, occurring at a rate of 2.5% in the NRT groups compared with 1.4% in the control groups in the 15 trials in which it was reported at all. Appendix 3 summarises the main adverse events reported in the included and excluded studies, where the data were available.

The four trials assessing NRT use in pregnant women did not detect significant increases in serious adverse events amongst the treatment groups ([Coleman 2012](#); [Oncken 2008](#); [Pollak 2007](#); [Wisborg 2000](#)). Recruitment for [Pollak 2007](#) was suspended early when interim analysis found a higher rate of negative birth outcomes in the NRT arm (primarily preterm birth); however, when adjusted for previous birth outcomes the adverse event rate between the two groups was not significantly different in final analysis. The effects of NRT use on neonatal health are discussed further in a separate Cochrane review, which found no statistically significant differences in rates of any serious adverse events between treatment and control groups ([Coleman 2012a](#)).

DISCUSSION

This review provides reliable evidence from trials including over 50,000 participants that offering nicotine replacement therapy (NRT) to dependent smokers who are prepared to try to quit increases their chance of success over that achieved with the same level of support without NRT. This applies to all forms of NRT and is independent of any variations in methodology or design characteristics of trials included in the meta-analysis. In particular we did not find evidence that the relative effect of NRT was smaller in trials with longer follow-up beyond our six-month minimum for inclusion. We did not compare end of treatment risk ratios with post-treatment follow-up, and relapse rates may be higher in active treatment participants once they stop using NRT products, but later relapse is probably unrelated to NRT use.

The absolute effects of NRT use will depend on the baseline quit rate, which varies in different clinical settings. Studies of people attempting to quit on their own suggest that success rates after six to 12 months are 3 to 5% ([Hughes 2004a](#)). Use of NRT might be

expected to increase the rate by 2 to 3%, giving a number needed to treat to benefit (NNTB) of 56. If however the quit rate without pharmacotherapy was estimated to be 15%, either because the population had other predictors of successful quitting or received intensive behavioural support, then another 8% might be expected to quit, giving an NNTB of 11.

Type and dose of NRT

The conclusion that the relative effects of the different forms of NRT are similar is largely based on indirect comparisons. Although the estimated risk ratio was highest for the nasal and oral sprays the confidence intervals are wide. In this update we did not find evidence using meta-regression of a significant difference between any forms. Most of the trials included in the comparison of nicotine gum versus placebo used 2 mg gum, although the 4 mg dose has been shown to be better for highly dependent smokers. A recent trial, in which 4 mg gum could be used by dependent smokers, has increased the estimate for nicotine gum (Shiffman 2009 (4mg)). This trial also instructed participants to gradually reduce cigarette consumption while using gum. Although the treatment effects were large, especially for 4 mg gum, the control quit rates were notably low. The study provided very low levels of behavioural support, and many participants did not achieve initial abstinence. One lozenge study used a 4 mg dose, and excluding this would reduce the difference between gum and tablet/lozenge subgroups. There have been no direct comparisons between these different forms. Six studies have directly compared different types, and non-significant differences between them at individual and pooled level. One study that randomized people to use nicotine gum, patch, spray or inhaler did not detect significant differences in abstinence rates after 12 weeks (Hajek 1999), supporting the indirect estimates from the longer term studies. Where a range of products are available, choice of product may be guided by patients' preferences (McClure 2006), although one study showed that allowing people to try different products may alter their perceptions (Schneider 2004). In one study directly comparing nicotine patch and nasal spray there were no overall differences in quit rates but there were three significant subgroup/treatment interactions (Lerman 2004). The patch showed better results for white smokers, while the spray showed better results for obese smokers and for highly nicotine-dependent smokers. These effects need confirmation in additional studies before they can be relied on for treatment matching.

Direct comparisons support the use of 4 mg gum for more nicotine-dependent smokers. There is borderline evidence for a small benefit of nicotine patch at doses above the standard dose (21 mg for 24 hours or 15 mg for 16 hours). Use of these may be considered for heavy smokers (i.e. smoking 30 or more cigarettes a day) or for patients relapsing because of persistent craving and withdrawal symptoms on standard dose therapy (Hughes 1995).

Intensity of additional support

We did not detect important differences in relative effect within patch or gum studies by our classification of level of support. A letter (Walsh 2007) prior to the previous update of this review identified inconsistencies in the classification of low and high intensity support in this review. In response we changed the classification of a small number of trials. This did not alter the conclusion that intensity of support does not appear to be an important moderator of NRT effect. Most of the trials in the low intensity category were conducted in medical settings and the cut-off for level of support was not intended to distinguish between 'over-the-counter' (OTC) use of NRT and use with support from healthcare providers. We performed a separate analysis of OTC-type trials in the treatment setting subgroup analysis. As judged by the average control group quit rate, people receiving support and placebo had similar quit rates in low intensity and high intensity individual support groups. One interpretation of this is that although the latter group typically had more frequent contact with study co-ordinators, this did not markedly increase quitting or prevent relapse. Control group quit rates were, however, higher when people had intensive group-based support provided by specialists.

Treatment setting

We did not detect differences in relative effect according to the setting of recruitment and treatment, and in a post hoc meta-regression there was no evidence that the type of NRT influenced effect sizes differently in different settings. This subgroup analysis had considerable overlap with the support subgroup since, for example, people recruited in primary care settings typically had lower intensity support. Again there was variation between the control group quit rates, attributable to differences in motivation and to the level of behavioural support. People recruited from primary care who received placebo had average quit rates around 5 to 7%. The weighted average rate amongst community volunteers who were treated in OTC settings is lower in this update, at just 2%, due to one study with low control group quit rates Shiffman 2009 (2mg); Shiffman 2009 (4mg), which also had a large treatment effect. This makes the relative effect in trials in OTC settings higher than in other settings, even though the absolute increase in quit rates is small. People recruited in smoking clinics had much higher control group quit rates, averaging 15%, but this reflects both their motivation and the high level of behavioural support provided. Although some trials of NRT use in hospital inpatients have reported relatively less successful results, there was evidence of benefit in the subgroups of four studies of nicotine patch and two studies of choice of NRT amongst people recruited in inpatient and outpatient settings. The effects for nicotine gum and a single trial of a combination of products were smaller and not statistically significant.

There has been continuing debate about the amount of evidence for efficacy of NRT when obtained OTC without advice or sup-

port from a healthcare professional (Hughes 2001; Walsh 2000; Walsh 2001). The small number of placebo-controlled trials in settings intended to replicate OTC settings support the conclusion that the relative effect of NRT is similar to settings where more advice and behavioural support is provided, although quit rates in both control and intervention groups have been low. One other meta-analysis supports the conclusion of efficacy, although it differs in its inclusion criteria (Hughes 2003). In addition to the same three trials comparing nicotine patch to placebo in an OTC setting (Davidson 1998; Hays 1999; Sonderskov 1997), that review includes one study excluded here due to short follow-up (Shiffman 2002a). It also pools four trials comparing NRT provided OTC to NRT provided under prescription. We exclude one trial that compared both gum and patch in these settings, but was not randomized (Shiffman 2002b), and another that has not been published and for which we have been unable to obtain reliable data for inclusion (Korberly 1999). The abstract reported that there were no significant differences in quit rates between users of nicotine patch who purchased it via a non-healthcare facility, and those receiving it on prescription. On the basis of one published and one unpublished study we find a marginally significant benefit of NRT with prescription compared to OTC, but the confidence intervals are wide.

A report of a recent prospective cohort study questioned the effectiveness of NRT outside of the clinical trial setting after finding no difference in relative relapse rates between smokers trying to quit who used NRT and those who did not use NRT (Alpert 2012). The design of this study has been criticised for not addressing initial quit rates in the two groups (Stapleton 2012). It has also been suggested that the 'real world' effectiveness of NRT declines or disappears once it becomes available to purchase without requiring contact with a health professional who can offer behavioural support and guidance on appropriate use (Pierce 2002). Based on a comparison of two cross sectional surveys in California, the latter study finds that prior to OTC availability quit rates for self selected NRT users were higher than rates for non-users, but after the switch to OTC this difference disappeared. We and others have questioned the conclusions from this study (Franzon 2002; Stead 2002). The level of addiction of people who chose to use NRT compared to those who did not is a source of confounding which may have been incompletely controlled (Shiffman 2005). People who have used NRT may also be more likely to recall quit attempts. A third study suggested that both use of NRT and quit rates rose in the immediate aftermath of OTC availability (Hyland 2005). In this longitudinal study of smokers in the COMMIT study cohort there was a small reduction in the average success rates for patch users after the switch but no reduction in success rates for gum users. However a review on the impact of NRT on population trends in smoking behaviour at that time concluded that not enough smokers had been using NRT during quit attempts for there to have been a measurable effect (Cummings 2005). A multi-country prospective study (West 2007) found that NRT users who

did not use formal behavioural support had higher quit rates than non-users, even when controlling for baseline differences in motivation and other possible predictors of success. Another multi-country prospective cohort analysis using the International Tobacco Control Four Country Survey which controlled for possible bias in recall of quit attempts found that people who attempted to quit with nicotine patch, varenicline or bupropion had higher quit rates than those not using medication, but no effect was detected for oral nicotine products (Kasza 2012). Although no study in which participants self select treatment can be free from the possibility of bias due to unmeasured confounders, some results from these studies provide additional evidence for real world effects.

Trials in special populations

Four trials of NRT in pregnant women are now included in the review (Coleman 2012; Oncken 2007; Pollak 2007; Wisborg 2000) with Coleman 2012 contributing over 1000 of ~1600 participants. For these trials we evaluated cessation at the closest follow-up to end of pregnancy as well as at the longest follow-up. At the end of pregnancy the confidence interval just reached significance, but this was sensitive to the inclusion of the smallest trial, while results of the largest trial were not statistically significant. No significant benefit of treatment was detected at longest follow-up/postpartum follow-up. Two of the studies (Oncken 2007 and Wisborg 2000) found significant increases in birth weight amongst the NRT arms (a better perinatal outcome). None of the studies found evidence of a significant increase in serious adverse events in the NRT arms. Adherence to recommended use of NRT was low in all four included studies. We excluded two small trials of nicotine patch in pregnancy: Kapur 2001 had follow-up only to end of treatment at 12 weeks. In this trial 0/13 in the placebo group quit compared to 4/17 (24%) in the active treatment group. Enrolment was ended early in this study because of a possible adverse event in the placebo arm. A second small study without placebo control had high rates of withdrawal and non-compliance (Hotham 2006), although 3/20 in the patch group were abstinent at delivery compared to 0/20 in the counselling-only control. A study measuring nicotine metabolism in smokers during their pregnancy and postpartum has suggested that nicotine is metabolised more quickly by pregnant women and that this may affect the dose of NRT required (Dempsey 2002). More studies are needed to establish whether or not NRT does aid quitting in pregnancy and what effects there are on birth outcomes (Benowitz 2000). There is now a separate Cochrane review (Coleman 2012a) on pharmacotherapies for smoking cessation in pregnancy. That review did not detect a benefit of NRT (RR for cessation in later pregnancy 1.33, 95% CI 0.93 to 1.91). It included Kapur 2001 and Hotham 2006, but our results are broadly consistent with its findings. Differences in the point estimates and confidence intervals between Coleman 2012a and this review are attributable to our use of a fixed-effect rather than a random effects model. These results do not provide con-

clusive evidence that NRT helps pregnant women to quit, but the confidence intervals in our analysis do not exclude a small clinical benefit. As the confidence intervals overlap the point estimate of the effect in non-pregnant populations, our results also do not rule out the possibility that NRT is as effective in pregnant women as it is in non-pregnant people.

Trials generally restricted recruitment to adults over the age of 18; in a small number of trials the age range was not specified. One trial in adolescents, which is now included (Moolchan 2005), compared nicotine patch, gum, and double placebo. Two trials in adolescents with less than six months follow-up were excluded: one trial examining the effects of the nicotine patch on craving and withdrawal symptoms, safety, and compliance among 100 adolescents had 10 weeks follow-up, with no significant difference detected at that point (Hanson 2003). In a second trial of the patch with 13 weeks follow-up there were no quitters in either group at that point (Roddy 2006). Adherence to therapy and participant retention were both reported to be problems.

Evidence for differential treatment effects in different subgroups

We made no attempt to conduct separate analyses for any subgroups of trial participants, because subgroup results are uncommon in trial reports, and where data cannot be obtained from all studies there is a risk of bias from using incomplete data. Munafò and colleagues have reported the results of a meta-analysis of nicotine patch by sex (Munafò 2004a). They were able to include data from 11 out of 31 (35%) of eligible trials and 36% of study participants. They found no evidence that the nicotine patch was more effective for men than women as has been hypothesised; although men showed a somewhat bigger benefit from NRT at 12 months, the difference was not significant. There was also no difference in average placebo quit rates between men and women, which has been reported in some studies. In a commentary (Perkins 2004) some additional data were identified, but this did not alter the conclusions (Munafò 2004b). A second meta-analysis of any type of NRT (Cepeda-Benito 2004) reported that in women the odds ratio for cessation declined with increasing length of follow-up, with a non-significant difference at 12 months. Amongst males the odds ratio declined less over time and remained significant. Based on a further subgroup analysis they also reported that the decline in long-term efficacy in women was greater in trials with low intensity support than with high intensity support, suggesting that the more intensive support helped prevent late relapse in women who had initially received NRT. Although there was no evidence of bias, the review could only include a subset of published studies, so the finding should be regarded as hypothesis-generating. All review authors agreed that trials are underpowered to identify any interaction between treatment and any type of individual characteristics, and recommended public archiving of data from studies, as well as new research specifically designed to test

group-by-treatment interactions. At the moment there does not appear to be sufficient evidence of clinically important differences between men and women to guide treatment matching.

Combinations of NRT products

The evidence now suggests more strongly that using a combination of NRT products is better than one product alone. Two recent trials (Piper 2009; Smith 2009) have increased the evidence base. Both compared a combination of patch and lozenge with either alone. The trials showed fairly consistent effects, with a range of different comparators. The combined therapies all included the patch and an acute dosing type. In a sensitivity analysis we did not find any difference according to whether the control was the patch or an acute dosing form. The 2008 US clinical practice guidelines (Fiore 2008) state that the long-term use of nicotine patch with another form of ad lib NRT is more effective than nicotine patch alone and recommend that physicians consider this option. It is not entirely clear whether the benefit of combination therapy is due to the sensory effects provided by multiple types of delivery systems, to the higher percentage of nicotine substitution achieved, the better relief of craving by ad lib use of acute dosing forms or some combination of these and other factors (Sweeney 2001).

Pre-cessation use of NRT

When nicotine replacement therapies were first introduced there was concern that any smoking whilst using a product would increase the potential for adverse effects such as nausea and vomiting, due to nicotine overdose. However studies with higher dose products and combinations of products have found no evidence of harm from moderate increases in nicotine intake. There is some evidence that smokers who use NRT whilst not trying to alter their smoking behaviour either smoke less or reduce their nicotine from cigarettes, especially when using acute dosing types of NRT (Fagerstrom 2002). Trials have now investigated two situations in which it has been proposed that use of an NRT product can help long-term abstinence if initially used while continuing to smoke. The first of these is to begin using NRT for a short period before a quit attempt on the theoretical basis that it might diminish the reinforcing effects of cigarette smoking or reduce the dependence on inhaled nicotine (Rose 2006). This is often referred to as 'preloading'. Meta-analysis of seven trials now included in this review suggests a moderate but non-significant increase in quit rates in those using NRT pre-cessation over those achieved by post-quit use of NRT alone. However, of the seven trials pooled only one detected a significant effect (Rose 2009), and a recent large trial of pre-cessation use of choice of NRT product did not detect a significant effect (Bullen 2010). Findings suggest patch use pre-quit date may be more effective than pre-cessation use of acute forms of NRT, and are consistent with results from a recent meta-analysis of nicotine preloading (Lindson 2011).

The second proposed use of NRT pre-cessation is for a period of weeks to months while people not willing or able to quit abruptly gradually reduce the number of cigarettes, before quitting completely. The use of two forms of NRT, gum and inhaler, has now been approved by licensing authorities in some European countries for this cessation approach, described variously as 'Reduce to Stop' or 'Cut Down to Quit'. Trials of this approach are included in a Cochrane review of interventions for reducing harm from continued smoking (Stead 2007). The long-term use of NRT whilst continuing to smoke smaller numbers of cigarettes cannot be supported by the evidence because it is not clear what reduction in consumption is needed for a useful health benefit.

Re-treating relapsed smokers

Whilst end of treatment success rates may be quite high, many people relapse after the end of therapy. There is suggestive evidence (Gourlay 1995) that repeated use of NRT in patients who have relapsed after an initial course may produce further quitters, though the absolute effect is small. A subgroup analysis in another trial (Jorenby 1999, reported in Durcan 2002) indicated that the relative effect of treatment with nicotine patch compared to placebo was at least as high for people who had used NRT before. The authors noted that there was no way to distinguish between people who had completely failed to quit using NRT and those who had been initially successful but relapsed.

Direct comparison and combination with non-nicotine pharmacotherapies

Five trials directly comparing nicotine with bupropion are now included in this review; pooled together they do not suggest a difference between the two in terms of long-term cessation. However, there was a significant increase in long-term cessation with a combination of NRT and bupropion, as opposed to nicotine or bupropion alone. There has not yet been a trial of a direct comparison between NRT and varenicline with follow-up long enough to include in this review.

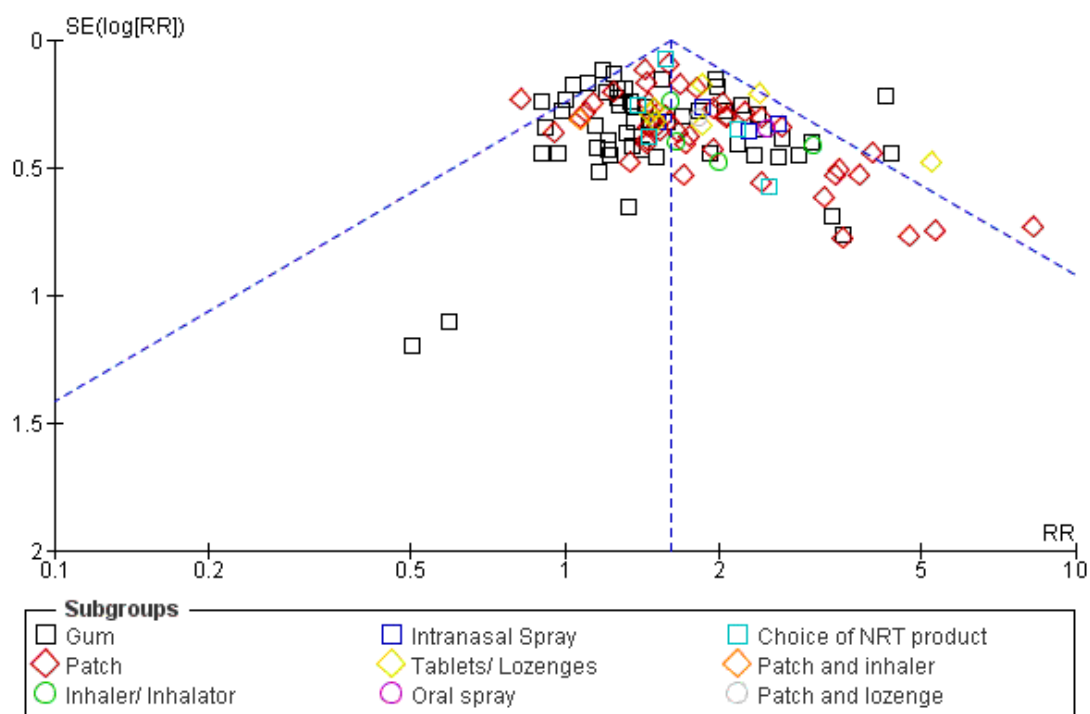
Addictive potential of NRT

Some successful quitters continue to use NRT products beyond the recommended treatment period (Shiffman 2003), but few develop true dependence (Hughes 2004b; Hughes 2005). Although nicotine has the potential to cause harm, it is very much less harmful than tobacco smoke, so while complete abstinence from nicotine is preferred, the risk to health from NRT use is small compared to the risk from continued smoking.

Methodological limitations

There are two possible methodological limitations of this review, which need to be borne in mind: use of data predominantly derived from published reports (Stewart 1993), and publication bias (Simes 1986). We tried to partly address any shortcomings from having limited our analysis to reported data by approaching investigators, where necessary, to obtain additional unpublished data or to clarify areas of uncertainty. Although steps were taken to minimize publication bias by writing to the manufacturers of NRT products when this review was first prepared, the response was poor and we have not repeated this exercise. It is therefore possible that there are some unpublished trials, with less favourable results, that we have not identified despite our efforts to do so. A statistical analysis (Egger 1997, personal communication) suggests that this is the case. A funnel plot (Figure 3) shows some evidence of asymmetry for trials in the main comparison, with a few small to moderately sized trials producing RRs to the left of the pooled RR; however, given the large number of trials in the review, the funnel plot does not suggest the results would be altered significantly were smaller studies with lower RRs included. A meta-analysis has also demonstrated that nicotine gum and patch studies that received pharmaceutical industry funding have on average slightly higher effect sizes than other studies after controlling for some trial characteristics (Etter 2007). The practical effect of these considerations is that the magnitude of the effectiveness of NRT may be smaller than our estimates suggest.

Figure 3. Funnel plot of comparison: I Any type of NRT versus placebo/ no NRT control, outcome: I.I Smoking cessation at 6+ months follow up.



This review excludes studies with less than a six month follow-up from the start of treatment; the outcome used reflects the effect of NRT after the end of active treatment. A comparison of abstinence rates during treatment and abstinence at one year ([Fagerstrom 2003](#)) suggests that the relative effect of NRT declines once active therapy stops, that is, people who quit with the help of NRT are a little more likely to relapse after they discontinue treatment than those on placebo. The relative effect of NRT could continue to decline even after a year of follow-up. A meta-analysis comparing one-year and long-term outcomes in twelve NRT trials with follow-up beyond one year suggested that the relative efficacy did not change, with similar relapse rates in the active and placebo groups, but further relapse does reduce the absolute difference in quit rates ([Etter 2006](#)).

AUTHORS' CONCLUSIONS

Implications for practice

1. All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhaler, oral spray, lozenge and sublingual tablet, are effective as part of a

strategy to promote smoking cessation. They increase the rate of long-term quitting by approximately 50% to 70% regardless of setting. These conclusions apply to smokers who are motivated to quit and who have high levels of nicotine dependence. There is little evidence about the role of NRT for individuals smoking fewer than 10 to 15 cigarettes a day.

2. The choice of which form to use should reflect patient needs, tolerability and cost considerations. Patches are likely to be easier to use than gum, nasal spray or inhaler, but patches cannot be used for relief of acute cravings.

3. Eight weeks of patch therapy is as effective as longer courses, and there is no evidence that tapered therapy is better than abrupt withdrawal. Wearing the patch during waking hours only (16 hours a day) is as effective as wearing one for 24 hours a day.

4. If gum is used, it may be offered on a fixed dose or ad lib basis. For highly dependent smokers, or those who have failed with 2 mg gum, 4 mg gum should be offered.

5. There is borderline evidence for a small benefit from use of the nicotine patch at doses higher than the standard dose (21 mg for 24 hours or 15 mg for 16 hours).

6. There is evidence of benefit from combining the nicotine patch with an acute dosing type (e.g. gum) to allow ad lib dosing compared to use of a single form.

7. The effectiveness of NRT in terms of the risk ratio appears to be largely independent of the intensity of additional support provided. Provision of more intensive levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT. But it should be noted that the absolute increase in success rates attributable to the use of NRT will be larger when the baseline chance of success is already raised by the provision of intensive behavioural support.

8. There is minimal evidence that a repeated course of NRT in patients who have relapsed after recent use of nicotine patches will result in a small additional probability of quitting.

9. NRT does not lead to an increased risk of adverse cardiovascular events in smokers with a history of cardiovascular disease.

10. NRT appears as effective as bupropion. Any decision about which pharmacotherapies to use should take into account potential adverse effects as well as benefits.

11. Initiating patch use for a short period before making a quit attempt is moderately more effective than patch use initiated on the quit date itself. There is no evidence that suggests use of other forms of NRT pre-cessation is more effective than starting use on the quit day.

Implications for research

Further research is required in several areas:

1. Direct comparisons between the various forms of NRT and between different doses and durations of treatment.
2. Use of combinations of different forms of NRT.
3. Direct comparisons between NRT and newer pharmacotherapies including varenicline.
4. Use of combinations of NRT and newer pharmacotherapies including varenicline.
5. Safety and benefits of NRT use during pregnancy.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abelin 1989

Methods	Country: Switzerland Recruitment: 21 primary care clinics
Participants	199 primary care patients 40% F, av.age 41, av.cpd 27. Pts were motivated to quit.
Interventions	1. Nicotine patch, 24hr, 12 wks with weaning; 21 mg smokers of >20 cpd, 14 mg for <20 cpd 2. Placebo patch Level of support: low (number of visits unclear)
Outcomes	Sustained abstinence at 12m (0-3 cigs/wk) Validation: expired CO
Notes	Methods in Lancet paper, final follow up in Muller 1990. Sources of support not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated; described as "randomised, between-subjects, double-blind, and placebo-controlled"
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", no further details. 75% of NRT group and 76% of placebo group correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs similar between groups (NRT 20, placebo 21); 36/41 drop-outs continued to smoke, but all 41 counted as treatment failures in ITT analysis
Other bias	High risk	If smoking from 0-3 cigs/wk, and CO 0-11 ppm, counted as abstinent

Ahluwalia 1998

Methods	Country: USA Recruitment: hospital in- and outpatients
Participants	410 African American smokers Av.age 47, FTND 6. Pts were motivated to quit.
Interventions	1. Nicotine patch (21 mg with weaning, 10 wks) 2. Placebo patch Level of support: high (1 hr initial visit and brief follow-up visits)
Outcomes	Prolonged abstinence at 6m (self report of no smoking since end of treatment) Validation: none
Notes	Study funded by American Cancer Society Career Development Award, Marion Merrell Dow Inc, and Emory Medical Care Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated random numbers table with a block size set at 20"
Allocation concealment (selection bias)	Low risk	Study staff blinded - see below.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both study staff and patients were blinded to patch treatment". 63% of NRT pts and 44% of placebo pts correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses similar between groups at 6m: NRT 53, placebo 58. Counted as treatment failures for ITT analyses

Ahluwalia 2006

Methods	Country: USA Recruitment: community volunteers
Participants	755 African American light smokers (≤ 10 cpd) 67% F, av.age 45, av.cpd 8 Pts were motivated to quit.
Interventions	Factorial trial, behavioural interventions collapsed for this review 1. Nicotine gum (2 mg), recommended use tailored to cpd. Highest 10/day for 4 wks, tapering for 4 wks 2. Placebo gum, 8 wks

Ahluwalia 2006 (Continued)

	Level of support: high: 3 in-person visits at randomization, wk 1, wk 8, and phone contact at wk 3, wk 6, wk 16, content based on either motivational interviewing or health education principles
Outcomes	PP abstinence at 6m (7 day PP) Validation: cotinine ≤ 20 ng/ml
Notes	New for 2008 update Study funded by National Cancer Institute; products supplied by Glaxo-SmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization codes were generated in blocks of 36". For counselling support "a sealed envelope with pre-assigned randomization numbers was drawn"
Allocation concealment (selection bias)	Low risk	"Study staff ... were blinded"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Study staff and participants were blinded". "Assignment to MI counselling versus HE was not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pts receiving active gum and HE counselling were more likely to remain in the study, but interaction not statistically significant. Losses to follow up at wk 26: NRT+MI: 32; NRT+HE 21; Placebo+MI 39; Placebo+HE 26

Areechon 1988

Methods	Country: Thailand Recruitment: community volunteers
Participants	200 smokers (≥ 15 cpd) 6% F, av.age 39, av.cpd 24. Pts were motivated to quit.
Interventions	1. Gum (2 mg) x 8 boxes 2. Placebo gum x 8 boxes Level of support: high (weekly visits with physician, unspecified frequency & duration)
Outcomes	PP abstinence at 6m Validation: CO

Areechon 1988 (Continued)

Notes	Support level reclassified as high, 2008. Study funded by Merrel Dow (Bangkok, Thailand), with products supplied by A.B. Leo, Helsinborg, Sweden	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. "Neither the investigators nor the subjects knew which subjects received the active gum and which received the placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Significant differences between NRT (20 drop-outs) and placebo (37 drop-outs; P<0.01) at 6m
Other bias	High risk	10/93 quitters did not provide CO validation, but distribution not reported. All are included in MA

Blondal 1989

Methods	Country: Iceland Recruitment: community volunteers invited to attend a smoking cessation clinic
Participants	182 smokers (included pipe & cigar users, smoked at least once a day) 57% F, av. age 42, av. tobacco use 21g/day. Pts were volunteers, but motivation not required or assessed
Interventions	1. Gum (4 mg) for at least 1m 2. Placebo gum (containing pepper) for 1m or more Level of support: high (group therapy, 5x1hr sessions, TQD at session 1)
Outcomes	Lapse-free abstinence at 12m (24m also reported, no validation) Validation: CO<10ppm
Notes	Lapse-free abstinence used since 2008. Study funded by Icelandic Ministry of Health and Social Security
<i>Risk of bias</i>	

Blondal 1989 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assignment was by group (6 to active gum, 6 to placebo); whether randomized or not is unclear
Allocation concealment (selection bias)	Unclear risk	Probably. "Each subgroup knew they would either get nicotine gum or a placebo"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/59 claiming abstinence at 12m were not CO-confirmed (4 missing and 3 >10ppm), and counted as continuing smokers
Other bias	Low risk	44/92 in NRT group were highly nicotine-dependent, compared with 28/90 in placebo group (P=0.03)

Blondal 1997

Methods	Country: Iceland Recruitment: community volunteers	
Participants	159 smokers (≥ 1 cpd) 44% F, av. age 42, av. tobacco use 25g/day. Pts had to be motivated to quit.	
Interventions	1. Nicotine nasal spray (NNS) ad lib use. Each dose (2 squirts) delivered 1 mg nicotine. Maximum dose 5 mg/hr and 40 mg/day. Recommended duration of use 3m. 2. Placebo nasal spray containing piperine to mimic sensory effect of nicotine. Level of support: high (Group therapy 6x1hr sessions)	
Outcomes	Sustained abstinence at 1yr (continuous abstinence from quit day, follow-up also at 2yrs) Validation: CO<10ppm at each of 5 follow-ups	
Notes	Abstinence at 24m 15/79 vs 11/78. OR 1.4. Study funded by Icelandic Ministry of Health and Social Security, with consumables supplied by Pharmacia & Upjohn	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Blondal 1997 (Continued)

Random sequence generation (selection bias)	Low risk	“computer-generated randomization code”, with spray dispensed by University pharmacy
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	“Subject and therapist were blind to treatment assignment”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One pt lost to follow-up, assumed to be a smoker. Drop-out rates not reported

Blondal 1999

Methods	Country: Iceland Recruitment: community volunteers
Participants	237 smokers (≥ 1 cpd) 67% F, av. age 41-43, av. tobacco use 25g/day
Interventions	1. Nicotine nasal spray (NNS) (0.5 mg/dose) + 15 mg nicotine patches for 3m, weaning over further 2m. NNS could be continued for 1 yr 2. Placebo nasal spray + 15 mg nicotine patches on same schedule Level of support: high (4 supportive group meetings)
Outcomes	Sustained abstinence at 12m (6 yr data also reported) Validation: CO<10ppm
Notes	Does not contribute to main comparisons, only combination. 6yr abstinence 19/118 vs 10/119, OR 2.1 Study supported by Pharmacia & Upjohn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“computer generated randomisation code at a local pharmacy”
Allocation concealment (selection bias)	Low risk	“Pharmacy staff were blinded to the content of the bottles”
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinic staff, pharmacy staff and pts all blinded to assignment. Codes not broken until after data entry and analyses completed

Blondal 1999 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All pts followed up for at least 12m.
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Bohadana 2000

Methods	Country: France Recruitment: community volunteers
Participants	400 smokers, 18-70 yrs, >10 cpd, >1 previous quit attempt, motivated. 51% F, Av cpd: Group 1: 26.1, Group 2: 23.5; FTND>6 Pts required to be motivated to quit.
Interventions	1: Nicotine inhaler, 26 wks, combined with nicotine patch (15 mg/16hr) for first 6 wks, placebo patch for next 6 wks 2: Nicotine inhaler, 26 wks, placebo patch for first 12 wks Level of support: high. All received brief counselling and support from investigator at each visit
Outcomes	Sustained abstinence at 12m (prolonged from wk 2, no slips allowed) Validation: CO<10ppm at each visit (2 wks, 6 wks, 6m, 12m) (Study also reports respiratory symptoms and pulmonary function tests for completely abstinent subjects)
Notes	Does not contribute to main comparisons, only combination. Gender subgroup results reported 2003 Study funded by Pharmacia & Upjohn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	"sealed randomization envelopes were provided for each subject and were held by the hospital pharmacy, which was responsible for dispensing medication"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses over 12m were steep but similar in both groups, i.e. 148 from NRT group and 155 from placebo group. Losses counted as continuing smokers

Bolin 1999

Methods	Country: USA Recruitment: smoking cessation clinic
Participants	98 smokers 16% F, av.age 54, av.cpd 20
Interventions	1. Nicotine patch for 12 wks (21 mg/3 wks, 14 mg/3 wks, 7mg/3 wks) 2. Nicotine patch for 3 wks (21 mg/1 wk, 14 mg/1 wk, 7mg/1 wk) Level of support: high (group). All received intensive group programme, 5 sessions prior to quit day
Outcomes	Continuous abstinence at 5m (PP also recorded) Validation: CO
Notes	Contributes only to length of treatment comparison Borderline follow-up length - 20 wks from beginning of programme, 16 wks since start of NRT Sources of support not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly assigned ... random assignment took place on the first day of patch administration"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both participants and experimenters were unaware of assignment during the baseline phase of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates not reported; any drop-outs counted as treatment failures in analysis

Bolliger 2000a

Methods	
Participants	
Interventions	
Outcomes	
Notes	Excluded study, but contributing data on adverse events

Br Thor Society 1983

Methods	Country: UK (95 centres) Recruitment: hospital chest clinics (80%) and inpatient wards	
Participants	1618 clinic patients age 18-65 with a smoking-related illness (pulmonary or vascular) 39% F, av.age 49, av.cpd 24	
Interventions	1. Brief advice from physician 2. Brief advice + booklet 3. Brief advice + booklet + placebo chewing gum 4. Brief advice + booklet + nicotine chewing gum (2 mg for up to 3m, up to 6m on request) Level of support: low (1m & 3m follow-up visits)	
Outcomes	Sustained validated abstinence at 6m and 12m Validation: Venous carboxyhaemoglobin	
Notes	Includes both placebo and no-placebo groups. 4 vs 1+2+3 used in main comparison. 4 vs 3 has lower OR (0.8) but does not alter MA notably. Study was funded by Health Education Council and Lundbeck Ltd	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each physician had a balanced block of 12 treatments. Assignment was by numbered envelope
Allocation concealment (selection bias)	Low risk	Physician opened envelope at first treatment session.
Blinding (performance bias and detection bias) All outcomes	Low risk	“Placebo and nicotine gums were indistinguishable in appearance and taste, and neither the physician nor the patient knew which gum had been issued”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lower losses from gum groups (10 and 10) than from Advice groups (24 and 24) , but 18 VA and VAB pts were prescribed Nicorette in error; removing these made differences non-significant

Brantmark 1973a

Methods	
Participants	
Interventions	
Outcomes	
Notes	Excluded study, but contributing data on adverse events

Buchkremer 1988

Methods	Country: Germany Recruitment: community volunteers
Participants	131 smokers 50% F, av.age 35, av.cpd 29. Pts were motivated to give up.
Interventions	1. Nicotine patch (24hr/day, 8 wks, 15cm with weaning) + behavioural therapy 2. Placebo patch + behavioural therapy 3. Behavioural therapy alone Level of support: high (9 weekly group sessions)
Outcomes	Abstinence (not stated how assessed) at 12m Validation: none
Notes	Placebo & no-placebo groups. 1 vs 2+3 used in main comparison. Study was funded by Deutsche Forschungsgemeinschaft.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"smokers were randomly assigned ... Randomization included matching by age, sex and initial cigarette consumption"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind; "checked by questioning both the training personnel and the probands of nicotine- and placebo-groups". No significant differences in right and wrong guesses
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates not reported.

Bullen 2010

Methods	Country: New Zealand Recruitment: callers to New Zealand Quitline
Participants	1100 smokers. 60% F, mean age 40, av.cpd 19. Motivated to quit.
Interventions	Trial of precessation NRT Intervention: NRT initiated 14 days before quit date, continued for 8 wks after quit date. 91% used patch only, 6% gum only, 3% both Control: NRT for 8 wks from quit date. 85% patch, 11% gum, 4% both Level of support: high (counselling offered via Quitline)
Outcomes	Continuous abstinence at 6m (data supplied by 1st author) (Self reported 7d PP at 6m reported in paper) Validation: salivary cotinine in subgroup only. Self reported outcomes used in analysis
Notes	New for 2012 update. Contributes to pre-cessation analysis only. Participants able to select their treatment (patch, gum, or patch+gum) after discussion with adviser. Patch and gum outcomes supplied by 1st author, contribute to separate subgroups, 39 participants using combination not included in analysis Study funded by Health Research Council and Heart Foundation of New Zealand

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"People giving verbal consent by telephone were allocated randomly using central computerized randomization."
Allocation concealment (selection bias)	Low risk	"randomization sequence concealed until interventions were assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo. Single blinding: "Participants were aware of the group to which they were allocated but 3- and 6- month follow-up methods were identical for all participants, and all follow-up telephone calls and outcome verification procedures were made by research assistants blind to treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of drop-outs in treatment and control groups (148 treatment, 139 control). Participants lost to follow-up included as smokers in outcome data

Campbell 1987

Methods	Country: UK Recruitment: primary care (45 GPs in 11 centres)
Participants	836 primary care patients agreeing to try to stop smoking after brief advice from their doctor 61% F, av.age 39
Interventions	1. Nicotine gum (2 mg) x 6 boxes 2. Placebo gum x 6 boxes Level of support: low (no further face-to-face contact, 2/3rds received a letter after 1m)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	Study funded by Chest, Heart and Stroke Association; discounted Nicorette gum supplied by Lunbeck, free chewing gum by Wrigleys

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"in a double-blind random fashion". Control pts were recruited sequentially after the gum cohort had been assembled
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37% losses at 12m.
Other bias	Unclear risk	Placebo gum was actually Wrigleys gum, repackaged and labelled

Campbell 1991

Methods	Country: UK Recruitment: hospital inpatients
Participants	212 patients with smoking-related diseases 44% F, 53% aged 50+, 61% smoked >15cpd
Interventions	1. Nicotine gum 2-4 mg (3m) 2. Placebo gum Level of support: high (support at 2, 3, 5 wks, 3m, 6m)

Campbell 1991 (Continued)

Outcomes	Sustained abstinence at 12m Validation: CO	
Notes	Study was supported by Pharmacia LEO.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“those who had agreed were given packages of identical appearance randomly containing either nicotine (2 mg) or placebo gum”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	“Non-attenders were classified as failures”; rate of drop-outs not reported

Campbell 1996

Methods	Country: UK Recruitment: hospital inpatients and outpatients	
Participants	234 adult smokers (>1 cpd in previous wk) (172 outpatients, 62 inpatients) Stratified on FTND. Pts were motivated to quit. 54% F, av.age 49	
Interventions	1. Nicotine patch (21 mg, 24hr, 12 wks with dose tapering) 2. Placebo patch Level of support: high (counselling at 2, 4, 8,12 wks)	
Outcomes	Continuous abstinence at 12m Validation: CO	
Notes	Originally included as Burton 1992 which was an abstract of the same trial. Study was funded and supplied by Ciba-Geigy Ltd.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Campbell 1996 (Continued)

Random sequence generation (selection bias)	Unclear risk	Pts stratified by inpatient/outpatient status, and outpatients also by FTND score. Pts “were randomized”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Abstract describes the trial as “double-blind”, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	57 NRT and 56 placebo pts did not complete the 12 wk course. By 52 wks, 28 pts had dropped out of the NRT group, and 40 from the placebo group

CEASE 1999

Methods	Country: Multi-centre - 36 clinic centres in 17 European countries Recruitment: community volunteers	
Participants	3575 smokers (>14 cpd) 48% F, av.age 41, av.cpd 27 (34% had previously used NRT)	
Interventions	Factorial design compared 2 patch doses and 2 treatment durations. Dose 15 mg or 25 mg (16hr), duration of active treatment 28 wks (incl 4 wk fading) or 12 wks (incl 4 wk fading). 1. 25 mg patch for 28 wks 2. 25 mg patch for 12 wks 3. 15 mg patch for 28 wks 4. 15 mg patch for 12 wks 5. Placebo Level of support: high (brief advice & self help brochure, visits at enrolment, TQD, wk 1, 2, 4, 8, 12, 22, 26)	
Outcomes	Prolonged abstinence at 12m, sustained from wk 2 Validation: expired CO<10ppm at each clinic visit	
Notes	Doses and durations collapsed in main analyses. Durations compared in Analysis 9.2 dosages in Analysis 7.1 Level of support reclassified to high for 2007 because of repeated visits. Limited support at these visits. Study was sponsored by the European Respiratory Society, with support from Pharmacia & Upjohn, Sweden	

Risk of bias

Bias	Authors' judgement	Support for judgement
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CEASE 1999 (Continued)

Random sequence generation (selection bias)	Low risk	"A computer-generated allocation list was prepared centrally and allocated subjects to treatment numbers". Randomization stratified by centre
Allocation concealment (selection bias)	Low risk	See process above.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Active and placebo patches were identical in appearance and packaging. In order to maintain blinding, all subjects continued to use two patches for a total of 26 weeks", i.e. non-tapered groups were switched to placebo patches
Incomplete outcome data (attrition bias) All outcomes	Low risk	22% lost to 12m follow-up, and 54% withdrew.

Cinciripini 1996

Methods	Country: USA Recruitment: community volunteers
Participants	64 smokers (>15 cpd) 70% F, av.cpd 29/22
Interventions	1. Nicotine patch (21 mg, 12 wks incl weaning) 2. Behaviour therapy only (no placebo) Level of support: High (group therapy weekly for 9 wks)
Outcomes	Sustained abstinence, 12m post-treatment and all previous points (EOT, 1, 3, 6m) Validation: CO<6ppm at each point
Notes	121 smokers recruited but only the first 64 followed up for 1 yr. 6m quit rates for whole cohort were approx 53% vs 30% (personal communication 2004). Study was supported by a DHHS grant, and by Ciba Geigy Corporation and Marion Merrell Dow

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Sixty-four participants ... were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated

Cinciripini 1996 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs not reported, but failures and missing were counted as non-abstinent

Clavel 1985

Methods	Country: France Recruitment: community volunteers
Participants	427 smokers (≥ 5 cpd) 51% F, av.age 34, av.cpd 22 for intermediate group (Clavel 1984). Pts were motivated to quit
Interventions	1. Nicotine gum (2 mg) x 1 box 2. Control group (time lock controlled cigarette case) (Acupuncture arm not included in this review) Level of support: High (3x1hr group therapy sessions in first month)
Outcomes	Sustained abstinence at 13m Validation: "Smoking cessation adjusted using exhaled CO figures from published trials"
Notes	Classification of support corrected to high in 2008 update. Study was supported by the Haut Comité d'Aide à la Lutte Contre le Cancer, and Laboratoire Léo, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Treatment ... was allocated by balanced randomisation"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	Those still smoking at 1m were not followed and were counted as failures, as were the 6% non-responders. Half the abstainers were visited at home at 13m and tested for expired CO

Clavel-Chapelon 1992

Methods	Country: France Recruitment: community volunteers
Participants	996 smokers (≥ 10 cpd) 45% F, av.age 34
Interventions	Factorial trial with active/placebo acupuncture arms, collapsed for this review 1. Nicotine gum (2 mg) for up to 6m, max 30/day 2. Placebo gum (contained 1 mg unbuffered nicotine) Level of support: high (3 acupuncture session at 0, 7, 28 days)
Outcomes	Abstinence at 13m (1m quitters followed up). 4yr follow-up reported in 1997 with different 1yr results Validation: none at 1yr
Notes	First included in 2008 update. Question over inclusion because placebo contained small amount of nicotine. Abstinence at 4yrs 30/481 vs 32/515. Study was supported by CIBA-GEIGY.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Treatments were administrated blindly"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only pts abstinent at 1m were followed up. Two pts were lost between ms 9 and 12, and 32 between yr1 and yr4. Losses "were considered successes until the date of the last follow-up and afterwards were not considered anymore"

Coleman 2012

Methods	Country: UK Recruitment: pregnant women attending hospital clinics
Participants	1050 pregnant women at 12-24 wks gestation smoking ≥ 5 cpd av.age 26, av.cpd at time of recruitment 14, av.cpd before pregnancy 20

Coleman 2012 (Continued)

Interventions	1. Nicotine patch 15 mg/16hrs for 8 wks (participants given 4 wk supply at outset, if not smoking at 4 wks given another 4 wk supply) 2. 'Visually identical' placebo on same schedule Level of support: high. Behavioural cessation support ≤1hr at enrolment + 3 phone calls (on quit date, 3d after quit date, 4 wks after quit date). If collecting another 4 wk supply of NRT/placebo, participants given another face-to-face session	
Outcomes	Continuous abstinence from quit date to delivery. Lapses of up to 5 cigs (on 5 occasions) permitted Validation: salivary cotinine <10ng/ml, CO≥8ppm, primary outcomes required saliva cotinine validation, with or without CO	
Notes	New for 2012 update (previously listed as Coleman 2007 in ongoing studies) Funded by NIHR Health Assessment Technology Programme. Similar rates of adverse pregnancy and birth outcomes in both groups Low compliance in both arms (7.2% active treatment and 2.8% placebo group reported using patch for more than 1m)	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“computer-generated sequence, in random permuted blocks of randomly varying size and with stratification by recruiting site”
Allocation concealment (selection bias)	Low risk	“eligibility criteria were entered into a secure online database before randomization”
Blinding (performance bias and detection bias) All outcomes	Low risk	“identically packaged study patches were dispensed, and all participants and study personnel were unaware of the study assignments”
Incomplete outcome data (attrition bias) All outcomes	Low risk	981/1050 participants provided data at delivery; participants missing data counted as smokers

Cooney 2009

Methods	<p>Country: USA</p> <p>Recruitment: community volunteers and referrals from substance abuse clinic</p>
Participants	<p>96 alcohol-dependent tobacco smokers (≥15 cpd)</p> <p>25% F, av.age 45, av.cpd 25, motivated to quit, av.FTND 6, 31% veterans</p>

Cooney 2009 (Continued)

Interventions	1. Nicotine patch (titrated, 21 mg/d for 8 wks, 14 mg/d for 2 wks, 7mg/d for 2 wks) + nicotine gum (2 mg for 24 wks, ad lib but advised 6-20/day) 2. Nicotine patch + placebo gum (doses as above) Level of support: high. 16 individual 1hr weekly outpatient sessions of behavioural alcohol and smoking treatment over 6m
Outcomes	Continuous abstinence at 12m (with 30d grace period immediately following quit date) Validation: CO<10ppm
Notes	New for 2012 update. Used in combinations of NRT Analysis 11.1 only. Funding from National Institute on Alcohol Abuse and Alcoholism and Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"urn randomization computer program that balanced the two groups for history of previous substance use treatment, age, sex, baseline drinks/drinking day and baseline cpd."
Allocation concealment (selection bias)	Low risk	Randomization procedure required participant characteristics to be provided before allocation assigned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind." "Research assistants who collected these data were blind to medication assignment and did not conduct psychosocial treatments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	26 drop-outs at 12m included as smokers; all previously verified as having relapsed

Cooper 2005

Methods	Country: USA Recruitment: community volunteers
Participants	439 female smokers (≥ 10 cpd) Av.age 38, av.cpd 23
Interventions	1. Nicotine gum (2 mg), 10-12 pieces/day recommended, for 9 wks, weaning last 3 wks. 2. Placebo gum Level of support: high. 13x1hr weekly cognitive behavioural group sessions. Reduction

Cooper 2005 (Continued)

	prior to TQD wk 5 (3rd arm tested phenylpropanolamine gum, not included in review)	
Outcomes	PP abstinence at 12m Validation: CO<10ppm (Weight change in quitters was also a primary outcome in the trial)	
Notes	First included as Cooper 2003. Published report from 2007. Sources of support not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Eligible participants ... were randomized”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs not reported, all analyses conducted as ITT. Drop-outs (if any) counted as treatment failures in our analysis

Croghan 2003

Methods	Country: USA Recruitment: multi-centre community volunteers
Participants	1384 smokers (≥15cpd) 58% F, av.age 42, av.cpd 26
Interventions	1. 15 mg/16hr nicotine patch plus 0.5 mg/dose nasal spray, max 5/hr, 40/day, for 6 wks 2. Nicotine nasal spray only 3. Nicotine patch only Level of support: low (advice at each visit, 30-45 mins total)
Outcomes	PP abstinence at 6m Validation: CO
Notes	Does not contribute to main comparison, combination only. Study was funded by the National Cancer Institute; Medication provided by McNeil Consumer Products
Risk of bias	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by Mayo Clinic Co-ordinating Centre
Allocation concealment (selection bias)	Low risk	"Treatment assignment was carried out using a dynamic allocation procedure" which took account of stratification by gender, cpd, yrs smoking, study site
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs reported in detail. 34% of pts completed study. Losses to follow-up similar across groups, treated as non-abstinent

Dale 1995

Methods	Country: USA Recruitment: community volunteers and smoking clinic attenders
Participants	71 smokers stratified according to light, moderate and heavy smoking rates, and motivated to quit. 56% F, av.age 48, av.cpd 26
Interventions	1. 11 mg/24hr nicotine patch 2. 22 mg/24hr nicotine patch 3. 44 mg/24hr nicotine patch 4. Placebo patch for 1 wk followed by 11 or 22 mg patch for 7 wks. Duration of patch use 8 wks. Level of support: high (including 6-day inpatient stay)
Outcomes	PP abstinence at 12m Validation: Blood cotinine
Notes	Does not contribute to main comparison. Contributes to comparison 8 of high and standard dose patch. Study was supported by Lederle Laboratories, Pearl River, NY

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects ... were randomly assigned"

Dale 1995 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	“To blind the subjects, staff, and investigators, each subject simultaneously wore three patches during the 6-day inpatient phase”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apart from one light smoker dropping out from 44 mg group for nicotine toxicity in wk 1, apparently no drop-outs

Daughton 1991

Methods	Country: USA Recruitment: community volunteers at 2 sites
Participants	158 smokers (at least 1 pack cpd) 53% F, av.age 42, av.cpd 33
Interventions	1. Nicotine patch (15cm ² , 4 wks) worn for 16hr/day 2. Nicotine patch (15cm ² , 4 wks) worn for 24hr/day 3. Placebo patch, 4 wks Level of support: unclear & differed between sites
Outcomes	Sustained abstinence at 6m Validation: None after 4 wks (CO at 2-4 wks)
Notes	1 +2 vs 3 in Analysis 1.1. 16 vs 24 hr in Analysis 8.1. Not used in support intensity subgroup analysis. Study was funded by ALZA Corp, Palo Alto, CA, through a contract with the Merrell Dow Research Institute, Cincinnati, OH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“All 158 study-eligible volunteers were randomly assigned”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as “double-blind”; “All of the patches were physically identical in appearance”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs (if any) not reported; included as treatment failures in our analysis; results

Daughton 1991 (Continued)

	presented on an ITT basis
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Daughton 1998

Methods	Country: USA (21 sites) Recruitment: patients at family practices - self referred to study or recruited by physician
Participants	369 smokers (> 20 cpd) Av.age 37, av.cpd 27-30; Pts were variously motivated to quit
Interventions	1. Nicotine patch (21 mg, 16hr, 10 wks with weaning) 2. Placebo patch Level of support: low (Nicoderm Committed Quitters Programme support booklet + follow-up visit 1 wk after quit day)
Outcomes	Sustained abstinence (continuous self reported from quit day) at 12m Validation: CO \leq 8ppm and saliva cotinine < 20mg/mL
Notes	There were differences in quit rates between self referred and physician-selected recruits and between smokers recruited during an illness and at another visit. Study was funded by Marion Merrell Dow Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a random code was generated" for equal numbers of active and placebo within blocks of ten
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Participants were assigned randomly, in a double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses low at 3m (1.1%), 6m (1.6%) and 12m (2.2%). Those lost to follow-up were included as failures

Dautzenberg 2001

Methods	Country: France Recruitment: community volunteers
Participants	433 smokers (excludes 25 from ITT population) 52% F, av.age 39, av.cpd 21

Dautzenberg 2001 (Continued)

Interventions	1. Nicotine lozenge (1 mg, 8-24/day, 6 wks + 6 wks weaning for quitters) 2. Placebo lozenge Level of support: not stated
Outcomes	PP abstinence at 26 wks Validation: CO<10ppm
Notes	Based on published abstract. Study was funded by Novartis Consumer Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind", but no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Higher losses in placebo than active group (44% vs 37%); analyses conducted as ITT counting drop-outs as treatment failures

Davidson 1998

Methods	Country: USA (4 centres) Recruitment: community volunteers in shopping malls (OTC setting)
Participants	802 smokers (>20 cpd) who scored 5+ on a questionnaire assessing motivation. 54% F, av.age 39, av.cpd 29
Interventions	1. Nicotine patch (22 mg, 24hr, for up to 6 wks) 2. Placebo patch Level of support: low (self help book provided. Participants visited mall weekly to obtain patches. CO levels were monitored)
Outcomes	Sustained abstinence at 24 wks (from wk 2) Validation: Expired CO≤8ppm at each weekly visit, but 24 wk quit based on self report
Notes	541/802 did not complete the 6 weekly visits. Study was funded by Elan Pharmaceutical Corporation.

Risk of bias

Davidson 1998 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses were included as failures. 67.5% withdrew before study completion; placebo losses higher than active, but differences not statistically significant

Ehrsam 1991

Methods	Country: Switzerland Recruitment: University (primary care)	
Participants	112 smokers at 2 universities Av.age 26, av.cpd 23	
Interventions	1. Nicotine patch (21 or 14 mg/24hr, 9 wks, tapered) 2. Placebo patch Level of support: high (no counselling)	
Outcomes	Sustained abstinence at 12m (0-3 cigs per wk) Validation: urinary cotinine	
Notes	Study funding not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "doppelblinden" but no further information.

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs included as failures. 36% dropped out of active group, and 55% out of placebo group
Other bias	Unclear risk	Abstinence defined as 0-3 cigs per wk, with CO<12ppm. Relapse defined as ≥ 1 cpd, or ≥ 14 cigs over 2 wks

Etter 2009

Methods	Country: Switzerland Recruitment: community volunteers
Participants	314 adult smokers motivated to quit. 58% M, av.age 43, av.cpd 24, av.FTND 5.5
Interventions	1. Gum pre- and postquit date (4 mg, min. 10/d, 4 wks pre- and 8 wks postquit date) 2. Gum postquit date only (dosage as above, 8 wks postquit date)
Outcomes	Abstinence at 12m for 4 wks (sustained self reported abstinence also recorded but not validated) Validation: cotinine <10ng/mL; secondary test of CO<10ppm as required
Notes	New for 2012 update. Included in pre-cessation Analysis 14.1 only. Choice of outcome has no effect on analysis. Funding from Swiss National Science Foundation. Nicotine gum provided at no charge by Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomization was based on a list of random numbers generated by a computer"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data included as smokers. Similar number of drop-outs in both groups

Fagerstrom 1982

Methods	Country: Sweden Recruitment: smoking cessation clinic
Participants	100 consecutive smokers; 43 referred by physician, 57 applied by phone to SC clinic. 59% F
Interventions	1. Nicotine gum (2 mg) for at least 4 wks 2. Placebo gum for at least 4 wks Level of support: high (individual counselling, average 7.7 sessions)
Outcomes	PP abstinence at 6m Validation: CO
Notes	Study funding source not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"patients were randomly assigned... in blocks of ten"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	"All patients were told that the chewing gum they received contained nicotine"; pts did not know that they were involved in a study. "the experimenter's guess of nicotine or placebo gum was in the direction of better than chance, but not significantly so"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four early drop-outs (3 active, 1 placebo) excluded from analysis; all other drop-outs counted as smokers in final analysis

Fagerstrom 1984

Methods	Country: Sweden Recruitment: general practices and industrial clinics (primary care)
Participants	145 smokers motivated to quit 56% F, av. age 40 years, av. cpd 19 Therapists: 10 Swedish GPs, 3 Swedish industrial physicians
Interventions	1. Short follow-up (advice plus 1 appointment) 2. Long follow-up (advice plus 2 appointments, phone call + letter) 3. Short follow-up plus nicotine gum (2 or 4 mg)

Fagerstrom 1984 (Continued)

	4. Long follow-up plus nicotine gum Level of support: low
Outcomes	Sustained abstinence at 12m (and at 1, 6m) Validation: 15% deception rate detected by expired CO>4ppm in a random subset of claimed non-smokers at 6m. Self reported 12m rates used in MA
Notes	3 & 4 vs 1 & 2 in Comparison 1. 1 vs 2 in Comparison 3.3 Study funding not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Patients were randomly assigned" by birthdate; Pts born 1st-20th received active gum, 21st-31st no gum. Those born on even dates got long follow-up, odd dates short follow-up
Allocation concealment (selection bias)	High risk	Not used.
Blinding (performance bias and detection bias) All outcomes	High risk	Not used.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only pts abstinent at one follow-up were seen again for the next one. All losses counted as failures
Other bias	High risk	Physicians selected for the study were personal acquaintances of the author, and all except one were non-smokers

Fee 1982

Methods	Country: UK Recruitment: smoking cessation clinic
Participants	352 smokers, no other demographic data
Interventions	1. Gum (2 mg) given for 5 wks 2. Placebo gum given for 5 wks Level of support: high (10 group therapy sessions)
Outcomes	PP abstinence at 12m Validation: Blood carboxyhaemoglobin

Notes	Study was supported by LEO Laboratories, Sweden	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	“Allocation was carried out by external staff, using a random selection procedure unknown to the authors”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significantly higher losses from placebo (47.7%) than from active group (36.7%). Losses taken as failures

Fiore 1994A

Methods	Country: USA Recruitment: community volunteers	
Participants	88 smokers (>15 cpd), motivated to quit.	
Interventions	1. Nicotine patch (22 mg/24hr, 8 wks, no weaning) 2. Placebo patch Level of support: high (intensive group counselling)	
Outcomes	PP abstinence at 6m (7 days PP) Validation: CO	
Notes	Reported in same paper as Fiore 1994B. Studies supported by Elan Pharmaceutical Research Corporation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“a pregenerated computer sequence” and stratified by FTQ score
Allocation concealment (selection bias)	Low risk	See above

Fiore 1994A (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ten placebo and 1 active pt failed to complete the NRT course. 25 pts lost to follow-up at 6m were included as failures

Fiore 1994B

Methods	Country: USA Recruitment: community volunteers
Participants	112 smokers (>15 cpd)
Interventions	1. Nicotine patch (22 mg/24hr, 6 wks incl weaning) 2. Placebo patch Level of support: high (8 weekly 10-20 min individual counselling)
Outcomes	PP abstinence at 6m (7 days PP) Validation: CO
Notes	Reported in same paper as Fiore 1994A. Studies supported by Elan Pharmaceutical Research Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a pregenerated computer sequence" and stratified by FTQ score
Allocation concealment (selection bias)	Unclear risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	29% did not complete treatment phase and were included as failures (15 on active patch, 18 on placebo). 36% lost to follow-up, and were included as failures

Fortmann 1995

Methods	Country: USA Setting: community volunteers (telephone recruitment)
Participants	1044 smokers aged 18-65, able to quit for 24hr, and without serious illness. Motivated to maintain abstinence. 42% F, av.age 40, av.cpd 20
Interventions	1. Nicotine gum (2 mg, 1 per hr, at least 10/day and not more than 30/day) 2. Self help materials 3. Nicotine gum plus materials 4. Incentive alone. All groups offered incentive of US\$100 for quitting at 6m. Level of support: low
Outcomes	PP abstinence at 12m Validation: CO<9 ppm/salivary cotinine<20 ng/ml
Notes	Until 2008 only groups 1 and 4 compared. Since the trial was factorial and shows no evidence of interaction, both gum groups now used; 1&3 vs 2&4. The RR is unaltered but CIs narrow. Study was funded by the National Heart, Lung, and Blood Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was stratified by gender and cigarette consumption". No further detail
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3.9% dropped out at 6m, and 6.2% at 12m. Unclear whether drop-outs were included, though disconfirmations were reclassified as smokers.

Garcia 1989

Methods	Country: Spain Recruitment: primary care
Participants	106 adult smokers (excludes 81 not beginning treatment) 65% F, av.age 36, av.cpd 25

Garcia 1989 (Continued)

Interventions	1. Gum (2 mg) for 3-4m 2. Placebo gum for 3-4m Level of support: high (group therapy, 7 sessions over 3m)	
Outcomes	Sustained abstinence at 6m Validation: CO \leq 7ppm	
Notes	Sources of support not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	“La asignación a los grupos de estudio se realizaba aleatoriamente al acudir a la primera entrevista”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind (“doble ciego”)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs reported at 1, 3 and 6m. Analyses appear to be ITT-based, counting drop-outs as failures

Gariti 2009

Methods	Country: USA Recruitment: community volunteers	
Participants	260 light smokers (6-15 cpd) motivated to quit 57% F, av.age 54, av.cpd 11, av.FTND 4	
Interventions	1. Patch (for participants>10 cpd: 21 mg/day for wks1-4, 14 mg/day wks 5-6, 7mg/day wks 7-8; participants \leq 10cpd: 14 mg/day for 6 wks, 7mg/day for wks 7-8) + 9 wks placebo bupropion + 10 wks individualized counselling sessions 2. Patch (dose as above) for 8 wks + 9 wks placebo bupropion + four 5-10min counselling sessions 3. Placebo patch for 8 wks + 9 wks bupropion SR + 10 wks individualized counselling sessions 4. Placebo patch for 8 wks + 9 wks bupropion SR + 4x5-10min counselling sessions Level of support: high	
Outcomes	7d PP at 12m. Validation: CO<10ppm; urinary cotinine <200ng/ml	

Gariti 2009 (Continued)

Notes	New for 2012 update. Used in direct comparison of NRT and bupropion only, pooling 1+2 versus 3+4 Funding: National Institute on Drug Abuse.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized 'urn randomization'
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	Low risk	'double-blind, double-dummy' for medication component. 'Neither the nurses nor the participants knew which of the two formulations contained the active formulation.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data included as smokers. Similar losses to follow-up across both groups

Garvey 2000

Methods	Country: USA Recruitment: community volunteers
Participants	608 smokers, aged>20, smoking>5 cpd. 51% F, av.cpd 23
Interventions	1. 4 mg nicotine gum (recommended 9-15 pieces), weaning from 2m 2. 2 mg nicotine gum, use as 1. 3. Placebo gum All received brief counselling (5-10 mins) at each study visit (1, 7, 14, 30 days, 2, 3, 6, 9, 12m) Level of support: high
Outcomes	Sustained abstinence at 12m (relapse defined as 7+ consecutive days or episodes of smoking) Validation: CO≤8ppm
Notes	4 + 2 mg doses combined in main comparison. 4 mg compared to 2 mg in comparison of doses. Study was funded by National Institute of Drug Abuse and Department of Veterans Affairs. Gum supplied by Marion Merrell Dow
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified by dependence level (high/low) and then allocated "using a randomized, double-blind procedure"
Allocation concealment (selection bias)	Unclear risk	No further detail
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information.
Incomplete outcome data (attrition bias) All outcomes	High risk	Relapsers were included as failures. Drop-out rates not reported

Gilbert 1989

Methods	Country: Canada Recruitment: primary care
Participants	223 patients presenting to primary care doctors and smoking at least 1 cpd (not selected by motivation)
Interventions	1. Support from physician plus offer of nicotine gum prescription (2 mg) 2. Support from physician (no placebo) Level of support: low (enrolment, quit day, offer of 4 support visits, 2 in wk 1, 1m, 2m)
Outcomes	Sustained abstinence at 12m (for 3m) Validation: salivary cotinine
Notes	~30% of gum group did not use any, 14% of support only group did use gum. ~70% attended quit day visit, ~43% attendance for follow-up visits. Study was funded by US National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"physicians were presented with a sealed envelope indicating treatment allocation by the receptionist"; "allocation was balanced within each block of four patients for each physician"

Gilbert 1989 (Continued)

Blinding (performance bias and detection bias) All outcomes	High risk	No placebo gum used. Control group pts could request gum, and physician would decide whether or not to prescribe
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up at 1yr of 91.5%; those lost to follow-up were included as failures
Other bias	Unclear risk	Pts using gum were required to pay for their prescription. Pts claiming abstinence were visited for validation test without being aware this would happen

Glavas 2003a

Methods	Country: Croatia Recruitment: hospital health professionals
Participants	112 healthcare professionals smoking at least 1 cpd. 26% had FTND score 6+. 66% F, av.age 34, av.cpd: 24
Interventions	1. Nicotine patch, 24hr, 25 mg/15 mg/8mg starting dose depending on baseline cpd. 3 wks 2. Placebo patch Level of support: low (visits to pick up patch at 7, 14, 21 days, no details about advice given)
Outcomes	Sustained abstinence (3 or fewer cigs/wk) at 1yr (5yr abstinence also reported, not used in MA) Validation: CO<11ppm
Notes	Study was supported by Novartis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Low risk	"each examinee received a presealed envelope, labeled after random numbering, which contained either 8 transdermal nicotine system patches or matching placebo stickers"

Glavas 2003a (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further detail.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 drop-outs by yr1 and yr5, classified as failures.

Glavas 2003b

Methods	Country: Croatia Recruitment: community volunteers
Participants	160 smokers
Interventions	1. Nicotine patch, 24hr, 25 mg/15 mg/8mg starting dose depending on baseline cpd. 6 wks 2. Nicotine patch, 24hr, 25 mg/15 mg starting dose depending on baseline cpd. 3 wks 3. Placebo patch. 6 wks 4. Placebo patch 3 wks Level of support: low
Outcomes	Abstinence at 6m after EOT Validation: CO<11ppm
Notes	Both durations pooled for main comparison. Study funding information not reported. Author supplied additional details in personal communication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Low risk	"presealed numbered envelopes"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The envelopes were prepared well in advance and the distribution was commissioned to a nurse not taking part in the evaluation process"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Other bias	Unclear risk	Abstinence defined as ≤ 2 cigs per wk.

Glover 2002

Methods	Country: USA Recruitment: community volunteers
Participants	241 smokers (≥ 10 cpd), motivated to quit. 54%F, av.age 42, av.cpd 29
Interventions	1. Nicotine sublingual tablet (2 mg). Recommended dosage 1 tab/hr for smokers with FTND <7 , 2 tabs/hr for scores ≥ 7 . After 3m treatment, tapering period of 3m if necessary 2. Placebo tablet Level of support: high (brief counselling at all visits 1, 2, 3, 6 wks, 3, 6, 12m)
Outcomes	Sustained abstinence at 12m Validation: CO <10 ppm
Notes	Study was funded by Pharmacia & Upjohn.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	"subjects were sequentially randomized"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All tablets were identical in appearance... each placebo tablet contained 3 μ g of capsaicin to mimic the oral effects of nicotine and to maintain blinding"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up included as failures. Drop-out rates not reported

Goldstein 1989

Methods	Country: USA Recruitment: community volunteers
Participants	89 smokers (excluding 18 early treatment drop-outs not included in results)
Interventions	Factorial design of 2 types of group treatment, and 2 schedules for use of nicotine gum. Behaviour therapy arms collapsed 1. Fixed schedule nicotine gum (2 mg); 1 piece/hr for 1st wk with tapering over 10 wks 2. Ad lib nicotine gum; to be used when urge to smoke, max 30/day Level of support: high (10x1hr sessions of either intensive cognitive and behavioural skills training or non-specific education and support)

Goldstein 1989 (Continued)

Outcomes	PP abstinence at 6m Validation: Saliva cotinine<10ng/ml or CO<8ppm for people still using gum	
Notes	Does not contribute to main comparison. Used in comparison of fixed to ad lib schedule gum. Study was funded by American Cancer Society and National Heart, Lung, and Blood Institute	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	“each subject was assigned”
Blinding (performance bias and detection bias) All outcomes	High risk	Not relevant; placebo gum not used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 early drop-outs (16.8%) not included. Drop-out rate by EoT was 7.9%, by 6m 3.4%; losses included as failures
Other bias	Unclear risk	Each pt paid US\$130 at start of study, of which they recovered \$30 for supplying follow-up information

Gourlay 1995

Methods	Country: Australia Recruitment: community volunteers	
Participants	629 smokers (>15 cpd) who had relapsed after transdermal nicotine and behavioural counselling in an earlier phase of the study. Minimal additional support	
Interventions	1. Nicotine patch 30cm ² (21 mg/24 hr) for 4 wks, 20cm ² (14 mg/24hr) for 4 wks, 10cm ² (7mg/24 hrs) for 4 wks. 2. Placebo patch	
Outcomes	Sustained abstinence at 6m Validation: expired CO<10ppm	
Notes	Does not contribute to main comparison. Test of patches vs placebo in recently relapsed smokers. Results given in text.	

Gourlay 1995 (Continued)

	Study was funded by Ciba-Geigy Australia, the Anti-Cancer Council of Australia and the Victorian Health Promotion Foundation	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	“Subjects were randomised”
Blinding (performance bias and detection bias) All outcomes	Low risk	Pts invited at wk 11 to guess their assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs at each stage reported in full. Losses to follow-up included as failures

Gross 1995

Methods	Country: USA Recruitment: community volunteers	
Participants	177 smokers 51% F, av. age 42, av.cpd 33, av. FTND 7.8	
Interventions	1. Nicotine gum (2 mg), tapered from wk 12. Active gum groups further randomized to chew 7, 15 or 30 pieces of gum. 2. No gum Level of support: high (1 pre-quit group counselling session, 14 clinic visits in 10 wks)	
Outcomes	Continuous abstinence at 6m (up to 3 cigs allowed) Validation: CO≤10ppm. Saliva thiocyanate in wk 2.	
Notes	No placebo. Long-term abstinence rates not affected by amount of gum, so these groups collapsed for comparison with no gum condition. Study was funded by National Institute of Drug Abuse, and supported by Marion Merrell Dow	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.

Gross 1995 (Continued)

Allocation concealment (selection bias)	Unclear risk	“Random assignment”, stratified by dependence measures.
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Relapsers or non-quitters included as failures.

Hall 1985

Methods	Country: USA Recruitment: community volunteers and physician referrals
Participants	120 smokers (77 in arms contributing to MA) 47% F, av. age 38, av.cpd 31
Interventions	1. Intensive behavioural treatment (14 group sessions over an 8 wk period) 2. Combined - 2 mg nicotine gum (period of use not specified) and intensive behavioural treatment 3. Low contact behavioural treatment (4 meetings over 3 wks) and 2 mg gum Level of support: high
Outcomes	Abstinence at 12m Validation: CO<10ppm and blood thiocyanate<85 mg/mL.
Notes	No placebo. 2 vs 1 in main comparison. 3 not used in MA. Quit rate higher than arm 1. Study was funded by National Institute of Drug Abuse and Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	“Subjects were randomly assigned within time constraints to one of the three treatment conditions”
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo; no blinding.

Hall 1985 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs reported.
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Hall 1987

Methods	Country: USA Recruitment: community volunteers
Participants	139 adult smokers 47% F, av.age 39, av.cpd 30
Interventions	2x2 factorial trial of gum and behavioural support 1. Nicotine gum (2 mg) up to 12m 2. Placebo gum up to 12m Both levels of behavioural support classified as high intensity & collapsed in analysis (both group-based, 14x75 min sessions, or 5x60min sessions)
Outcomes	PP abstinence at 12m Validation: CO<8ppm & serum thiocyanate<95 mm/l
Notes	Study funded by National Institute of Drug Abuse and Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"Within their time constraints, subjects were randomly assigned to 5-6 member groups across conditions"
Blinding (performance bias and detection bias) All outcomes	Low risk	Group leaders blinded to gum use. Leaders and pts tried to guess assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates reported, but no detail.

Hall 1996

Methods	Country: USA Recruitment: community volunteers
Participants	207 smokers of which 6 excluded from analyses because of protocol breaches 52% F, av.age 40, av.cpd 24

Hall 1996 (Continued)

Interventions	2x2 factorial trial of gum and psychological treatment 1. Nicotine gum (2 mg) for 8 wks, 1 piece/hr for 12 hrs/day recommended 2. Placebo gum, same schedule Both levels of behavioural support classified as high intensity & collapsed in analysis (both group-based, 10 sessions over 8 wks, TQD session 3)
Outcomes	Sustained abstinence at 12m (abstinent at all assessments) Validation: CO \leq 10ppm at 8, 12, 26 wks and urinary cotinine \leq 60ng/ml at 52 wks
Notes	Psychological treatment arms collapsed, no evidence of a significant interaction. Study was funded by National Institute of Drug Abuse and Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"Patients were stratified according to depression history and number of cigarettes smoked per day; they were then randomly assigned from within stratified blocks"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six pts excluded from analyses for protocol violations. No further information on drop-outs

Hand 2002

Methods	Country: UK Recruitment: hospital in- or outpatients referred by hospital doctor
Participants	245 patients with smoking-related disease. 46% M, typically aged 50+, smoking 15+ cpd; Pts were motivated to try and quit
Interventions	1. Nicotine patch (initially 30 or 20mg based on smoking rate) and inhaler for 3 wks including patch tapering. Same counselling as control 2. Individual counselling, 4 sessions in 4 wks. No placebo Level of support: high

Outcomes	Sustained abstinence at 12m (abstinent at all assessments) Validation: CO<10ppm
Notes	No placebo. Compliance with NRT was low, 28% did not use, 30% used full supply. Used in main comparisons and comparison 9, combination. Study was funded from one author's endowment fund.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	High risk	"randomised, according to month of entry"; unequal months, with imbalance in favour of NRT group
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo, so not applicable.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates not reported, but all included in analyses.

Harackiewicz 1988

Methods	Country: USA Recruitment: primary care (University Health Centre)
Participants	197 smokers (151 used in MA), motivated to quit. 63% F, av.age 36, av.cpd 26
Interventions	1. Nicotine gum (2 mg, 6 wks initial supply, suggested tapering after 3m, available for 6m) plus self help manual 2. Self help manual 3. Control (booklet) Level of support: low (single appointment with doctor or nurse, length not specified)
Outcomes	Sustained abstinence at 12m Validation: CO in all subjects, cotinine and carboxyhemaglobin in a subsample of subjects
Notes	No placebo. Arm 3 not included in MA control group - it had a lower quit rate so inclusion would increase the gum treatment effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"randomly assigned to one of three conditions"
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo, so not applicable; but researchers were blinded to treatment condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% of pts did not return for any follow-up, and were not included in the analyses. Remaining 175 included in all analyses, whether or not they attended all follow-ups

Hays 1999

Methods	Country: USA (3 sites) Recruitment: community volunteers
Participants	958 smokers, >15 cpd, motivated to quit. 50% F, av. age 44, typically smoked 21-40 cpd
Interventions	1. Nicotine patches (22 mg, 24hr for 6 wks) purchased by participants, open label 2. Nicotine patches (22 mg, 24hr for 6 wks) provided, double blind 3. Placebo patches provided The intervention replicated an OTC environment, with no counselling intervention and minimal study recording. Weekly visits required for CO measurement & adverse experience recording, but study sites were not in medical centres and there was no advice, counselling or interaction with medical personnel. Level of support: low
Outcomes	Abstinence at 6m (7 day PP) Validation: CO ≤ 8ppm
Notes	1 & 2 vs 3 in patch vs placebo comparisons 2 vs 1 in free versus paid comparison (Comparison 12.1). Study was supported by Elan Pharmaceutical Research Corp.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated random schedule"

Hays 1999 (Continued)

Allocation concealment (selection bias)	Low risk	2-stage process. 1. random allocation to 1 of 2 trials, i.e. open-label pay trial or placebo-controlled. 2. Those in placebo trial were then assigned "by means of a computer-generated code, in blocks of 20"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The randomization code was not revealed to any of the investigators until completion of the study." Packaging identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Pts who missed follow-up visits classified as failures. Drop-out rates not reported

Herrera 1995

Methods	Country: Venezuela Recruitment: community volunteers
Participants	322 smokers >10 cpd, scoring ≥ 4 on FTND, no serious illness. Only those who were ready to quit after 4 wks of behavioural treatment were randomized. 43% F, av.age ~38, av. cpd 33 for high dependence, 16 for low dependence
Interventions	Low dependence smokers (FTND 4-6): 1. 2 mg nicotine gum 2. Placebo gum High dependence smokers (FTND 7-11): 1. 4 mg nicotine gum plus 2. 2 mg nicotine gum Level of support: high for all (12 group sessions over 6 wks + 6 weekly maintenance sessions) Participants also randomized to starting medication with increasing dose for 1 wk before TQD, or to start at full dose on TQD - there was no blinding for this
Outcomes	Sustained abstinence at 2yrs (1yr also reported) Validation: expired CO<6ppm
Notes	Low dependence smokers included in comparison 1. High dependence smokers in comparison 2, 4 mg vs 2 mg gum. Relapse between 1 & 2 yrs similar between low dependence groups. Higher relapse in 4 mg high dependence than 2 mg. No information on support or funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Herrera 1995 (Continued)

Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	Stratified on dependency scores, to determine dosage. Then “randomly assigned”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	68 pts dropped out in Phase 1 (wks 1-2) and 10 pts in Phase 2 (wks 4-6), i.e. before randomization. Drop-out rates not reported, but classified as relapsed “and not further analyzed”

Hilleman 1994

Methods	Country: USA Recruitment: community volunteers
Participants	140 smokers (excluding a buspirone treatment group), smoking >20/day, FTND ≥ 8 55%F, av.age 46, av.cpd 25-26
Interventions	1. Nicotine patch (21 mg/24hr) for 6 wks, no weaning 2. Nicotine patch, 21 mg 4 wks, weaning to 14 mg 4 wks, 7mg 4 wks Level of support: high (12 weekly behaviour therapy sessions), does not contribute to intensity subgroup comparison
Outcomes	Abstinence at 6m Validation: Plasma thiocyanate
Notes	Does not contribute to main comparison. Contributes to both tapering versus no tapering and length of treatment comparisons. No information on support or funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	“open-label, randomized”
Blinding (performance bias and detection bias)	High risk	Not relevant.

Hilleman 1994 (Continued)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The number of patients discontinuing therapy among the three treatment groups was not significantly different"; analyses included all randomized

Hjalmarson 1984

Methods	Country: Sweden Recruitment: smoking cessation clinic.
Participants	206 smokers 56% F, av. age 42, av. cpd 24
Interventions	1. Nicotine gum (2 mg) (no restrictions on amount or duration of use) 2. Placebo gum Level of support: high (6 group sessions in 6 wks)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	No information on support or funding.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	26 groups "were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Low risk	Both therapists and nurse distributing gum were blinded to assignment of groups. Placebo gum was flavoured with capsaicin to mimic nicotine
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three drop-outs from each cohort during follow-up; they were counted as smokers. Three more from each cohort relapsed and were re-treated, but counted as smokers within the study

Hjalmarson 1994

Methods	Country: Sweden Recruitment: smoking cessation clinic
Participants	248 smokers 57% F, av.age 45, av. cpd 22
Interventions	1. Nicotine nasal spray (0.5 mg/spray) used as required up to 40mg/day for up to 1yr. 2. Placebo spray Level of support: high (8x45-60 min group sessions over 6 wks with clinical psychologist)
Outcomes	Sustained abstinence at 12m Validation: CO<10ppm
Notes	Study was supported by Kabi Pharmacia AB, Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"Subjects ... were randomized" to 26 groups.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Procedure was blind to both subject and therapist", but where more than one household member was enrolled all members got the same treatment (6 couples thus affected, 3 in active and 3 in placebo). At 12m, 60% of responders correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	By 12m, 20% had relapsed.

Hjalmarson 1997

Methods	Country: Sweden Recruitment: smoking cessation clinic
Participants	247 smokers (>10 cpd) who had previously made a serious attempt to stop using nicotine gum, and were motivated to quit. 64% F, av.age 48, av.cpd 21
Interventions	1. Nicotine Inhaler (recommended minimum 4/day, tapering after 3m, use permitted to 6m) 2. Placebo inhaler

Hjalmarson 1997 (Continued)

	Level of support: high (8 group meetings over 6 wks)	
Outcomes	Sustained abstinence at 12m Validation: CO<10ppm at 2 and 6 wks and 3, 6, 12m.	
Notes	Study was funded by Pharmacia & Upjohn, Sweden.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“All numbers were on a list for random allocation to medication”
Allocation concealment (selection bias)	Low risk	Pts received “a subject number consecutively” at the first group session
Blinding (performance bias and detection bias) All outcomes	Low risk	“The randomization was blinded to both the participant and the therapist”, but members of the same household received the same treatment. At 12m follow-up, 86% of the active group and 90% of placebo group correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and relapsers all counted as failures. Details fully reported

Huber 1988

Methods	Country: Germany Recruitment: community volunteers
Participants	225 smokers (109 contribute to MA) No demographic information
Interventions	1. Nicotine gum alone 2. Behaviour therapy, 5 weekly group meetings 3. Nicotine gum (no details of dose) and behaviour therapy Level of support: high 4. 6m waiting list control
Outcomes	Abstinence at 12m Validation: none
Notes	3 vs 2 in comparison 1. No placebo. Quit rates derived from graphs. The nicotine alone group was not used in the MA; quit rates were higher than intervention 2. Study funding and support not reported.

Huber 1988 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated.
Allocation concealment (selection bias)	Unclear risk	"225 interested subjects ... were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% had dropped out after 1yr.

Hughes 1989

Methods	Country: USA Recruitment: primary care	
Participants	315 daily smokers, motivated to quit. 56% F, av. age 37, av.cpd 29	
Interventions	1. Nicotine gum (2 mg for 3-4m) 2. Placebo gum Level of support: low (29-35 min at 1st visit including nurse & physician advice, & materials, follow-up appointment 1-2 wks later)	
Outcomes	Sustained abstinence at 12m Validation: salivary cotinine<15ng/mL or thiocyanate<1.6mmol/L	
Notes	Time spent at 1st visit is marginal for inclusion in low intensity support category. Study was funded by National Institute on Drug Abuse; gum supplied by Merrel-Dow Research Institute	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A 4th random digit (1-9) was added to their 3-digit subject ID number. Only exception was members of same household got the same treatment

Hughes 1989 (Continued)

Allocation concealment (selection bias)	Low risk	2:1 randomization scheme. "Subjects were assigned randomly in a double-blind manner"
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacists dispensed gum from numbered bins, and were unaware of assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and lost to follow-up were included as smokers. Full details of losses reported

Hughes 1990

Methods	Country: USA Recruitment: community volunteers
Participants	78 smokers, motivated to quit. 54% F, av.age 34-44, av.cpd 24-30
Interventions	1. Placebo gum 2. 1 mg nicotine gum (unbuffered formula, available dose approx 0.5 mg) 3. 2 mg nicotine gum 4. 4 mg nicotine gum Gum use not recommended for longer than 3m Level of support: low (similar to Hughes 1989)
Outcomes	Sustained abstinence at 6m Validation: Independent observer report
Notes	2+3+4 vs 1 in Comparison 1. Excluding the lowest dose would increase the treatment effect. 4 vs 3 in Comparison 2, low dependence smokers. Study was funded by National Institute on Drug Abuse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"Subjects were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"in a double-blind manner"; subjects guessed which group they had been assigned to

Hughes 1990 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Subjects unable to be contacted were counted as smokers". Losses not reported
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Hughes 1991

Methods	Country: USA Recruitment: primary care patients
Participants	106 smokers, motivation to quit not required. 52% F, av.age 38, av.cpd 26
Interventions	1. Free prescription for nicotine gum for up to 6m 2. Nicotine gum at cost of US\$6/box (96 pieces 2 mg) 2. Nicotine gum at US\$20/box All participants received brief physician advice with 1 follow-up
Outcomes	Abstinence at 6m Validation: observer verification of all 6m quitters
Notes	Tested effect of price on gum use and efficacy. Results given in text, not included in any MA. Study was funded by National Institute on Drug Abuse, and supported by Merrell-Dow Research institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	"Physician opened a sealed envelope" which assigned to a price group
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blind, as described above. But physicians knew how much each pt paid, and therefore which group they were in, so could have managed them differently ("no anecdotal evidence that this occurred")
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses at 6m reported; all were counted as failures, but distribution across the groups not reported

Hughes 1999

Methods	Country: USA (12 sites), Australia (1 site) Recruitment: community volunteers & referrals
Participants	1039 smokers (≥ 30 cpd) who had made a prior quit attempt, motivated to try again 50% M, av.age 43, av.cpd 38
Interventions	1. 42 mg nicotine patch (24hr, 6 wks + 10 wks tapering) 2. 35 mg nicotine patch 3. 21 mg nicotine patch 4. Placebo patch Level of support: high (group behaviour therapy for 7 wks, brief individual counselling at 5 dose tapering meetings. Self help booklet)
Outcomes	Prolonged abstinence at 6m (from 2 wks postquit) verified at each follow-up visit. (12m follow-up only completed for 11/13 sites) Validation: CO \leq 10ppm
Notes	All doses pooled in Analysis 1.1 against placebo. 44 mg vs 22 mg in Analysis 7.1 6m abstinence rates used in analyses since not all centres completed 12m follow-up due to sponsor termination of study. Denominators confirmed by author. Study was funded by National Institute on Drug Abuse, ALZA and Hoechst Marion Roussel

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"Subjects were randomly assigned in a double-blind manner"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind" but no further detail.
Incomplete outcome data (attrition bias) All outcomes	High risk	Early termination by sponsor, resulting in incomplete long-term follow-up data collection. Losses were included as failures

Hughes 2003

Methods	Country: USA Recruitment: community volunteers
Participants	115 smokers with a history of alcohol dependence, motivated to quit, ≥ 30 cpd 68% M, av.cpd 30

Hughes 2003 (Continued)

Interventions	1.Nicotine patch (21 mg, 24hr, 6 wks + 4 wks tapering + 2 wks placebo) 2. Placebo patch 12 wks Level of support: high (Group behaviour therapy x 6, brief individual counselling x3)
Outcomes	Sustained abstinence at 6m (from 2 wks postquit) Validation: CO \leq 10ppm at each follow-up visit
Notes	Unadjusted ORs used in MA not significant, significant when adjusted for smoking variables. Study was supported by GlaxoSmithKline, and funded by National Institute on Drug Abuse

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"Subjects were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"we assumed that missing data indicated smoking". Losses reported, but not distribution across groups

Hughes 2010

Methods	Country: USA Recruitment: community volunteers
Participants	746 smokers of \geq 15cpd, wanting to quit gradually 54% F, av.age 48, av.cpd 23, av.FTND 5.9
Interventions	1. Gradual cessation: 2 or 4 mg lozenges according to recommended labelling (4 mg for those who smoked within 30min of waking, 2 mg for everyone else) for 3 wks pre-cessation and 12 wks post-cessation; instructions to cut down cpd gradually pre-quit date; 5 counselling sessions 2. Abrupt cessation: 2 or 4 mg lozenges according to dosage instructions above for 12 wks post-cessation; 5 counselling sessions 3. Minimal intervention: 2 or 4 mg lozenges according to dosage instructions above for 12 wks post-cessation; 2 short counselling sessions Level of support: high. Gradual: 4 calls pre- and 1 call postquit date; abrupt 2 calls pre- and 3 calls post; minimal intervention: 1 pre-, 1 postquit date

Hughes 2010 (Continued)

Outcomes	6m sustained abstinence Validation: CO<10ppm
Notes	New for 2012 analysis. 1 and 2 used in pre-cessation Analysis 14.1; 3 does not contribute to review. Study of gradual cessation aided by NRT vs abrupt cessation with NRT use from quit date. pre-cessation NRT may be confounded with other gradual cessation techniques Funding provided by US National Institute on Drug Abuse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"upon receipt of consent, our statistician generated a concealed allocation sequence and randomized participants...using blocked randomization (stratified by city and counsellor)"
Allocation concealment (selection bias)	Low risk	Allocation unknown until consent obtained
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo. "All follow-ups... were collected via phone by research assistants who were blind to study condition and had no role in the intervention."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number lost to follow-up in both groups. Missing data counted as smokers
Other bias	High risk	"Counseling time in the gradual condition was spent mostly on teaching gradual reduction, not on problem-solving ways to cope with high-risk-for-smoking situations"

Hurt 1990

Methods	Country: USA Recruitment: community volunteers
Participants	62 adult smokers (>20 cpd); only accepted if willing to make a quit attempt. 53% F, av.age 39, av.cpd 30
Interventions	1. Nicotine patch (30mg 24hrs, 6 wks + option of further 12 wks +/- tapering) 2. Placebo patch (continuing smokers at 6 wks were offered active patch) Level of support: high (brief advice from nurse co-ordinator at 6 weekly visits)

Hurt 1990 (Continued)

Outcomes	Sustained abstinence at 12m (quit by wk 6, & all subsequent visits) Validation: CO≤8ppm	
Notes	Study was in part supported by Elan Pharmaceutical Research Corporation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	“subjects were assigned randomly”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated; initial double-blind was broken after 6 wks of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 drop-outs from each group in first 6 wks; smoking status of all drop-outs ascertained “at last contact”. Early drop-outs were excluded from later analyses

Hurt 1994

Methods	Country: USA Recruitment: community volunteers	
Participants	240 adult smokers (>20 cpd), motivated to quit. 53% F, av.age 43, av.cpd 30	
Interventions	1. Nicotine patch (22 mg/24hr, 8 wks, no tapering) 2. Placebo patch Level of support: high (nurse counselling at 8 weekly visits, weekly phone calls to wk 12)	
Outcomes	Abstinence at 12m (no puff since 9m visit) Validation: CO≤8ppm	
Notes	Study was supported by Lederle Laboratories, NY.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Hurt 1994 (Continued)

Allocation concealment (selection bias)	Unclear risk	“subjects were randomly assigned to active or placebo patches”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind; no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	“subjects with missing information or who dropped out... were considered to be smoking”. Drop-out rates and reasons fully reported

ICRF 1994

Methods	Country: UK Setting: primary care (19 general practices)
Participants	1686 smokers (>15 cpd), not necessarily motivated to quit. 55% F, av.age 43, av.cpd 24
Interventions	1. Nicotine patch (21 mg/24hr, 12 wks incl tapering) 2. Placebo patch Level of support: high (brief advice from nurse at 4 study visits)
Outcomes	Sustained abstinence at 12m (from wk 1) Validation: Salivary cotinine or CO
Notes	8yr follow-up in Yudkin 2003, OR remained similar. Study supported by Ciba-Geigy Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	“prior random allocation of study numbers to each intervention group and by sequential allocation of a study number to patients on entry”
Blinding (performance bias and detection bias) All outcomes	Low risk	Pts and nurses blinded to patches but not to support materials. Pts invited to guess assignment at end of treatment

ICRF 1994 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Disconfirmations and drop-outs counted as smokers
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Jamrozik 1984

Methods	Country: UK Recruitment: primary care (6 general practices)
Participants	200 adult smokers who had failed to stop smoking during a previous study of the effect of physician advice No demographic information
Interventions	1. Nicotine gum (2 mg) for 3m+ 2. Placebo gum Level of support: low (follow-up visits at 2, 4, 12 wks for data collection, no counselling reported)
Outcomes	PP abstinence at 6m Validation: expired CO \leq 12ppm
Notes	Study was funded by Oxford District Research Committee and Nuffield Dominions Trust, and supported by Lundbeck Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The codes were balanced to give equal numbers of patients receiving either the active gum ... or a placebo"
Allocation concealment (selection bias)	Low risk	"allocated to next available of ten alphabetical codes" from lists held in each practice
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatments were "identical in appearance and packaging". "No one doctor or member of staff was likely to see sufficient numbers of patients to be able to break the 10 code system"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up included as failures.

Jarvis 1982

Methods	Country: UK Recruitment: smoking cessation clinic
Participants	116 clinic attenders, motivated to quit. 55% F, av.age 41/38, av.cpd 31/27 (P<0.05)
Interventions	1. NicotineU gum (2 mg) unrestricted amount for at least 3m 2. Placebo gum (1 mg unbuffered nicotine) Level of support: high (group therapy 6x1hr weekly)
Outcomes	Sustained abstinence at 12m (6m & 12m PP) Validation: CO (small number by confirmation from friend/relative only)
Notes	The placebo gum was intended to match the active gum in taste but deliver minimal amounts of nicotine. Study was funded by Medical Research Council and Dept of Health and Social Security, and supported by AB Leo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"treated in groups of about ten, taken in order from the waiting list"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Therapists and subjects were blind to the allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One subject lost to follow-up counted as a failure
Other bias	High risk	"Placebo" patch contained nicotine

Jensen 1991

Methods	Country: Denmark Recruitment: smoking cessation clinic
Participants	293 adult smokers (>10 cpd) in relevant arms 54% F, av. age 42, av.cpd 21-22
Interventions	1. Nicotine gum (2 mg for 3m) 2. Silver acetate chewing gum (not used in MA) 3. Standard chewing gum

Jensen 1991 (Continued)

	Level of support: high (9 group meetings over a year, weekly to wk 4)	
Outcomes	Sustained abstinence at 12m Validation: CO	
Notes	12m data reported in Thorax 1990 paper, used from 2008. Sources of support not stated.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	“smokers were randomised to 24 smaller groups and each group was randomly allocated to treatment”. No further information
Blinding (performance bias and detection bias) All outcomes	High risk	“The study was not blind”, because of restrictions on use of silver acetate gum
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21 trial-wide losses reported, but not included in the analyses. Distribution not stated, so not possible to include those lost to follow-up in the final denominator

Jorenby 1995

Methods	Country: USA Recruitment: community volunteers
Participants	504 adult smokers (≥ 15 cpd) 53% F, av.age 44, av.cpd ~27
Interventions	1. Nicotine patch 22 mg for 6 wks then 2 wks 11 mg with minimal counselling 2. Same patch, individual counselling 3. Same patch, group counselling. 4. 44 mg patch for 4 wks then 2 wks 22 mg then 2 wks 11 mg with minimal counselling 5. Same patch, individual counselling 6. Same patch, group counselling.
Outcomes	Abstinence (>1 wk) at 6m Validation: CO<10ppm

Jorenby 1995 (Continued)

Notes	Does not contribute to comparison 1. Support levels collapsed in comparison 8 between high and standard dose. Study was funded by Elan Pharmaceutical Research Corporation	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	“randomly assigned”; “All participants were also randomly assigned to one of the three types of counselling”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	“in a double-blind manner” for wks 1-4, then open-label for wks 5-8
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses reported, but included as failures.

Jorenby 1999

Methods	Country: USA (4 sites) Recruitment: community volunteers
Participants	893 smokers, motivated to quit, (>15 cpd) 52% F, av.age 42-44, av.cpd 25-28
Interventions	1. Nicotine patch (21 mg/24hr for 6 wks, tapered for 2 wks) and sustained release bupropion 300mg for 9 wks from 1 wk before quit day 2. Bupropion 300mg and placebo patch 3. Nicotine patch and placebo tablets 4. Placebo patch and placebo tablets Level of support: high, <15 min individual counselling session at each weekly assessment. One phone call 3 days after quit day
Outcomes	Abstinence at 12m (primary outcome for study was PP abstinence; this analysis uses continuous abstinence since quit day) Validation: Expired CO<10ppm at each clinic visit
Notes	3 vs 4 in main analyses. NRT vs bupropion in Analysis 16.1 and as adjunct to bupropion in Analysis 16.2. Bupropion as adjunct to NRT no longer assessed in this review. Study was funded by Glaxo Wellcome.
<i>Risk of bias</i>	

Jorenby 1999 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	"subjects were randomly assigned to one of four treatments with use of an unequal-cell design... Randomization was not balanced within sites"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Medications were identical, but other blinding procedures not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	311 discontinued treatment, with 177 withdrawing completely from the trial. Full details reported. All were included in ITT analyses with losses to follow-up counted as smokers

Joseph 1996

Methods	Country: USA, multicentre trial Recruitment: 10 Veterans Affairs Medical Centers
Participants	584 smokers (>15 cpd) with a history of cardiac disease. Patients with cardiac events within the last 2 wks were excluded
Interventions	1. Nicotine patch, (21 mg/24hr for 6 wks, 14 mg for 2 wks, 7mg for 2 wks) 2. Placebo patch Level of support: High (self help pamphlets and brief behavioural counselling on 3 occasions)
Outcomes	PP abstinence at 6m (Joseph 1996), 12m (Joseph 1999) Validation: CO \leq 10ppm
Notes	Study was funded by Hoechst Marion Roussel.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated schedule" at the Minneapolis VAMC Co-ordinating Center
Allocation concealment (selection bias)	Unclear risk	Pts were randomly assigned in blocks of ten

Joseph 1996 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses and withdrawals fully reported, as primary and secondary endpoints

Kalman 2006

Methods	Country: USA Recruitment: Veterans Admin Medical Centre and community-based substance abuse treatment facility
Participants	130 smokers (≥ 20 cpd with history of alcohol dependence & ≥ 2 m abstinence from alcohol & illicit drugs) 84%M, av.age 47, av.cpd 32
Interventions	Dose response trial 1. Nicotine patch (42 mg (2x21 mg)) 4 wks, then tapered for 8 wks 2. Nicotine patch (21 mg & placebo) for 4 wks then same tapering as 1. (Level of support: high (5x1hr weekly group counselling sessions, 2 before TQD))
Outcomes	Abstinence at 36 wks (26 wks post EOT) (7 day PP) Validation: CO<10ppm
Notes	New for 2008 update. Study was funded by National Institute on Drug Abuse.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	"pts were randomly assigned".
Blinding (performance bias and detection bias) All outcomes	Unclear risk	double-blind for 4 wks, then open-label dose tapering phase.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 dropped out before treatment, and 4 excluded for protocol violation. Analyses were ITT, with drop-outs reported and counted as failures

Killen 1984

Methods	Country: USA Recruitment: community volunteers
Participants	64 adult smokers 72% F, av.age 44, av.cpd 32
Interventions	1. Nicotine gum (2 mg) for 7 wks 2. Skills training 3. Skills training plus nicotine gum Level of support: high (group therapy)
Outcomes	Sustained abstinence at 10.5m Validation: CO
Notes	1+3 vs 2 used in comparison. 3 vs 2 would increase effect. Study was funded by the National Institute of Health, and supported by Merrell-Dow Pharmaceuticals Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Pts "were blocked on sex and Fagerström score and assigned randomly to treatment group". "Therapists were assigned randomly to treatment conditions".
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding reported. "Interpretation of this data is hampered by the lack of a placebo control condition." Unclear if therapists aware of gum allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/75 recruited dropped out before full treatment, and are excluded from analyses

Killen 1990

Methods	Country: USA Recruitment: community volunteers who had abstained from smoking for 48 hrs
Participants	1218 adult smokers 52% F, av.age 43, av.cpd 25

Killen 1990 (Continued)

Interventions	1. Nicotine gum (2 mg, 8 wks) ad lib dosing 2. Nicotine gum on a fixed dose 3. Placebo gum 4. No gum Each group was also factorially randomized to 1 of 3 psychological interventions (all high support)
Outcomes	PP abstinence at 12m (7 day PP) Validation: cotinine, except participants who moved away
Notes	Quit rates were higher on fixed dose than ad lib gum. Quit rates identical (18%) in placebo and no gum groups at 12m. Study was funded by National Cancer Institute.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	"randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Assignment to gum condition was double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 deaths removed from final analyses. Pts moving out of the area were removed from the analyses. Unconfirmed claims of abstinence counted as smokers

Killen 1997

Methods	Country: USA Recruitment: community volunteers
Participants	424 smokers ~50% F, av.age ~45, av.cpd ~23
Interventions	2x2 factorial design, comparison between video & self help manuals and manuals alone collapsed. 1. Nicotine patch (21 mg/24hr) for 8 wks, 14 mg for 4 wks, 7mg for 4 wks 2. Placebo patch 3. Nicotine patch and video (The video was shown at initial visit and a copy supplied for home use) 4. Placebo patch and video Level of support: low (All treatment groups received a self help treatment manual designed

Killen 1997 (Continued)

	to develop self regulatory skills	
Outcomes	Sustained abstinence at 12m (7 day PP at 6 and 12m) Validation: saliva cotinine<20ng/ml with the exception of participants living outside the area	
Notes	There was evidence of an interaction between NRT and video/self help conditions but this does not alter the MA so the conditions are combined from 2007. Both self help conditions treated as low intensity - classifying video as high intensity would marginally reduce effect in high intensity subgroup. Study was funded by National Heart, Lung, and Blood Institute, and supported by Hoechst Marion Roussel Inc and Blue Shield Management	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	“Pts were randomized to treatment conditions”
Blinding (performance bias and detection bias) All outcomes	Low risk	“Assignment to the patch condition was double-blind”; pts invited to guess assignment at 6m follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pts leaving the area (10) were excluded from analyses; all other unconfirmed claims of abstinence were counted as failures

Killen 1999

Methods	Country: USA Recruitment: community volunteers responding to advertisements - heavy smokers selected from responders
Participants	408 heavy smokers (>25 cpd) 59% M, av.age 47, av.cpd 36, modified FTND score 18
Interventions	1. 25 mg nicotine patch for 6 wks (16hr, no tapering) 2. 15 mg nicotine patch for 6 wks Self help treatment manual, short video showing patch use and placement
Outcomes	Sustained abstinence at 12m (7 day PP abstinence at both 6 and 12m) Validation: Saliva cotinine<20 ng/ml (not required for 3 individuals not in area)

Killen 1999 (Continued)

Notes	Does not contribute to comparison 1. 85% of self reported quitters provided samples for validation at 12m	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	"Smokers ... were randomized"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Assignment to treatment dose was double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Pts leaving the area were excluded from analyses; all other unconfirmed claims of abstinence were counted as failures. Losses fully reported

Kornitzer 1987

Methods	Country: Belgium Recruitment: worksite primary care clinic	
Participants	199 smokers (av cpd 24-5)	
Interventions	1. Nicotine gum (4 mg) for at least 3m 2. Nicotine gum (2 mg) for same time period Level of support: low	
Outcomes	PP abstinence at 12m Validation: cotinine and carboxyhemaglobin in a subsample of subjects	
Notes	Contributes data only to 4 mg vs 2 mg Comparison 2. Sources of funding and support not stated.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	“subjects were randomised”

Kornitzer 1987 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	“in a double-blind way”; blinding was broken at 3m.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses evident in Tables II and IV

Kornitzer 1995

Methods	Country: Belgium Recruitment: worksite volunteers
Participants	374 healthy smokers (>10 cpd for >3yrs), motivated to quit. 61% M, av. age 40, av.cpd 25
Interventions	1. Nicotine patch (12 wks 15 mg/16hr, 6 wks 10mg, 6 wks 5 mg) and nicotine gum (2 mg, as required) 2. Nicotine patch and placebo gum 3. Placebo patch and placebo gum. Level of support: high (nurse counselling)
Outcomes	Sustained abstinence at 12m Validation: CO<10 ppm
Notes	Contributes data to main comparison (2 vs 3) and to patch plus gum vs patch alone comparison. Study was supported by Pharmacia Consumer Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See below
Allocation concealment (selection bias)	Low risk	“randomized list generated by a computer program”. Randomization balanced between companies 2/2/1
Blinding (performance bias and detection bias) All outcomes	Low risk	“The investigator and the subjects were completely blind concerning treatment”. “unblinding was never requested during the whole study”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Withdrawals counted as treatment failures. All analyses conducted on ITT basis. Drop-out and withdrawal rates not reported

Kralikova 2002

Methods	Country: Czech Republic Recruitment: community volunteers 'wanting to reduce'
Participants	314 smokers (≥ 15 cpd) 58% F, av.age 46, av.cpd 25
Interventions	1. Choice of 4 mg nicotine gum (up to 24/day) or 10mg inhaler (6-12 daily) for up to 6m with further 3m tapering 2. Placebo gum or inhaler Common components: brief behavioural cessation/reduction support at clinic visits (9 scheduled)
Outcomes	Sustained abstinence at 12m Validation: CO<10ppm
Notes	Trial also included assessment of reduction. Reduction outcomes contribute to Cochrane review on harm reduction. Study details are taken from a conference abstract. Published 2009 Study supported by Pharmacia CHC, Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind" - no further details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Leischow 1996

Methods	Country: USA Recruitment: community volunteers
Participants	222 smokers (>20 cpd). (2 excluded from analysis having received incorrect prescription) 55% F, av.age 44, av.cpd 26
Interventions	1. Nicotine Inhaler (10mg). Advised to use 4-20 cartridges/day for 3m. After this tapering was encouraged until 6m. 2. Placebo inhaler Participants received advice and watched a video showing proper use of the inhaler. Level of support: high (brief individual smoking cessation support at each study visit,

Leischow 1996 (Continued)

	10 in all)	
Outcomes	Sustained abstinence at 12m Validation: CO<10ppm at each follow-up	
Notes	Study was funded by Pharmacia Upjohn, Sweden.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“the randomization code was generated by computer”
Allocation concealment (selection bias)	Low risk	“subjects were sequentially and randomly assigned”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs reported at 12m visit. Losses to follow-up counted as failures

Leischow 1999

Methods	Country: USA Recruitment: community volunteers
Participants	300 smokers prepared to purchase patch and make a quit attempt 45% F, av.age 43, av.cpd 26
Interventions	1. Nicotine patch (15 mg/16hr) which could be purchased (1 wk supply for US\$15) for up to 26 wks. No behavioural support apart from patch package insert. 2. Nicotine patch for purchase as 1. Prescription for 12 wks provided after physician visit. Prescription renewed on request up to 26 wks. Behavioural support based on NCI guidelines, 5-10 mins. Study staff also allowed to give behavioural support
Outcomes	Continuous abstinence from date of first patch purchase at 12m (non-purchasers counted as failures) (PP rates also reported) Validation: CO<9ppm
Notes	Does not contribute to main comparison. Compared different ways of buying patch - simulating OTC, or with physician prescription and support. Study was funded by DHHS and Arizona Disease Control Commission, and supported by McNeil Pharmaceuticals

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"subjects were randomized"
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding not applicable due to nature of intervention. Use of CO minimizes detection bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs were included as treatment failures, in 1 of 3 analytical approaches, i.e. excluded from protocol completer and patch users analyses. Drop-out rates reported as "high" across both groups, but no further information

Leischow 2004

Methods	Country: USA Recruitment: community volunteers
Participants	520 smokers prepared to purchase inhaler and make a quit attempt 51% F, av.age 48, av.cpd 26
Interventions	1. Nicotine inhaler could be purchased ad lib. Standard package information, no further behavioural support 2. Nicotine inhaler could be purchased ad lib via healthcare provider. Support materials and brief behavioural intervention given at 1st clinic visit and wk 2, av time 8 mins, 47% discussed inhaler use
Outcomes	Continuous abstinence at 12m Validation: CO
Notes	First included as Leischow 2003 based on abstract. Does not contribute to comparison 1. See Leischow 1999. Study was funded by DHHS and supported by Pharmacia & Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated random allocation sequence was created by the study statistician"

Leischow 2004 (Continued)

Allocation concealment (selection bias)	Unclear risk	"Each participant ... was given the next available number"
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding not applicable due to nature of intervention. Use of CO minimizes detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully described in flow chart. Drop-outs included in ITT analyses as treatment failures

Lerman 2004

Methods	Country: USA Recruitment: community volunteers and referrals
Participants	350 smokers (≥ 10 cpd) (includes 51 who withdrew before treatment) 54% F, av.age 46, av.cpd 21
Interventions	1. Nicotine patch (21 mg/24hr) for 8 wks incl tapering 2. Nicotine nasal spray (8-40 doses/day, max 5/hr) for 8 wks, tapering over final 4 wks Level of support: 7x90 min behavioural group counselling sessions. TQD in wk 3
Outcomes	PP abstinence at 6m (Continuous no slips and prolonged lapse-free unvalidated outcomes also reported) Validation: CO<10ppm
Notes	First included 2004 based on Patterson 2003 paper. Minor changes to data using Lerman 2004 in 2008 update. Choice of outcome does not change conclusion of no significant difference. Does not contribute to main comparison, only head-to-head comparison. Study was funded by National Cancer Institute, National Institute on Drug Abuse and National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization scheme", stratified by study site
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Open-label treatment; Outcome assessment "interviewers were blinded to study group assignment"

Lerman 2004 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and withdrawals fully tabulated in Fig 1. ITT analyses confined to those known to have received treatment, with drop-outs included as treatment failures
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Lewis 1998

Methods	Country: USA Recruitment: hospitalised patients willing to make a quit attempt
Participants	185 smokers (≥ 10 cpd), motivated to quit 46% F, av. age 43-44, cpd 23-24
Interventions	1. Minimal intervention, 2-3 mins motivational message and self help pamphlet 2. As 1. plus placebo patch. Nurse provided brief telephone counselling at 1, 3, 6 and 24 wks 3. As 2. plus nicotine patch (22 mg/ 24hrs for 3 wks, tapered to 11 mg for 3 wks) Level of support: low (since initial support was brief and further contacts in 2 were by phone)
Outcomes	PP abstinence at 6m Validation: CO \leq 10ppm
Notes	3 vs 1+2 used in MAs (Restricting control to 2 only would reduce the OR to 1.6). Study was funded by Elan Pharmaceutical Research Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See below
Allocation concealment (selection bias)	Low risk	"using a predetermined computer-generated randomization code"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Both patients and study staff were blinded with respect to patch dose"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates not reported, but analyses count those lost to follow-up as treatment failures

Llivina 1988

Methods	Country: Spain Recruitment: smoking cessation clinic
Participants	216 smokers Av.cpd 28-30
Interventions	1. Nicotine gum (dose not stated) for 1m 2. Placebo gum Level of support: High (group support)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	Reclassified as high support 2008. Study was funded by el Fondo de Investigaciones Sanitarias de la Seguridad Social, la Sociedad Española de Patología Respiratoria, and los Laboratorios PENSA-ESTEVE

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"asignados al azar"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "doble ciego"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs and withdrawals reported (Tabla 2)

Malcolm 1980

Methods	Country: UK Recruitment: community volunteers
Participants	194 smokers 40-43% F, av.age 44-46, av.cpd 25-26
Interventions	1. Nicotine gum (2 mg) at least 10/day for at least 3m 2. Placebo gum 3. Control Level of support: high (weekly individual counselling for 1m)
Outcomes	Sustained abstinence at 6m Validation: venous carboxyhaemoglobin $\leq 1.6\%$

Malcolm 1980 (Continued)

Notes	Study was supported by AB Leo & Company, Helsinborg, Sweden.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	“randomly allocated”
Blinding (performance bias and detection bias) All outcomes	Unclear risk	“The trial was double blind between the gum groups”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only the 1m quitters were followed up at 6m (77/82 pts).
Other bias	Unclear risk	16 pts with dentures who could not chew gum were allocated to Controls but analysed separately

Marshall 1985

Methods	Country: UK Setting: primary care - patients responding to a postcard from a GP (i.e. selected by motivation)	
Participants	200 smokers, motivated to quit; 21% had a smoking-related disease Av. age 41, av.cpd 22	
Interventions	1. Physician advice plus nicotine gum 2. As 1. and offer of 4 follow-up visits over 3m	
Outcomes	Sustained abstinence at 12m (and 6m) Validation: CO	
Notes	Does not contribute to comparison 1. Test of different intensity of support. Study received running expenses and gum from Lundbeck Ltd.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.

Marshall 1985 (Continued)

Allocation concealment (selection bias)	Unclear risk	"Patients were assigned randomly"; married couples were allocated to the same group
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding not applicable due to nature of intervention. Use of CO minimizes detection bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Non-contacts were classified as smokers".
Other bias	Unclear risk	Only smokers abstinent at one timepoint were followed up subsequently

McGovern 1992

Methods	Country: USA Recruitment: community volunteers
Participants	293 adult smokers. Av.cpd not stated. 58% smoked >25 cpd.
Interventions	1. ALA Freedom from Smoking clinic program plus nicotine gum (2 mg for 3m) 2. ALA Freedom from Smoking clinic program alone (no placebo gum) Level of support: high (group)
Outcomes	PP abstinence at 12m Validation: salivary thiocyanate
Notes	Study was supported by Merrell-Dow Pharmaceuticals.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	"Participants were randomly assigned Assignment to condition was by clinic group rather than individual subject"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not relevant, as no placebo gum used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	% response rates at follow-up reported, with no differences between groups

Molyneux 2003

Methods	Country: UK Recruitment: hospital
Participants	274 smokers (182 in relevant arms) admitted to medical and surgical wards, smoked in last 28 days 60% M, av. age 60, median cpd 17, 81% had previous quit attempt
Interventions	1. Choice of NRT products (15 mg 16hr patch/2 mg or 4 mg gum, 10mg inhalator/2 mg sublingual tablet, 0.5 mg spray), Brief (20 min) bedside counselling from a research doctor or nurse. 2. Brief counselling only 3. Usual Care, no smoking advice (not used in MA) Level of support: low
Outcomes	Continuous abstinence at 12m Validation: CO<10ppm
Notes	No placebo. 63% chose patch, 13% inhalator, 11% gum, 8% tablets and 1% nasal spray, 4% declined use. Study was supported by Pharmacia Consumer Healthcare, Sweden

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised ... using a list generated for each centre, allocating equally in random permuted blocks of nine"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not relevant to pts, as NRT group chose their own type. Assessment and delivery blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up counted as failures. All losses fully detailed in flow chart
Other bias	Unclear risk	4% of counselling+NRT group refused NRT, and counselling-only group were advised about NRT but not given it; usage across groups not reported

Moolchan 2005

Methods	Country: USA Recruitment: community volunteers
Participants	120 adolescent (age 13-17) smokers (≥ 10 cpd), motivated to quit. 70% F, av.age 15, av.cpd 19
Interventions	1. Nicotine patch (21 mg, or 14 mg for <20 cpd) for 6 wks +placebo gum 2. Nicotine gum (4 mg, or 2 mg for <24 cpd) for 6 wks + placebo patch 3. Double placebo Level of support: high (11x45-min individual counselling over 12 wks)
Outcomes	PP abstinence at 6m Validation: CO & cotinine
Notes	New for 2008 update Placebo group contributes twice to MA - too small to affect total Sustained abstinence at 3&6m could be derived from text, relative effect greater since no quitters on placebo. Study was funded by National Institute on Drug Abuse, and supported by GlaxoSmithK-line

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized ... according to an algorithm held by the National Institute on Drug Abuse Pharmacy, with true replacement of the non-completers"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind, double-dummy", but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were included as failures for cessation. Losses fully reported

Mori 1992

Methods	Country: Japan Recruitment: hospital
Participants	364 smokers with smoking-related illness. Number of cpd not stated. Motivation to quit probably not required

Mori 1992 (Continued)

Interventions	1. Nicotine gum 2 mg for 3m 2. Placebo gum Level of support: low	
Outcomes	Abstinence (not defined) at 6m Validation: serum thiocyanate	
Notes	“Supported partially by FISs 90/0431 and SEPAR”. Trial report was abstract only	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as “double blind”, but no further information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Nakamura 1990

Methods	Country: Japan Recruitment: community volunteers	
Participants	60 adult smokers. Av. cpd 31	
Interventions	1. Nicotine gum (2 mg, 2m or longer) 2. Non-placebo control group received counselling Level of support: high	
Outcomes	Sustained abstinence at 6m Validation: CO	
Notes	Study was supported by Merrell-Dow Pharmaceuticals.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Nakamura 1990 (Continued)

Random sequence generation (selection bias)	Unclear risk	"Assignment was done ... by individual randomisation based on their screen's numbers [or] by group randomisation by worksite unit". 15 members for Group 3 were chosen from 19 applicants, based on distribution of employment.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Described as an "open controlled trial".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analyses conducted, with all drop-outs and non-compliers included as failures. But "smoking on one or two occasions in a single day was not considered a failure ... although occasional smoking was considered a failure"

Nebot 1992

Methods	Country: Spain Recruitment: primary care
Participants	425 unselected smokers. 60-70% smoking >15 cpd
Interventions	A. Brief counselling from physician B. Physician counselling plus nicotine gum C. Health education from nurse Level of support: low
Outcomes	PP abstinence at 12m Validation: CO
Notes	Study was supported by the Fondo de Investigaciones Sanitarias de la Seguridad Social

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not applicable; "each PCT was randomly allocated to perform the three different interventions successively". No information about avoidance of selection bias
Allocation concealment (selection bias)	Unclear risk	Not stated.

Nebot 1992 (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only those quit at 2m were followed up at 12m. All non-responders were included as failures
Other bias	Unclear risk	Unequal assignments to the 3 groups, with nurse and NRT groups outnumbered 1:2 by the medical advice group

Niaura 1994

Methods	Country: USA Recruitment: outpatient settings and physician referrals (primary care subgroup)
Participants	77 low dependence (FTND \leq 6) and 96 high dependence smokers 50% F, av.age 42, av.cpd 29, FTND 4.7 for low dependence, 8.0 for high dependence
Interventions	1. Nicotine gum 2 mg, ad lib for up to 4m (participants given prescription for gum, not free) 2. No gum Level of support: high (4 individual counselling sessions and ALA self help treatment manuals)
Outcomes	Continuous abstinence at 12m Validation: saliva cotinine, or CO for gum users
Notes	No placebo used. Data collapsed across dependence levels. As predicted by the study, smokers with lower dependence had lower quit rates with than without gum. The OR would be higher (4.40) if inclusion restricted to the high dependence group. Study was supported by National Cancer Institute and National Heart, Lung, and Blood Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pts stratified on level of nicotine dependence. "Within each of the high- and low-dependence groups, subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated.

Niaura 1994 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	No placebo - not relevant. But therapist and pt were blinded to FTQ score (level of dependency), and to match or mismatch status for gum use
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates fully reported.

Niaura 1999

Methods	Country: USA Recruitment: community volunteers
Participants	62 smokers in relevant arms 50% F, av.cpd 28, av.age 43.5
Interventions	1. Brief cognitive behavioral relapse prevention (CBRP) , 15 min sessions 2. Intensive CBRP with nicotine gum (2 mg) 3. Intensive CBRP with cue exposure 4. Intensive CBRP with cue exposure + nicotine gum Level of support: high (5 group sessions within 3 wks of TQD)
Outcomes	Sustained abstinence, 12m and all previous follow-ups (1, 3, 6m) Validation: CO<8ppm
Notes	4 vs 3, behavioural support not identical in others. No placebo. Study was supported by Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Counselors were kept blind to the relapse prevention condition to which subjects were assigned". Pts not blinded, and no placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported.

Ockene 1991

Methods	Country: USA Recruitment: primary care
Participants	1223 unselected smokers, 57% F, av.age 35, av.cpd 22-23
Interventions	1. Advice only 2. Patient-centred counselling 3. Patient-centred counselling and offer of nicotine gum (2 mg) plus minimal or intensive follow-up by telephone. Level of support: mixed (not used in subgroup analysis)
Outcomes	Sustained abstinence at 12m (quit at 6m & 12m, reported in Ockene 1994) Validation: none
Notes	69% of group 3 accepted prescription and received at least 1 box of gum. 12m sustained rates, 3 vs 2, used in MA since 2008. Study was funded by the National Cancer Institute.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned to the physician and follow-up conditions"
Allocation concealment (selection bias)	Low risk	Physicians opened "a packet containing the intervention materials, which they received at the beginning of the clinic encounter"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Pts not blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses and drop-outs were included as failures. 62 pts removed from denominator (4 deaths, 58 not contacted by study staff)

Oncken 2007

Methods	Country: USA Recruitment: community volunteers
Participants	152 postmenopausal women (≥ 10 cpd) Av.cigs/day 22, av.age 54/56.6
Interventions	1. Nicotine patch (21 mg for 13 wks incl 4 wks tapering) 2. Placebo patch Level of support: high (7 visits incl 4 x 2hr group counselling, 1 pre-TQD)

Oncken 2007 (Continued)

Outcomes	PP abstinence at 16m (12m post-EOT) Validation: CO<8ppm
Notes	Study was supported by The Patrick and Catherine Weldon Donaghue Foundation, The University of Connecticut Center on Aging, University of Connecticut General Clinical Research Center and the National Institute for Health. Pharmaceuticals supplied by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assignment ratio was 3:5; "152 women were randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs or missed visits included as failures. Losses at each follow-up fully reported

Oncken 2008

Methods	Country: USA Recruitment: volunteers from antenatal clinics
Participants	194 pregnant women smoking at least 1cpd. Av.age 25, av.cpd 10 in wk before study enrolment, av.cpd 18 prepregnancy, mean FTND<4
Interventions	1. 2 mg nicotine gum (first 6 wks: instructed to chew one piece for every cig usually smoked per day, not exceeding 20, followed by 6 wk tapering period) 2. Placebo gum, dosing and duration as above Level of support: high. In-person and telephone individual smoking cessation counselling
Outcomes	Abstinence at 32-34 wks of gestation and 7d PP at 6-12 wks postpartum (abstinence at 6 wks postquit date also reported) Validation: CO and urinary cotinine
Notes	New for 2012 update. Varying lengths of follow-up. Longest follow-up used in primary analysis NRT group had significantly higher birth weight and gestational age than placebo group. NRT group significantly more likely to attend follow-up visits Funded by the National Institutes of Health.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerized urn randomization program to balance participant assignment in the two treatment groups"
Allocation concealment (selection bias)	Low risk	Urn randomization procedure implies that allocation not known until after enrolment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind", methods not specified.
Incomplete outcome data (attrition bias) All outcomes	High risk	Significantly higher loss to follow-up in placebo group (50% as opposed to 35%) . Those lost to follow-up considered to be smoking

Ortega 2011

Methods	Country: Spain Recruitment: hospital inpatients	
Participants	1843 hospital inpatients who identified as smokers. 88% M, av.age 62, av. 56 packs/year	
Interventions	1. Nicotine patch or gum (max 12 wks; participant's choice) + CBT 2. CBT only 3. Declined to participate Level of support: high (standardized 30-45 min sessions every 3d until patient discharged from hospital; postdischarge participant could have telephone or in-person sessions at 1 wk, 15d, 2, 3, 6, and 12m)	
Outcomes	Continuous abstinence from quit day at 12m Validation: 34% of participants verified with CO measurement	
Notes	New for 2012 update. No placebo. Groups 1 and 2 included in primary analysis under 'choice of NRT'. 'No significant outcome differences between NRT types' (personal communication from author) 717 declined to participate but followed up at 12m. Funding not reported.	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Ortega 2011 (Continued)

Random sequence generation (selection bias)	Low risk	Participants were randomized "using a "computerized algorithm."
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	High risk	Participants not blinded; no placebo group. Not specified as to whether study personnel were blinded. "...the one-year abstinence in the telephone follow-up group was self declared and not validated, which may entail bias when evaluating whether these patients truly had stopped smoking."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost not specified. Participants lost to follow-up included as smokers in outcome data

Otero 2006

Methods	Country: Brazil Recruitment: community volunteers
Participants	1199 smokers (includes 254 non-attenders), motivated to quit. 63%F, av.age 42, 46% smoked >20 cpd
Interventions	Factorial design with multiple levels of behavioural support 1. Nicotine patch (21 mg, 14 mg for FTND<5) 8 wks incl tapering + behavioural support 2. Cognitive behavioural support only Level of support: Mixed - Low=single 20 min session. High= 1, 2, 3 or 4 weekly 1hr sessions. Maintenance or recycling sessions provided at 3, 6, 12m
Outcomes	PP abstinence at 12m Validation: none
Notes	Contributes to both high & low support subgroups. No placebo. Study was supported by the Institute for Global Tobacco Control and the Fogarty International Center of the National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated. Randomization was stratified by age and sex by an independent specialist
Allocation concealment (selection bias)	Unclear risk	Not stated.

Blinding (performance bias and detection bias) All outcomes	High risk	29% of control group participants asked for nicotine patch after the 3m follow-up which might have increased control group quit rates at 12m
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Page 1986

Methods	Country: Canada Recruitment: primary care (5 family practices in Ontario)
Participants	275 unselected smokers. Primary care attenders aged 18-65 yrs Number of cpd not stated
Interventions	1. No advice 2. Advice to quit 3. Advice to quit plus offer of nicotine chewing gum prescription (2 mg) Level of support: low
Outcomes	Sustained abstinence at 6m Validation: none
Notes	3 vs 1+2 No placebo. Study was funded by the Canadian College of Family Physicians of Canada and by the University of Waterloo Social Sciences and Humanities Research Grant Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomized by day of attendance. Post hoc tests of results by day of attendance showed no interaction
Allocation concealment (selection bias)	High risk	Not applicable.
Blinding (performance bias and detection bias) All outcomes	Low risk	Single-blinding: "subjects were not aware of their treatment group nor the fact that they were being evaluated against other experimental groups". Follow-up interviewers "remained blind to the patient's experimental group until the final section in the interview"

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses reported, but not included in analyses.
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Paoletti 1996

Methods	Country: Italy Recruitment: community volunteers
Participants	297 smokers (≥ 10 cpd), motivated to quit. Stratified according to baseline cotinine levels 40% F, av. age 43, av. cpd 24 in low cotinine group (n=120), 30 in high group (n= 177)
Interventions	Stratum A (Baseline cotinine < 250 ng/ml) 1. Nicotine patch (15 mg/16hr, 18 wks incl taper) 2. Placebo patch Stratum B (Baseline cotinine > 250 ng/ml) 3. Nicotine patch 15 mg 4. Nicotine patch 25 mg Level of support: low
Outcomes	PP abstinence at 12m Validation: CO and plasma cotinine
Notes	Stratum A in Comparison 1 Stratum B in Comparison 8 (high versus standard dose patch). Study was funded by Pharmacia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization stratified on plasma cotinine levels. No detail on methods used
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind. All pts got 2 patches, to ensure maintenance of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported.

Perng 1998

Methods	Country: Taiwan Recruitment: outpatient chest clinics, volunteers
Participants	62 smokers (>20 cpd) 94% M, av.age 62, av.cpd 26
Interventions	1. Nicotine patch (24 mg/24 hr for 6 wks, no weaning) 2. Placebo patch Level of support: High (weekly visit to outpatient department for assessment, unclear if counselling was provided)
Outcomes	Abstinence at 12m Validation: CO<10ppm during patch use, but no validation at 12m
Notes	Level of support reclassified as high, 2008 update. Study was funded by Orient Europharma Company Ltd, Taipei, Taiwan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was performed by an independent outside facility"
Allocation concealment (selection bias)	Unclear risk	See above.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind. No further detail.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Piper 2007

Methods	Country: USA Recruitment: community volunteers
Participants	608 smokers, motivated to quit. 58% F, av.age 42, av cpd 22, no details of depression history
Interventions	1. Nicotine gum (4 mg, 8 wks) and bupropion (300mg, 9 wks) 2. Placebo gum and bupropion 3. Double placebo (Not used in MA) All arms: 3x10 min counselling
Outcomes	PP abstinence at 12m Validation: CO & cotinine

Piper 2007 (Continued)

Notes	Identified from conference abstracts, we use data from paper published after date of search. Contributes to comparison of NRT + bupropion versus bupropion alone. Study was funded by National Institutes of Health.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Randomization was conducted in double-blind fashion using blocked randomization within each of the 10 cohorts”
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were included as failures. ITT analyses conducted unless otherwise noted. All losses fully reported

Piper 2009

Methods	Country: USA Participants: community volunteers
Participants	1504 smokers motivated to quit. 58% F, av.age 45, av.cpd 21.4.
Interventions	1. Nicotine lozenge 2 or 4 mg for 12 wks (based on dose-for-dependence level as per instructions) 2. Nicotine patch (24hr, 21, 14, and 7mg titrated down over 8 wk period postquit) 3. Bupropion SR (150mg bid, 1 wk pre-quit, 8 wks postquit) 4. Lozenge + patch (duration and dosage as above) 5. Bupropion + lozenge (duration and dosage as above) 6. Placebo (5 groups matched to above 5 interventions) Level of support: high. All participants received 7 one-to-one 10-20min counselling sessions
Outcomes	7d PP abstinence at 6m; initial cessation. Validation: CO<10ppm
Notes	New for 2012 update. Placebo outcomes not reported by subgroup; outcomes generated by applying overall percentage of events in placebo group to individual subgroups. 1, 2, 4 and 6 included in primary analysis. 1, 2 and 4 included in Analysis 11.1, combinations of different types of NRT. 1 and 2 included in Analysis 12.1 direct comparisons between NRT types. 1, 2,

Piper 2009 (Continued)

	3, 5 and 6 included in comparisons and combinations of NRT and bupropion, Analysis 16.1. Numbers used for bupropion comparison divided between analysis 16.1.1 and 16.1.2 to avoid double counting. Bupropion as adjunct to NRT not assessed in this review Analyses conducted using ITT. Majority of funding from National Institute on Drug Abuse and National Center for Research Resources. Medication provided to participants at no extra cost by GlaxoSmithKline	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was double-blind and used a block randomization scheme with sex and self-reported race as the blocking variables."
Allocation concealment (selection bias)	Low risk	"Staff did not know to which type(s) of medication a participant would be assigned until the moment of randomization, and study staff were blinded to whether the medication was active or placebo."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind." "Study staff were blinded to whether the medication was active or placebo" (Type of medication (i.e. patch, gum, pill) would have been apparent to both groups)
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 drop-outs (out of 1504). Analyses conducted using ITT. Individuals with missing data considered to be smoking

Pirie 1992

Methods	Country: USA Recruitment: community volunteers
Participants	417 women smokers. Av.cpd 25-27.
Interventions	<p>1. Group therapy</p> <p>2. Group therapy plus weight control programme</p> <p>3. Group therapy plus nicotine gum</p> <p>4. Group therapy plus weight control programme and nicotine gum.</p> <p>Gum type: 2 mg ad lib</p> <p>Level of support: high</p>

Pirie 1992 (Continued)

Outcomes	Sustained abstinence at 12m Validation: CO	
Notes	3 & 4 compared to 1 & 2. Study was funded by the National Cancer Institute.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“Participants were randomized to one of four groups”
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo. No detail reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Moved away completed assessments by phone or mail

Pollak 2007

Methods	Country: USA Recruitment: volunteers from antenatal clinic	
Participants	181 pregnant women smoking at least 5 cpd Av.age 27, av.cpd pre-pregnancy 19	
Interventions	1. CBT 2. CBT + free NRT (Choice of patch, gum, lozenge or no NRT. Patch: 16hr, encouraged to use for 6 wks, dose based on woman's smoking level, fewer than 10 cpd=7mg/d, 10-14 cpd=14 mg/d, ≥15 cpd=21 mg/d; gum or lozenge: 2 mg for every cpd) Level of support: high (6 one-to-one counselling sessions)	
Outcomes	7d PP at 38 wks of gestation and 3m postpartum Validation: salivary cotinine at 38 wks, self report ps	
Notes	New for 2012 update. Varying lengths of follow-up. Recruitment suspended early when interim analysis found higher rate of negative birth outcomes in CBT+NRT arm; not statistically different when adjusted for previous history of birth outcomes in final analysis 6 in NRT group opted to use no NRT; 4 in CBT-only arm reported use of NRT Funded by the National Cancer Institute.	

Pollak 2007 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computerised random number generator"
Allocation concealment (selection bias)	Low risk	"each support specialist had a handheld device that contained a randomization list"
Blinding (performance bias and detection bias) All outcomes	High risk	Open label, unblinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women lost to follow-up considered smokers; similar numbers in both groups
Other bias	Unclear risk	Women in CBT+NRT group significantly more likely to attend CBT sessions

Prapavessis 2007

Methods	Country: New Zealand Recruitment: community volunteers	
Participants	121 women smokers (>10 cpd) (excludes drop-outs not starting programme)	
Interventions	NRT as adjunct to either CBT or exercise programmes, collapsed for this review 1. Nicotine patch (21 mg/24hr for 10 wks, no weaning) 2. No patch Level of support: High (36x45 min session over 12 wks of group CBT or supervised vigorous exercise, starting 6 wks before TQD)	
Outcomes	Continuous abstinence since TQD at 12m from end of programme Validation: CO<10ppm, cotinine<0 ng/mL	
Notes	No placebo. Study was funded by the National Heart Foundation of New Zealand, and supported by GlaxoSmithKline	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Using a computer-generated program, participants were then randomly assigned"

Prapavessis 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Analyses were conducted by intent to treat". Missing data on smoking abstinence were counted as failures. % losses reported

Puska 1979

Methods	Country: Finland Recruitment: community volunteers
Participants	229 adult smokers, 80% smoking > 5 cpd
Interventions	1. Nicotine gum (4 mg) for 3 wks 2. Placebo gum for 3 wks Level of support: high (group therapy)
Outcomes	PP abstinence at 6m. Validation: none
Notes	Study was supported by AB Leo and Co, Helsinborg, Sweden.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Neither the subjects nor the course leaders were aware who received active and who placebo gum"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up were reported, but were not included in the analyses

Puska 1995

Methods	Country: Finland Recruitment: community volunteers
Participants	300 volunteers aged 20-65, smoking >10 cpd for >3 yrs, no serious illness
Interventions	1. Nicotine patch (15 mg/16hrs, 12 wks+ 6 wks taper) plus nicotine gum (2 mg at least 4 daily) 2. Placebo patch plus nicotine gum (same regimen) Level of support: low (advice from study nurses)
Outcomes	Sustained abstinence at 12m Validation: expired CO<10ppm
Notes	Does not contribute to main comparison & subgroups, only combinations. Sources of support not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The subjects were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"The study was carried out in a strictly double blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported.

Richmond 1993

Methods	Country: Australia Recruitment: primary care
Participants	450 adult smokers (350 in included arms). Av.cpd 15-21.
Interventions	1. Smokescreen programme plus nicotine gum, dose and duration not stated 2. Smokescreen programme alone 3. Brief advice & gum (Not included in MA) Level of support: high (5 visits during first 3m)
Outcomes	Continuous abstinence (from wk 1) at 12m Validation: expired CO<14ppm

Richmond 1993 (Continued)

Notes	<p>No placebo</p> <p>Continuous abstinence rates from Richmond 1993 paper used from 2007. Group 3 not included.</p> <p>Study was funded by the Department of Health, Housing and Community Services, Community Health Anti-Tuberculosis Association, Glaxo Australia, and the Drug and Alcohol Directorate, NSW Department of Health</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"random weekly assignment"
Allocation concealment (selection bias)	High risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up were included as failures.

Richmond 1994

Methods	<p>Country: Australia</p> <p>Recruitment: community volunteers</p>
Participants	315 smokers, av.cpd 29
Interventions	<p>1. Nicotine patch (24 hr, 22 mg/24 hr, 10 wks incl tapering)</p> <p>2. Placebo patch</p> <p>Level of support: high (group therapy)</p>
Outcomes	<p>Sustained abstinence at 12m (reported in Richmond 1997, which also reports 3yr follow-up, not used in MA)</p> <p>Validation: CO</p>
Notes	<p>3yr abstinence 21/153 vs 8/152, OR 2.9 - higher than at 12m.</p> <p>Study was funded by Marion Merrell Dow, and supported by the Drug and Alcohol Directorate, NSW Department of Health, and the Lifestyle Unit, Prince of Wales Hospital, Sydney</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
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Richmond 1994 (Continued)

Random sequence generation (selection bias)	Low risk	“Treatment and control patches were arranged in random order by Marion Merrell Dow, Sydney, then issued sequentially to patients as they attended”; married couples were assigned to same condition
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up included as failures. Drop-out rates fully reported

Rose 1994

Methods	Country: USA Recruitment: community volunteers
Participants	48 smokers (≥ 20 cpd) 60% F, av.age 34, av.cpd 27-29
Interventions	2x2 factorial trial. Mecamylamine arms collapsed. 1. Nicotine patch (21 mg/24 hr for 2 wks before TQD) 2. Placebo After TQD both groups received active patch for 6 wks, counselling at clinic visits & self help materials
Outcomes	Sustained abstinence at 12m Validation: CO \leq 8ppm
Notes	Contributes only to pre-cessation comparison. Study was funded by the American Cancer Society, the National institute on Drug Abuse and the Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias)	Unclear risk	Assessment of blinding indicated higher-than-chance subject awareness of treatment

Rose 1994 (Continued)

All outcomes		regimen
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rate reported (low).

Rose 1998

Methods	Country: USA Recruitment: community volunteers
Participants	80 smokers (≥ 20 cpd) 49% F, av.age 41, av.cpd 30
Interventions	2x2 factorial trial. Mecamylamine pretreatment arms collapsed. 1. Nicotine patch (21 mg/24 hr for 4 wks before TQD) 2. Placebo After TQD both groups received active patch & mecamylamine for 6 wks, counselling at clinic visits & self help materials
Outcomes	Sustained abstinence at 6m Validation: CO \leq 8ppm
Notes	Contributes only to pre-cessation comparison. Study was funded by the American Cancer Society and the Department of Veterans Affairs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"participants were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Placebo patches not used, but pts were blinded to mecamylamine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Early drop-outs (up to 4 wks pre-cessation) reported, but not long-term

Rose 2006

Methods	Country: USA Recruitment: community volunteers
Participants	96 smokers (≥ 20 cpd), motivated to quit. 53% F, av.age 45, av.cpd 29
Interventions	2x3x3 factorial trial - only pre-cessation patch condition contributes to MA, other conditions collapsed. 1. Nicotine patch (21 mg/24hr for 2 wks before TQD) 2. Placebo All participants received mecamlamine 2.5 mg bid for 4 wks post-TQD, and either 0, 21 or 42 mg patch
Outcomes	PP abstinence at 6m Validation: CO \leq 8ppm
Notes	Contributes only to pre-cessation comparison. Postquit conditions did not affect cessation, data not reported in paper. Study was funded by the National Institute on Drug Abuse

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Patch assignment was blinded, but not cigarette type. After quit-date, all pts received mecamlamine
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	8.3% of pts dropped out before TQD, and were excluded from analyses

Rose 2009

Methods	Country: USA Recruitment: community volunteers
Participants	379 participants, smoking >15 cpd for ≥ 3 yrs, motivated to quit 43% M, av.age 42, av.cpd 23, av.FTND 6
Interventions	1. Usual brand of cig + 21 mg/24hr patch for 2 wks pre-quit 2. Usual brand of cig + placebo patch for 2 wks pre-quit 3. Low tar and nic cig + 21 mg/24hr patch for 2 wks pre-quit 4. Low tar and nic cig + placebo patch for 2 wks pre-quit

Rose 2009 (Continued)

	All groups received same treatment postquit: 6 wks 21 mg/24hr, following 2 wks 14 mg/24hr, remaining 2 wks 7mg/24hr Level of support: Not specified	
Outcomes	Continuous abstinence at 6m Validation: CO≤8ppm	
Notes	New for 2012 update. Used in pre-cessation analysis only. Data from graph confirmed by author No effect by cig condition; 1+3 vs 2+4 in analysis. Treatment had greater effect for those with low FTND Funding provided through grant to Duke University by Philip Morris, USA	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“a total of 400 subjects were randomly assigned to one of four treatment groups”
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	Low risk	“two members of the study team...placed the required number of active or placebo patches into individual plastic bags labelled with subject number and session number... In order to maintain blinding, these members of the study team did not interact with study participants.”
Incomplete outcome data (attrition bias) All outcomes	High risk	High number lost to follow-up (169/379).

Rose 2010

Methods	Country: USA Recruitment: community volunteers
Participants	479 smokers of ≥ 10 cpd, motivated to quit 43% M, av.age 44, av.cpd 24
Interventions	1. Nicotine patch, 21 mg group: wks 1-7 21 mg/24hr (1 active 21 mg/24hr patch, 1 placebo patch) 2. Nicotine patch, 42 mg group: wks 1-7 42 mg/24hr (2 active 21 mg/24hr patches) TQD set at 2 wks. Wks 7-12: all participants receive same NRT dose (wks 7-8 21 mg/24hr, wks 9-10 14 mg/24hr, wks 11-12 7mg/24hr). All participants provided with denicotinized cigarettes during 2 wk pre-cessation period to minimize adverse effects of high dose NRT

	Level of support: high (7 in person counselling sessions ≤ 15 min)
Outcomes	Point abstinence at 6m Validation: CO ≤ 10 ppm
Notes	New for 2012 update. Primarily a study of effects of genotype on smoking cessation. Included in higher vs. standard dose patches Analysis 7.1 only. Funded by National Institutes of Health, National Institute on Drug Abuse, Department of Health and Social Services, grant to Duke University from Philip Morris, USA Number of successful quitters at 6m obtained through communication with author Subjects with difficulty sleeping instructed to remove patch at bedtime and apply new ones when they awoke. Subjects with other symptoms of nicotine toxicity instructed to reduce dose

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" but method not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo used, method of blinding not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	197 lost to follow-up before 10 wks (not known how many lost at 6m); similar numbers across groups; participants lost to follow-up counted as smokers

Roto 1987

Methods	Country: Finland Recruitment: primary care (occupational health centres)
Participants	121 smokers (>10 cpd, >1 yr) 43% F
Interventions	1. Nicotine gum (2 mg and 4 mg), + advice 2. Advice only (no placebo) Level of support: low
Outcomes	Abstinence at 6m (not defined) Validation: not described

Roto 1987 (Continued)

Notes	Study funding and support not reported.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs classified as smokers.

Russell 1983

Methods	Country: UK Recruitment: primary care - consecutive attenders admitting to being cigarette smokers and consenting to participate at 6 general practices	
Participants	2106 unselected adult smokers. Av.cpd 17.5	
Interventions	1. No intervention 2. Advised to stop smoking plus provided with a “give up smoking” booklet 3. As group 2, plus offer of nicotine gum prescription, Individual therapy, Single visit, 1 minimal content, 1 more intensive content, untrained therapist Level of support: low	
Outcomes	Sustained abstinence at 4 and 12m Validation: 66% of those claiming to have quit validated with CO	
Notes	3 vs 2+1 used in comparison. Using only 2 as control has negligible effect on OR Only 53% of group 3 tried the gum Use of quit rates adjusted for estimated validation failure and protocol violation would increase relative effect of gum. Study was funded by the Medical Research Council, and the AB Leo Research Foundation, Sweden	
Risk of bias		
Bias	Authors’ judgement	Support for judgement

Russell 1983 (Continued)

Random sequence generation (selection bias)	High risk	Pts assigned "according to their week of attendance".
Allocation concealment (selection bias)	High risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Not stated. Correct procedure was not followed by 10.4% in Grp 1, 15.4% in Grp 2 and 16.2% in Grp 3. Only 53% of Grp 3 ever tried the gum
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 deaths and 152 who moved away were excluded from analyses. 327 with no or inadequate data at follow-up were included as failures

Sachs 1993

Methods	Country: USA Recruitment: community volunteers
Participants	220 adult smokers. Av.cpd 28-9.
Interventions	1. Nicotine patch (15 mg/16hr, 12 wks + 6 wks tapering) 2. Placebo patch Level of support: high (physician advice, 8 visits during treatment period)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	Study was funded by National Institute on Drug Abuse, Kabi Pharmacia AB and Parke-Davis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Subjects were sequentially and randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-out rates not fully reported, but all pts included in ITT analyses with drop-outs counted as smokers

Schneider 1985A

Methods	Country: USA Recruitment: community volunteers
Participants	60 heavy smokers (>1 pack/day) 60%F, av.age 40/37, av.cpd 35/31
Interventions	Study A (clinic support): 1. Nicotine gum, (2 mg duration not stated) 2. Placebo gum Level of support: high (individual support at multiple clinic assessment visits, daily during week 1, weekly to wk 5)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	Reported in same papers as Schneider 1985B. Shared study ID until 2008. Schneider 1983 provides demographic data so now used as primary reference. Jarvik & Schneider 1984 reports outcomes by dependency score for 48/60 participants. Study was funded by National Institute on Drug Abuse and by the Medical Research Service of the Veterans Administration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"gum was dispensed in a double-blind procedure"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Schneider 1985B

Methods	Country: USA Recruitment: community volunteers
Participants	36 heavy smokers (>1 pack/day) no demographic details
Interventions	Study B (pilot dispensary study): 1. Nicotine gum, (2 mg duration not stated) 2. Placebo gum

Schneider 1985B (Continued)

	Level of support: low (weekly laboratory visits for 5 wks but no support provided)	
Outcomes	Sustained abstinence at 12m Validation: CO	
Notes	Reported in same papers as Schneider 1985A. Shared study ID until 2008. Study was funded by National Institute on Drug Abuse and by the Medical Research Service of the Veterans Administration	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	“subjects were randomly assigned”
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	“gum was dispensed in a double-blind procedure”
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Schneider 1995

Methods	Country: USA Recruitment: community volunteers (radio and newspaper ads)	
Participants	255 adults with no serious illness, motivated to quit, smoking >15 cpd for >2 yrs with baseline CO level >20ppm. Av.cpd 28-29	
Interventions	1. Nicotine nasal spray 2. Placebo spray Nicotine dosage: 0.5 mg of nicotine per spray. No fewer than 8 and no more than 32 doses/day for 6 wks, with free use for further 6m Level of support: high (repeated clinic visits for assessment)	
Outcomes	Sustained abstinence at 12m Validation: CO<8 ppm.	
Notes	Study was funded by Veteran Affairs and Pharmacia (Sweden).	
Risk of bias		
Bias	Authors' judgement	Support for judgement

Schneider 1995 (Continued)

Random sequence generation (selection bias)	Unclear risk	"Subjects were randomly assigned to conditions"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"the trial was double-blind". Pt guesses reported as confirmation of blinding success
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Limited information.

Schneider 1996

Methods	Country: USA Recruitment: community volunteers
Participants	223 adult smokers (≥ 10 cpd) 37% F, av.age 44, av.cpd 29/26 (significantly higher in active group)
Interventions	1. Nicotine inhaler (4-20 inhalers per day) for up to 6m, with weaning from 3m 2. Placebo inhaler Level of support: high (repeated clinic visits for assessment)
Outcomes	Sustained abstinence at 12m Validation: CO and salivary cotinine
Notes	Study was funded by Veteran Affairs and by Pharmacia & Upjohn (Sweden)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer generated randomization list was prepared by the manufacturers"
Allocation concealment (selection bias)	Low risk	"An independent "randomizer" packaged drug from the list."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Subjects and all personnel connected with the trial (including the PI) were kept blind". Pts guessed their allocation as a test of the blinding at final assessment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.

Schnoll 2010a

Methods	Country: USA Recruitment: community volunteers
Participants	575 adult smokers of >10cpd for >1yr, motivated to quit 47% F, av.age 48, av.cpd 21.1, av.FTND 5.3
Interventions	1. 21 mg/24hr patch for 24 wks 2. 21 mg/24hr patch for 8 wks, followed by 16 wks placebo patch Level of support: high. Behavioural counselling provided at wks -2, 0, 1, 4, 8, 12, 16, and 20
Outcomes	7d PP at 12m (also reported for 24 wks). Validation: CO \leq 10ppm
Notes	New for 2012 update. Included in duration of treatment Analysis 9.2 only. Extended therapy group reported higher levels of adherence at wks 12, 16, 20 and 24. Significant effect of treatment at wk24 Funding provided by National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-based randomization table"
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	Low risk	"supply of patches was prepackaged and coded with participant information. The computer program linked the randomization to the patch supply, and only the database manager could link identification with treatment allocation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs included as smokers in outcome data. Similar number of drop-outs in both groups

Schnoll 2010b

Methods	Country: USA Recruitment: Community volunteers and physician referrals
Participants	642 treatment-seeking smokers smoking \geq 10cpd 57% F, av.age 45, av.cpd 20.3, av.FTND 5.1; av.yrs smoking 26.7

Schnoll 2010b (Continued)

Interventions	Direct comparison of patch vs lozenge. 1. Patch: 21 mg/d for first 6 wks, 14 mg/d for wks 7+8, 7mg/d for wks 9-12 2. Lozenge: 4 mg for participants who smoked first cig of day w/in 30min of waking; 2 mg for all other participants. Asked to use 9/d for first 6 wks, 5/d for wks 7-9, 3/d for wks10-12 Level of support: high. 5 individual counselling sessions.
Outcomes	24hr PP at 6m Validation: CO \leq 10ppm
Notes	New for 2012 update. Used in direct comparison of NRT types only. Funded by American Cancer Society and National Institutes of Health

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomization was coordinated by Fox Chase Cancer Center and was stratified at each site."
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label trial and although both treatments were active, 2/3 participants had preference for patch
Incomplete outcome data (attrition bias) All outcomes	Low risk	46% loss to follow-up by 6m, similar between groups. Missing data reported as smokers
Other bias	High risk	Lower adherence in lozenge group.

Schuermans 2004

Methods	Country: South Africa Recruitment: community volunteers
Participants	200 smokers 44% F, av.age 43, av.cpd 23/26
Interventions	1. Pretreatment with nicotine patch for 2 wks prior to quit date. Then active patch (15 mg) patch for 12 wks including weaning. 4 sessions of counselling over 10 wks. 2. Pretreatment with placebo patch. The active patch as 1.

Outcomes	Sustained abstinence at 6m Validation: CO<10ppm at each visit	
Notes	Does not contribute to main comparison. Study was funded by the Swiss Science Foundation, and by Pfizer Inc	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“a computer-generated list”
Allocation concealment (selection bias)	Low risk	“Numbering of identical boxes containing patches was carried out prior to the study by a person not involved in the study”
Blinding (performance bias and detection bias) All outcomes	Low risk	“The treatment code was broken only after the last follow-up visit had been completed and the data recorded”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs fully recorded at all stages, ITT analyses used and participants lost to follow-up counted as smokers

Segnan 1991

Methods	Country: Italy Recruitment: primary care - consecutive patients attending 44 general practices
Participants	923 practice attenders aged 20-60. Av.cpd not stated. Therapists: GPs who had undergone a 3hr training session
Interventions	1. Advice and leaflet 2. Repeated counselling (follow-up at 1, 3, 6, 9m) 3. Repeated counselling plus prescription for nicotine gum unless contraindicated, dose not stated, up to 3m 4. Repeated counselling plus spirometry Level of support: high
Outcomes	Sustained abstinence at 12m Validation: urinary cotinine
Notes	3 vs 1+2+4. Study was supported by SIMG (Italian Association of General Practice), and by Serono SPA

Segnan 1991 (Continued)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a predetermined randomized sequence of the four interventions"
Allocation concealment (selection bias)	Low risk	"a package of closed numbered envelopes . . . was provided to each GP". Research staff checked the integrity of the process
Blinding (performance bias and detection bias) All outcomes	Low risk	Interviews were conducted by "trained interviewers, independent of the study staff"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out rates reported.

Shiffman 2002 (2mg)

Methods	Country: USA & UK (15 sites) Recruitment: community volunteers
Participants	917 smokers, motivated to quit, time to first cigarette >30 mins. 58% F, Av age 41, cpd 17
Interventions	1. Nicotine lozenge, 2 mg. Recommended dose 1 every 1-2hrs, min 9, max 20/day for 6 wks, decreasing 7-12 wks, available as needed 13-24 wks 2. Placebo lozenge, same schedule Level of support: high (brief advice at 4 visits in 4 wks from enrolment)
Outcomes	Continuous abstinence at 12m (Sustained from 2 wks, no slips allowed). Validation: CO \leq 10ppm at all follow-ups. (only abstainers continued in study)
Notes	Dose based on dependence level. Low dependence group here. High dependence group in Shiffman 2002 (4 mg). Study was supported by GlaxoSmithKline Consumer Healthcare.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"smokers were randomized" after stratification for dependency by time to first cigarette of the day
Allocation concealment (selection bias)	Unclear risk	Not stated.

Shiffman 2002 (2mg) (Continued)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only abstainers were followed up. "Participants who did not appear for a visit were counted as treatment failures". Losses fully reported

Shiffman 2002 (4mg)

Methods	Country: USA & UK (15 sites) Recruitment: community volunteers
Participants	901 smokers, time to first cigarette <30 mins 55% F, Av age 44, cpd 26
Interventions	1. Nicotine lozenge, 4 mg. Recommended dose 1 every 1-2hrs, min 9, max 20/day for 6 wks, decreasing 7-12 wks, available as needed 13-24 wks. 2. Placebo lozenge, same schedule
Outcomes	Continuous abstinence at 12m. (Sustained from 2 wks, no slips allowed). Validation: CO \leq 10ppm at all follow-ups. (only abstainers continued in study)
Notes	Dose based on dependence level. High dependence group here. Low dependence group in Shiffman 2002 (2 mg)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See above (Shiffman 2002 2mg)
Allocation concealment (selection bias)	Unclear risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See above

Shiffman 2009 (2mg)

Methods	Country: USA Recruitment: community volunteers
Participants	1636 smokers wishing to quit by gradual reduction (RTQ technique) 64% F, av.age 42, av.cpd 9.4, av.FTND 4.4
Interventions	1. Nicotine gum 2 mg. Instructed to gradually reduce smoking while increasing gum use for up to 8 wks. Postquit instructed to use 1 piece every 1-2hrs for first 6 wks; 1 every 2-4hrs for next 3 wks; 1 every 4-8hrs for final 3 wks 2. Placebo gum, same schedule as above. Level of support: low (designed to simulate OTC setting)
Outcomes	Abstinence at 6m from start of treatment (initial abstinence had to be achieved within 8 wks of start of treatment, so duration of abstinence was at least 4m) Validation: CO \leq 10ppm
Notes	New for 2012 update. Included in main analyses Dose based on dependence level. Participants read labelling which recommended 4 mg dose for smokers of >25 cpd and selected appropriate dose. Low dependence group here. High dependence group reported in Shiffman 2009 (4mg) Funding provided by GlaxoSmithKline Consumer Healthcare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"using a 1:1 computer-generated randomization scheme, balanced across study sites and generated separately for the 2- and 4-mg groups"
Allocation concealment (selection bias)	Unclear risk	Not specified.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", method not specified.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Those who had not succeeded at 28d follow-up not followed up at 6m. All missing data considered to be smoking

Shiffman 2009 (4mg)

Methods	Country: USA Recruitment: community volunteers
Participants	1661 smokers wishing to quit by gradual reduction (RTQ technique) 50% F, av.age 46, av.cpd 32, av.FTND 6.9
Interventions	1. Nicotine gum 4 mg. Instructed to gradually reduce smoking while increasing gum use for up to 8 wks. Postquit instructed to use 1 piece every 1-2hrs for first 6 wks; 1 every 2-4hrs for next 3 wks; 1 every 4-8hrs for final 3 wks 2. Placebo gum, same schedule as above. Level of support: low (designed to simulate OTC setting)
Outcomes	Abstinence at 6m from start of treatment (initial abstinence had to be achieved within 8 wks of start of treatment, so duration of abstinence was at least 4m) Validation: CO \leq 10ppm
Notes	New for 2012 update. Dose based on dependence level. High dependence group here. Low dependence group reported in Shiffman 2009 (2mg) Funding provided by GlaxoSmithKline Consumer Healthcare.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See above (Shiffman 2009 2mg)
Allocation concealment (selection bias)	Unclear risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See above

Smith 2009

Methods	Country: USA Recruitment: primary care (12 clinics)
Participants	1346 smokers of >10 cpd for past 6m. 56% F, av.age 44, av.cpd 20.3, motivated to quit
Interventions	1. Bupropion only (up-titrated during wk pre-quit, 150mg bid for 8 wks postquit) 2. Nicotine lozenge only (4 mg lozenge if first cig of day smoked >30 min after waking, 2 mg otherwise. 1 lozenge every 1-2hrs postquit wk 1-6; 1 lozenge every 2-4hrs wk 7-9; 1 lozenge every 4-8hrs wk 10-12)

Smith 2009 (Continued)

	<p>3. Nicotine patch only (21 mg post-quit wk 1-4; 14 mg wk 5-6; 7mg wk 7-8)</p> <p>4. Bupropion and lozenge (dosage as above)</p> <p>5. Patch and lozenge (dosage as above)</p> <p>Level of support: high (behavioural support optional)</p>
Outcomes	<p>7d PP at 6m and number of days to relapse.</p> <p>Validation: none</p>
Notes	<p>New for 2012 update.</p> <p>No control so does not contribute to primary analysis. Interventions 1, 2, 3 and 4 used in direct comparisons and combinations of NRT and bupropion. 2, 3 and 5 used in Analysis 11.1 combinations of different types of NRT. 2 and 3 used in Analysis 12.1 comparisons between NRT types. Numbers used for bupropion comparison divided between analysis 16.1.1 and 16.1.2 to avoid double counting. Bupropion as adjunct to NRT not assessed in this review</p> <p>Analyses completed on ITT basis.</p> <p>Majority of funding from National Institutes of Health, National Institute on Drug Abuse, and National Cancer Institute. Medication provided to participants at no cost by GlaxoSmithKline</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Smokers were randomized to the 5 treatment conditions within each clinic with blocking on sex and self-identified race."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	158 individuals who did not pick up study medication at first point not included in analyses; 122 withdrawals & 9 deaths considered to be smoking

Sondervskov 1997

Methods	<p>Country: Denmark</p> <p>Recruitment: customers seeking to buy nicotine patches OTC at 42 pharmacies</p> <p>Randomization: sequential treatment packages, stratified by smoking level</p>
Participants	<p>522 smokers of >10 cpd. Smokers of >20 cpd used a higher dose patch than lower rate smokers.</p> <p>50% F, av.age 39</p>

Sonderskov 1997 (Continued)

Interventions	1. Nicotine patch (24 hr). >20/day smokers used 21 mg for 4 wks, 14 mg for 4 wks, 7mg for 4 wks. Smokers of <20/day used 14 mg for first 8 wks, 7mg for 4 wks 2. Placebo patches Level of support: Low (brief instructions on patch use at baseline, visit to collect further patches at 4 & 8 wks, no behavioural support)	
Outcomes	Abstinence at 6m - no reported smoking in the last 4 wks, by telephone interview with neutral independent assessor Validation: none	
Notes	Study was partly funded by Ciba-Geigy.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized sequential treatment packages"
Allocation concealment (selection bias)	Low risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo patches contained "a pharmacologically negligible amount of nicotine". "The blinding procedure was not broken until all the main results were tabulated"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Participants lost to follow-up (n=19) were classified as smokers". Losses and reasons fully reported

Stapleton 1995

Methods	Country: UK Setting: primary care	
Participants	1200 smokers considered by GP to be highly dependent and motivated to give up. Av. cpd 23-4	
Interventions	1. Nicotine patch standard dose (15 mg/16hr for 18 wks) 2. Nicotine patch with dose increase to 25 mg at 1 wk if required 3. Placebo patch group The nicotine patch groups were further randomized to gradual tapering or abrupt withdrawal at wk 12. Level of support: High (physician advice & brief support at 1, 3, 6, 12 wks)	
Outcomes	Sustained abstinence at 12m Validation: CO	

Stapleton 1995 (Continued)

Notes	The dose increase after 1 wk did not affect cessation, 1+2 vs 3 in comparison 1. Study as funded by Kabi Pharmacia (Sweden).	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	“ a computer generated list, complied in blocks of six (four active, two placebo)”
Allocation concealment (selection bias)	Low risk	Numbered packages
Blinding (performance bias and detection bias) All outcomes	Low risk	“Both subjects and their doctors or nurses were blind to whether the dose increase was real or placebo”. Study conduct throughout was monitored by clinical research associates of the pharmaceutical company
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analyses, with losses/failures included as smokers. Number of drop-outs not specified

Sutherland 1992

Methods	Country: UK Recruitment: smoking cessation clinic	
Participants	227 smokers, motivated to quit. Av.cpd 25-27	
Interventions	1. Nicotine nasal spray, maximum 40mg/day 2. Placebo spray Level of support: High (4 wks group support)	
Outcomes	Sustained abstinence at 12m Validation: CO	
Notes	Follow-up beyond 1yr reported in Stapleton 1998 Abstinence for 3yrs 19/116 vs 7/111, OR 2.9. Study was funded by the Medical Research Council and by the Imperial Cancer Research Fund	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"They drew a card marked A or P for allocation to active or placebo group"

Sutherland 1992 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	"Subjects and therapists were blind to spray assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up briefly reported.

TNSG 1991

Methods	Country: USA (9 sites) Recruitment: community volunteers (treated at smoking cessation clinics)
Participants	808 unselected smokers 60% F, av.age 43, av.cpd 31
Interventions	1. Nicotine patch (21 mg /24 hr, 6 wks+) 2. Nicotine patch 14 mg 3. Placebo patch Abstainers at end of wk 6 entered a randomized blinded trial of weaning. Level of support: high (group therapy, 6+ sessions)
Outcomes	Sustained abstinence at 6m Validation: CO
Notes	2 trials pooled and data relating to a 7mg patch group used in only 1 trial omitted. Long-term (4-5 yr) follow-up data reported for 7/9 sites (Daughton 1999). Data not used in MA -OR would be higher. Study was supported by Alza Corp.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated: "patients were ... randomized", but members of same household received same assignment, with one randomly selected for inclusion in the analyses
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind

Incomplete outcome data (attrition bias) All outcomes	Low risk	"All pts were included in outcome evaluations except for the excluded members of couples (49 pts) and nine pts with major protocol infractions". Losses and withdrawals were included as treatment failures
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Tonnesen 1988

Methods	Country: Denmark Recruitment: primary care
Participants	113 low to medium dependence smokers, motivated to quit (19 or less on Horn-Russell scale) 56% F, av.age 45, av.cpd 20 60 highly dependent smokers 58% F, av.age 45, av.cpd 26-28
Interventions	Group A: Low/medium dependence 1. Nicotine Gum (2 mg) for 16 wks 2. Placebo Group B: High dependence 1. Nicotine gum 4 mg for 6 wks then 2 mg 2. Nicotine gum 2 mg Level of support: high (informal group support, 6 sessions)
Outcomes	Sustained abstinence at 12m (24m also reported) Validation: CO
Notes	Group A in comparison 1, Group B in comparison 2, Abstinence at 24m 17/60 vs 5/53, OR 3.8, relative effect greater than at 12m. Study was supported by A.B. Leo (Sweden) and H. Lundbeck A.S. (Denmark)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pts stratified by dependence, then "subjects on each list were then randomly assigned to treatment in blocks of two"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Gum was packaged and produced to be indistinguishable between 2 mg, 4 mg and placebo

Tonnesen 1988 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All subjects who attended 1st counselling session were included in analyses, regardless of attendance or level of gum use. Only 2/173 were lost to follow-up
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Tonnesen 1991

Methods	Country: Denmark Recruitment: community volunteers
Participants	289 smokers (≥ 10 cpd) 70% F, av.age 45, av.cpd 22
Interventions	1. Nicotine patch (15 mg/16hr for 12 wks with tapering) 2. Placebo patch Level of support: High (7 clinic visits including a few minutes of advice)
Outcomes	Sustained abstinence at 12m (also reported 24m in Tonnesen 1992, 3 yrs in Mikkelsen 1994) Validation: CO
Notes	Classification of support corrected to high in 2008 update. 2 yr abstinence 17/145 vs 6/144, OR 4.6. 3 yr abstinence 15/145 vs 4/144, OR 4.0. Study was supported in part by Kabi Pharmacia Therapeutics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"subjects were sequentially and randomly assigned to either active treatment or placebo according to a computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	"Patches were packaged and labeled with consecutive numbers"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo patches were identical to the active patches in appearance, packaging and labeling, but contained no nicotine". Blinding code was broken after wk 26.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All who attended the 1st session were included in the analyses. Losses to follow-up were included as smokers

Tonnesen 1993

Methods	Country: Denmark Recruitment: community volunteers
Participants	286 smokers (≥ 10 cpd) 60% F, av.age 39, av.cpd 20
Interventions	1. Nicotine inhaler (2-10/day) up to 6m 2. Placebo inhaler Level of support: High (brief advice at 8 clinic visits, 0, 1, 2, 3, 6, 12, 24, 52 wks)
Outcomes	Sustained abstinence at 12m (from wk 2, paper also reports with slips outcome) Validation: CO
Notes	Study was supported by Kabi Pharmacia Therapeutics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization code for assignment to either active or placebo inhaler was generated by a computer program"
Allocation concealment (selection bias)	Low risk	See above.
Blinding (performance bias and detection bias) All outcomes	Low risk	"The placebo inhaler contained only the additive and was identical in appearance to the active inhaler". Pts were asked at 12m to guess their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Subjects unavailable for follow-up were assumed to be smokers". Relapsers were dropped from the study, but were all contacted at one year. Six were lost to follow-up and 7 excluded for protocol violations

Tonnesen 2000

Methods	Country: Denmark Recruitment: referrals to lung clinic
Participants	446 smokers ≥ 10 cpd 52% F, av.age 49, av.cpd 18
Interventions	1. 5 mg nicotine patch (placebo) 2. 15 mg (16hr) nicotine patch for 12 wks (up to 9m on request) 3. Nicotine inhaler (4-12/day ad lib) 4. Combination, 15 mg patch and inhaler

Tonnesen 2000 (Continued)

	Level of support: High (Physician advice at baseline, brief (15min) nurse counselling at 2, 6 wks, 3, 6, 9, 12m)
Outcomes	Sustained abstinence at 12m, (from wk 2, paper also reports PP and with slips rates) Validation: CO<10ppm at all visits
Notes	In main comparison for patch vs placebo but not inhaler. Also 1 & 2 vs 4 in combination, and 3 vs 2 in head-to-head comparisons. Study funding and support not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a computer-generated list with random numbers"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not used - open trial.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Non-attenders or lost to follow-up were included as smokers.

Tonnesen 2006

Methods	Country: Denmark Recruitment: lung clinic patients & newspaper adverts
Participants	370 smokers (at least 1 cpd) with COPD (Mean FEV1 was 56% of predicted) 52% F, av. age 61, av. cpd 20 (8% <7/day), 71% had previously tried NRT
Interventions	2x2 factorial trial of lozenge and behavioural support. 1. Nicotine sublingual tablet (2 mg), recommended dose depended on baseline cpd, from min 3 to max 40 per day 2. Placebo Level of support: high -Either 4 clinic visits (0, 2 wks, 6, 12m) & 6 phone calls, total time 2.5hrs, or 7 visits (0, 2, 4, 8, 12 wks) & 5 calls, total 4.5h
Outcomes	Sustained abstinence at 12 months (from 2 wks) Validation: CO<10ppm at all visits
Notes	New for 2008 update Behavioural support arms collapsed. Both involved multiple clinic visits Study was funded by the Danish Medical Research Council, and supported by Pfizer Consumer Healthcare (Sweden)

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were allocated to one of the four treatment groups using a block randomization list at each center"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further detail.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported.

Tønnesen 2012

Methods	Country: Germany (2 sites) and Denmark (1 site) Recruitment: Community volunteers
Participants	479 adult smokers of ≥ 1 cpd motivated to quit. 56% M, av.age 47, av.cpd 22.7, av.FTND 5.3
Interventions	1 mg/spray oral nicotine spray (in development, name not provided) Active: wks 1-6: 1-2 sprays when participants would normally have smoked a cigarette or experienced a craving, up to 4 sprays/hr and 64 sprays/day. Tapered down wks 7-12 (end of wk 9 instructed to be using half as much as in wks 1-6, reducing to max 4 sprays/day by wk 12). Occasional use (max 4 sprays/day) permitted wks 13-24 Control: placebo on same schedule. Level of support: high. General written and oral advice (less than 10min) at study start and less than 3mins at subsequent visits up to and including wk 24 (9 visits total)
Outcomes	Prolonged abstinence from wk 2-52 (also recorded AEs and prolonged abstinence to wks 6 and 24) Validation: CO<10ppm
Notes	New for 2012 update. Funded by McNeil AB, Sweden. Setting: smoking cessation clinics.

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	"Subject randomization list stratified by study site"
Allocation concealment (selection bias)	Low risk	"The supply or resupply of study medication to a subject was determined via an Interactive Voice Response System involving a dispenser pack number randomization list. Both randomization lists were computer-generated."
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind....The supply or resupply of study medication to a subject was determined via an Interactive Voice Response System...the placebo was identical in appearance, but contained capsaicin instead of nicotine to mimic the taste of nicotine"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar percentage lost in both groups (151/318 active, 81/161 placebo). 9% of active group and 7.5% of placebo group withdrew due to adverse events. Those not present at 52 wk follow-up counted as smokers

Villa 1999

Methods	Country: Spain Recruitment: volunteers working in a university health and safety department
Participants	47 smokers (excludes 5 who did not attend at least 2 sessions) 72% F, av.age 36, cpd 24-26
Interventions	1. Nicotine gum (2 mg) 2. No gum Level of support: High (8 weekly group sessions, 5 before TQD. Reduction prior to quitting)
Outcomes	Abstinence at 12m (not defined) Validation: none
Notes	No placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Los participantes fueron distribuidos aleatoriamente"

Villa 1999 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated.

Wallstrom 2000

Methods	Country: Sweden Recruitment: community volunteers
Participants	247 smokers (≥ 10 cpd), motivated to quit. 59% F, av.age 45, av.cpd 18-20
Interventions	1. Nicotine sublingual tablet. Recommended dosage 1 tab/hr for smokers with FTND <7 , 2 tabs/hr for scores ≥ 7 . After 3m treatment, tapering period of 3m if necessary 2. Placebo tablet Level of support: High (brief 5 mins counselling at study visits (0, 1, 2, 3, 6 wks, 3, 6m)
Outcomes	Sustained abstinence at 12m (from wk 2, paper also reports with slips rates Validation: CO <10 ppm
Notes	study was supported by Pharmacia & Upjohn Consumer Health Care

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Subjects were randomized ... using a computer program".
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	"All medication was dispensed by staff who were not involved in treating the subjects"; placebo tablets identical, but without nicotine and with capsaicin
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analyses were based on intention-to-treat. Losses not reported in detail

Wennike 2003a

Methods	
Participants	
Interventions	
Outcomes	
Notes	Excluded study, but contributing data on adverse events

Westman 1993

Methods	Country: USA Recruitment: community volunteers
Participants	158 smokers motivated to quit (excludes 1 participant who used nicotine gum throughout) 57% F, av.age 41, av.cpd 30
Interventions	1. Nicotine patch (25 mg/24hr, 6 wks incl weaning) 2. Placebo patches Level of support: High (Brief counsellor support at 3 clinic visits, 4 telephone counselling sessions, self help materials)
Outcomes	Sustained abstinence at 6m (from 2 wks post-TQD) Validation: CO<8ppm
Notes	study was supported by TBS Laboratories, Piscataway, NJ

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Using simple randomization, the subjects were assigned to active or placebo treatment groups"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	Low risk	"At all times, the subjects and study staff were masked to the treatment assignments". Subject blinding was assessed at wk 6
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs fully reported.

Wisborg 2000

Methods	Country: Denmark Recruitment: volunteers, antenatal clinic
Participants	250 pregnant women who continued to smoke after 1st trimester Av.age 28, av.cpd 14; 43% primiparous
Interventions	1. Nicotine patch (15 mg/16hr, tapering to 10mg, 11 wks total) 2. Placebo patch Level of support: high. 4x15-20 min sessions of midwife counselling at 0, 4, 11 wks from enrolment, and 4 wks before expected delivery
Outcomes	Abstinence at 4 wks prior to delivery and at 1yr postpartum (telephone interview). (Rates at 3m postpartum also reported) Validation: Cotinine <26ng/ml at 4 wks pre-delivery visit only
Notes	First long-term study of nicotine patch in pregnancy. Compliance with patch use was low. Only 17% of active and 8% of placebo used all patches. Data used in Analysis 15. 1 from 2012 is abstinence at 4th prenatal visit rather than continuous abstinence from 2nd to 4th prenatal visit, for consistency with Coleman 2012a . The effect estimate is not altered. Study was funded by the Danish Cancer Society and the Department of Health, and supported by Pharmacia & Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization. "Pharmacia & Upjohn ... generated the randomization list, supplied the patches with randomization numbers, and kept the code between patch number and the specific treatment until data collection was finished"
Allocation concealment (selection bias)	Low risk	"Women ... were assigned consecutive numbers on the randomization list"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Treatment status was not known by the women or the midwife throughout the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data reported, and included as smokers. Analyses were intention-to-treat

Wittchen 2011

Methods	Country: Germany Recruitment: 167 primary care clinics
Participants	467 'current regular smokers' attending primary care clinic for any reason and willing to consider treatment in next 7d 48% M, av.age 43, av.cpd 20
Interventions	1. Minimal intervention (not used in review) 2. CBT 3. CBT + bupropion SR (9-12 wks, 150mg;1/d for first 6d; 2/d thereafter) 4. CBT + NRT for 9-12 wks, patient's choice of patch (7mg-52.5 mg), gum (2 or 4 mg) or spray (10mg/ml) Level of support: high for 2, 3 and 4 (1 excluded from analysis). 4-5 one on one counselling sessions for 20-30min
Outcomes	Abstinence at 12m (from EoT) Validation: none
Notes	New for 2012 update 4 vs 2 included in primary analyses. 4 vs 3 included in Analysis 16.1 comparison of NRT with bupropion. 1 not used as results vs. NRT would be confounded with CBT Patients covered all costs for pharmaceutical treatments. Sponsored by the Federal Ministry of Education and Research; additional support provided by GlaxoSmithKline GmbH & Co and Pharmacia GmbH

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Generated by the study center"; used to put 4 different coloured questionnaires in random order
Allocation concealment (selection bias)	High risk	No concealment: "questionnaires were distributed consecutively to all attending patients on the target days by nurses. Thus, the assignment of patients was entirely dependent on the consecutive attendance of patients and the random assignment of a color. Doctors were not allowed to interfere with this study procedure." But numbers allocated to groups very uneven and discussion states: "Random checks of this procedure [randomization] and quality assurance tests by study monitors revealed that in some cases in the latter part of the study treatment was based on patient and physician preferences."

Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor providers were blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of drop-outs between groups; participants lost to follow-up considered smokers for MA

Wong 1999

Methods	Country: USA Recruitment: community volunteers
Participants	100 smokers (>10 cpd for >1yr) 53% F, av.age 42, av.cpd 28
Interventions	Factorial study of nicotine patch and naltrexone, no placebo patch Nicotine patch: 21 mg (24hr) for 8 wks, tapering to 14 mg for 4 wks Naltrexone: 50mg/day for 12 wks Level of support: High (individual counselling, 15-20 mins at 8 study visits)
Outcomes	Continuous abstinence at 6m Validation: CO \leq 8ppm
Notes	One site from a multicentre trial. No significant main effects of naltrexone, so arms collapsed. Study was funded by DuPont Merck Pharmaceutical Company

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Identification numbers were randomized to the medication kits by computer-generated randomization schedules...[which] were retained by the study sponsor in sealed envelopes"
Allocation concealment (selection bias)	Low risk	Kits assigned sequentially from the appropriate strata (gender stratification)
Blinding (performance bias and detection bias) All outcomes	High risk	See above. Nicotine patch supply was open-label, and placebo patches not used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data assumed to be smoking, and included in the analyses. Losses fully re-

	ported
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Zelman 1992

Methods	Country: USA Recruitment: community volunteers
Participants	116 smokers (excludes 10 early treatment drop-outs evenly distributed across conditions) 54% F, av.age 29-35, av.cpd 25-27
Interventions	1. Rapid smoking + support counselling 2. Rapid smoking + skills training 3. Nicotine gum 2 mg, average 10 pieces/day, duration not stated + skills training 4. Nicotine gum + support counselling. Level of support: high (6x60-75 min group sessions over 2 wks, starting on quit day)
Outcomes	Sustained abstinence at 12m (not more than 2 consecutive days of smoking) Validation: Independent observer report
Notes	No placebo. Group support variants collapsed; 3 & 4 compared to 1 & 2. Study was funded by National Institutes of Health.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding (performance bias and detection bias) All outcomes	High risk	Placebos not used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Early drop-out rates reported, but not included in the analyses. Four 12m drop-outs included as smokers

ALA=American Lung Association; CBT=cognitive behavioural therapy; CO=carbon monoxide in exhaled air; cpd=cigarettes per day; COPD=chronic obstructive pulmonary disease; EOT=end of treatment; FTND=Fagerstrom Test for Nicotine Dependence; hr=hour; ITT=intention to treat; m=month(s); MA=meta-analysis; RTQ=reduce-to-quit; OTC=over-the-counter; PP=point prevalence; pts=participants; SC=smoking cessation; TQD=target quit date; wk=week; yr=year

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

Study	Reason for exclusion
Adelman 2009	Study of Nicotine nasal spray in adolescents. 12 wks follow-up
Allen 2005	Short-term study of effect of nicotine patch on weight change during early abstinence
Allen 2011	Trial of NRT for reduction of agitation and aggression in smokers with schizophrenia
Aubin 2006	Short-term study of the effect of different types of nicotine patch on sleep and smoking urges
Batra 2005	Trial of nicotine gum for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Berlin 2011	Trial of standard NRT dosing vs. dose adaptation according to salivary cotinine
Bock 2010	Trial of computer software quit programme, treatment group offered free NRT. Control group could also use NRT (unsubsidised)
Bolliger 2000	Trial of nicotine inhaler for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Bolliger 2007	Pilot study, not powered to detect efficacy differences between gum, inhaler and mouth spray
Brantmark 1973	Double-blind gum/placebo only for 1st week of clinic, then both groups offered active gum during 6m follow-up period
Carpenter 2003	Compared 2 methods of reducing smoking. Control group also offered NRT if a quit attempt planned
Carpenter 2011	Measured effect of providing NRT samples on participants not initially motivated to quit. Participants were encouraged but not required to make a practice quit attempt. Intervention participants were provided with up to 2 boxes of nicotine lozenges
Chan 2010	Measured effect of counselling + 2 wks free NRT. No data on whether control group also using NRT; unclear if outcome due to counselling or free NRT
Chan 2011	Measured effect of adherence counselling as opposed to effect of NRT itself
Chou 2004	Only 3m follow-up
Christen 1984	Only 15 wks follow-up
Cohen 1989a	Primarily a trial of training dentists. Included in Cochrane review of training of health professionals (Carson 2012)
Cohen 1989b	Primarily a trial of training doctors. Included in Cochrane review of training of health professionals (Carson 2012)

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Croghan 2007	Provides a short-term comparison between nicotine patch, bupropion, and combination therapy. Initial failures randomized to retreatment so no long-term control group
Cummings 2011	Compared provision of free NRT, but participants able to use additional NRT as desired
Dey 1999	Compared free and paid prescription for nicotine patch. Only 14 wks follow-up
Donny 2009	Endpoint not cessation
Ebbert 2009	Study of NRT for smokeless tobacco users
Ebbert 2010	Study of mailed NRT for smokeless tobacco users
Elan Pharm 88-02	No long-term follow-up. Long-term follow-up for 1 site included as Hurt 1990
Elan Pharm 90-03	No long-term follow-up. Long-term follow-up for 1 site included as Fiore 1994A
Etter 2004	Trial of a choice of NRT products for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Fagerstrom 1993	Endpoint withdrawal symptoms not cessation
Fagerstrom 1997	Short-term crossover trial of different types of NRT. For 2 wks smokers could choose a method, for other 2 they were randomly assigned to one of gum, patch, spray, inhaler or tablet. Smoking reduction assessed
Fagerstrom 2000	Short-term crossover trial comparing 2 nicotine delivery devices
Ferguson 2012	Study of offer of free NRT via NHS Quitline services. Control group had access to and used free NRT and other stop smoking medications at high levels; study conditions were very similar for both groups
Finland unpublished	Only 3m follow-up. Comparison of patch & nasal spray (n=51) versus nasal spray alone (n=50). Sustained abstinence rates 18% in each group. Used in a sensitivity analysis of combination therapies
Foulds 1993	Follow-up less than 6m
Garvey 2006	Not enough information currently available (abstract only)
Glover 1992	Follow-up less than 6m
Gross 1989	Study of weight gain. Abstinence outcomes not reported.
Guo 2006	Only 3m follow-up
Hajek 1999	Follow-up less than 6m. There were no significant differences in 12 wk abstinence rates between gum, patch, spray or inhaler groups

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Hanson 2003	Follow-up only 10 wks; primary outcomes were withdrawal, craving, safety and compliance among adolescents
Haustein 2003	Trial of nicotine gum for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Hoch 2006	Not enough information currently available (abstract only)
Hotham 2006	RCT of nicotine patch as adjunct to counselling for pregnant smokers. Only 20 people in each condition, with high withdrawal and low compliance. Results favoured patch condition at delivery (3 versus 0)
Hughes 1989b	No long-term follow-up, primarily a trial of the effect of instructions
Hurt 1995	Analysis of prior nicotine patch studies (to determine if recovering alcoholic smokers were more nicotine-dependent than non-alcoholics and whether the efficacy of nicotine patch therapy was comparable)
Hurt 2003	All participants received nicotine patch
Jarvik 1984	Reports subgroup analysis by level of nicotine dependence. See Schneider 1985A for main outcomes
Jibrail 2010	Only 12 wks follow-up. Study of NRT for smoking abstinence and relationship between CRP and depressed mood during nicotine abstinence
Kapur 2001	Only 12 wks follow-up. Trial of nicotine patch in pregnant smokers. 30 participants
Korberly 1999	Insufficient data in unpublished abstracts to include.
Kozak 1995	Open label study in which smokers with higher nicotine dependence scores were given higher patch doses
Kras 2010	Study of NRT and Hypericum perforatum extract. Only 10 wks follow-up
Krumpe 1989	Only 10 wks follow-up
Kupez 1996	Participants were randomized by month of treatment to group therapy with nicotine patch (n=21) or gum (n=17)
Landfeldt 1998	Only 12 wks follow-up reported in abstract. No evidence of benefit from combining patch and nasal spray compared to nasal spray alone
Leischow 1996b	Only 10 wks follow-up
Levin 1994	Only 9 wks follow-up
Lin 1996	Only 8 wks follow-up
Marsh 2005	Only 3m follow-up, safety study comparing 4 mg lozenge to 4 mg gum

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McCarthy 2006	Only 3m follow-up, study of withdrawal symptoms
McRobbie 2010	Short-term cross-over study assessing withdrawal symptoms and user satisfaction
Meier 1990	Short-term follow-up. Compared dependence individualized to standard dose patch
Merz 1993	Only 3m follow-up
Miller 2009	1377 low-income smokers with quitline and subsidized NRT. Participants informed what group they would be in when first invited to participate
Millie 1989	Only 2m follow-up
Minneker 1989	Only 9 wks follow-up
Molander 2000	Crossover study with 2-day smoke-free periods
Mooney 2005	All participants used nicotine gum
Mulligan 1990	Only 6 wks follow-up
Nackaerts 2009	Insufficient data in published abstract to include (longest follow-up reported in abstract 1m); NRT delivered for max. 7d
Okuyemi 2007	Intervention combined nicotine gum and multiple sessions of motivational interviewing
Oncken 2009	Study of short-term effects of NRT in pregnant smokers
Pomerleau 2003	Compared extended treatment (18 wks) to 10 wk treatment with nicotine patch. No follow-up beyond 18 wks
Rennard 2006	Trial of nicotine inhaler for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Rey 2009	All study participants received nicotine nasal spray. Comparison between different types of instructional guidance for dosing
Rigotti 2009	Assessed effectiveness of adding NRT to rimonabant which has not been licensed for smoking cessation and results may not be generalisable
Roddy 2006	Only 13 wks follow-up. At this point there were no quitters in either the treatment or control group. There were particularly high losses to follow-up (64% overall) and low compliance (median duration of patch use 1wk)
Rose 1990	Only 3 wks follow-up
Rubinstein 2008	Only 12 wks follow-up

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Sachs 1995	Only 6 wks follow-up
Schneider 2004	Short-term cross-over study
Schneider 2008	Outcome was craving and withdrawal, not abstinence
Shahab 2011	Short-term cross-over trial of withdrawal symptom relief
Shiffman 2000a	Compared 10 and 6 wks of patch treatment without longer follow-up. Main outcome was craving and withdrawal
Shiffman 2000b	Comparison between 24 and 16hr patches. Assessment of craving and abstinence over 2 wks
Shiffman 2002a	Only 10 wks follow-up
Shiffman 2002b	Not a randomized trial. Compared prescription and OTC patch in different populations using different methods
Shiffman 2006	Only 6 wks follow-up. High dose (35 mg) patch.
Stapleton 2011	Only 12 wks follow-up
Sun 2009	Only 3m follow-up
Sussman 2004	Presents Project EX program for adolescent tobacco use cessation. Mentions trial of nicotine gum vs herbal gum but insufficient detail provided
Sutherland 1999	Only 3m follow-up. Comparison of patch & nasal spray (n=104) versus patch alone (n=138) or nasal spray alone (n=138). Sustained abstinence rates after 12 wks of treatment 41%, 39%, 40%. Used in a sensitivity analysis of combination therapies
Sutherland 2005	Only 12 wks follow-up
Sutton 1987	Control group received no treatment so effect of nicotine gum is confounded with the brief counselling
Sutton 1988	Control group received no treatment so effect of nicotine gum is confounded with the behavioural support
Thorsteinsson 2001	No long-term follow-up reported
Tonnesen 1996	All study participants received nicotine nasal spray. Comparison between ad lib and fixed schedule dosing
Tsukahara 2010	Follow-up less than 6m. Direct comparison of varenicline and nicotine patch for smoking cessation
Tundulawessa 2010	Only 4 wks follow-up.
Tzivoni 1998	Follow-up less than 6m

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Uyar 2005	Unpublished, insufficient detail in abstract on nicotine patch dose, length of treatment, level of support
Velicer 2006	Participants were sent nicotine patches if they were assessed as potentially ready to quit. They did not have to set a quit date
Vial 2002	Treatment groups differed from control in amount of counselling as well as use of NRT
Vikhireva 2003	Trial of free choice of NRT product vs assigned NRT product from the outcome; no control group
Walker 2011	Trial of familiarisation with NRT and choice of NRT product pre-quit date vs. standard care. Choice of NRT versus patch and/or gum confounded by familiarisation period
Warner 2005	Goal of intervention was relief of stress and withdrawal postoperatively
Wennike 2003	Trial of nicotine gum for smoking reduction in people not making a quit attempt. See Cochrane review of harm reduction interventions, Stead 2007
Williams 2007	Only short-term outcomes reported in conference abstract. Trial terminated early when no benefit of higher dose detected in interim analysis
Wiseman 2005	2 wk crossover study
Working Group 1994	Follow-up less than 6m

OTC=over the counter; m=month(s); wk=week

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

Williams 2009

Trial name or title	Double-Blind, Placebo-Controlled Trial of Nicotine Nasal Spray as an Aid for Smoking Cessation in Schizophrenia
Methods	
Participants	60 individuals with schizophrenia
Interventions	Nicotine nasal spray or placebo spray with behavioural intervention
Outcomes	Abstinence at 12m
Starting date	August 2009
Contact information	Mia H Zimmerman, hanosma@umdnj.edu

Williams 2009 (Continued)

Notes	
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DATA AND ANALYSES

Comparison 1. Any type of NRT versus placebo/ no NRT control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation at 6+ months follow up	119	51265	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.53, 1.68]
1.1 Gum	56	22581	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.40, 1.60]
1.2 Patch	43	19586	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.78]
1.3 Inhaler/ Inhalator	4	976	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.36, 2.67]
1.4 Intranasal Spray	4	887	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.49, 2.73]
1.5 Tablets/ Lozenges	7	3405	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.61, 2.36]
1.6 Oral spray	1	479	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.24, 4.94]
1.7 Choice of NRT product	5	2798	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.39, 1.84]
1.8 Patch and inhaler	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]
1.9 Patch and lozenge	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.01, 3.31]

Comparison 2. Subgroup: Definition of abstinence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine gum. Smoking cessation	56	22581	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.40, 1.60]
1.1 Sustained 12m	32	13737	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.31, 1.56]
1.2 Sustained 6m	8	4187	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [2.14, 3.59]
1.3 PP/uncertain 12m	8	2501	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.12, 1.55]
1.4 PP/uncertain 6m	8	2156	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.20, 1.68]
2 Nicotine patch: Smoking cessation	43	19586	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.78]
2.1 Sustained 12m	21	10928	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.35, 1.70]
2.2 Sustained 6m	9	4640	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.48, 2.09]
2.3 PP/uncertain 12m	6	2582	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.46, 2.05]
2.4 PP/uncertain 6m	7	1436	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.45, 2.58]

Comparison 3. Subgroup: Level of behavioural support

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine gum. Smoking cessation	55	21759	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.40, 1.61]
1.1 Low intensity support	17	11257	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.46, 1.88]
1.2 High intensity individual support	18	6891	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.18, 1.49]
1.3 High intensity group-based support	20	3611	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.40, 1.76]
2 Nicotine patch. Smoking cessation	43	19585	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.78]
2.1 Low intensity support	12	4388	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.49, 2.12]
2.2 High intensity individual support	22	11559	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.41, 1.78]
2.3 High intensity group-based support	10	3638	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.43, 1.90]
3 Long versus short support	3	800	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.88, 1.47]
3.1 Nicotine gum	2	296	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.77, 1.92]
3.2 Nicotine patch	1	504	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.81, 1.49]

Comparison 4. Subgroup: Recruitment /treatment setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Community volunteer (treatment provided in medical setting)	66	24199	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.51, 1.70]
1.1 Nicotine gum	28	8336	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.28, 1.53]
1.2 Nicotine patch	28	10816	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.55, 1.89]
1.3 Nicotine inhaler/inhalator	2	443	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.98, 3.27]
1.4 Nicotine tablet/lozenge	7	3405	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.61, 2.36]
1.5 Nicotine intranasal spray	2	412	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.16, 2.95]
1.6 Combination of NRT	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.01, 3.31]
1.7 Nicotine oral spray	1	479	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.24, 4.94]
2 Smoking clinic	10	2291	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.48, 2.03]
2.1 Nicotine gum	6	1283	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.30, 1.91]
2.2 Nicotine inhaler/inhalator	2	533	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.30, 2.95]
2.3 Nicotine intranasal spray	2	475	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.44, 3.20]
3 Primary care	23	11705	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.34, 1.71]
3.1 Nicotine gum	16	7277	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.35, 1.85]
3.2 Nicotine patch	6	4150	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.17, 1.77]
3.3 Choice of NRT products	1	278	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.83, 2.30]
4 Hospitals	10	5506	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.28, 1.62]
4.1 Nicotine gum	3	2194	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.86, 1.43]
4.2 Nicotine patch	4	1042	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.16, 2.26]

4.3 Combination of NRT	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]
4.4 Choice of NRT products	2	2025	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.36, 1.86]
5 Antenatal clinic	4	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.92, 1.62]
5.1 Nicotine gum	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.50, 2.65]
5.2 Nicotine patch	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.66]
5.3 Choice of NRT products	1	181	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.69, 3.03]
6 Community volunteer (treatment provided in 'over- the-counter' setting)	5	5575	Risk Ratio (M-H, Fixed, 95% CI)	2.71 [2.11, 3.49]
6.1 Nicotine gum	2	3297	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [2.60, 5.52]
6.2 Nicotine patch	3	2278	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.40, 2.79]

Comparison 5. Nicotine gum: 4mg versus 2mg dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking Cessation	5	856	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.12, 1.83]
1.1 High dependency smokers	4	618	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.36, 2.50]
1.2 Low dependency Smokers	3	238	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.49, 1.21]

Comparison 6. Nicotine gum: Fixed versus ad lib dose schedule

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	2	689	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.92, 1.61]

Comparison 7. Nicotine patch: High versus standard dose patches

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation at maximum follow up	8	5101	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.01, 1.29]
1.1 44mg vs 22mg (Intensive counselling)	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.32]
1.2 42mg vs 21mg (pre- and post-cessation)	1	467	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.82, 1.53]
1.3 25mg vs 15mg patches	3	3446	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.00, 1.41]

Comparison 8. Nicotine patch: 16hr or 24hr use, subgroups & direct comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking Cessation	42		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 16 hour patch, active versus placebo	11	7618	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.40, 1.90]
1.2 24 hour patch, active versus placebo	32	10820	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.50, 1.86]
1.3 24 hour versus 16 hour nicotine patch	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.36, 1.34]

Comparison 9. Nicotine patch: Duration of therapy, subgroups & direct comparison

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking Cessation: Indirect comparison	42		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Patch provided for 8 weeks or less	17	6191	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.57, 2.04]
1.2 Patch provided for more than 8 weeks	26	9906	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.43, 1.79]
2 Smoking Cessation: Direct comparisons	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 28 weeks versus 12 weeks	1	2861	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.26]
2.2 24 weeks versus 8 weeks	1	568	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.68, 1.51]
2.3 12 weeks versus 3 weeks	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.41]
2.4 12 weeks versus 6 weeks	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.62, 1.71]
2.5 6 weeks versus 3 weeks	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.67]

Comparison 10. Nicotine patch: Effect of weaning/tapering dose at end of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking Cessation: Indirect comparison	41	17427	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.49, 1.76]
1.1 Nicotine patch versus placebo. No weaning	9	2807	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.50, 2.37]
1.2 Nicotine patch versus placebo. With Weaning	32	14620	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.44, 1.72]
2 Smoking Cessation: Direct comparison	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.32]

2.1 Nicotine patch. Abrupt withdrawal versus weaning	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.32]
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Comparison 11. Combinations of different types of NRT compared to a single type

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long-term smoking cessation	9	4664	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.18, 1.51]
1.1 Patch plus gum versus patch alone	2	395	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.04, 2.94]
1.2 Patch plus gum versus gum alone	1	300	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.88, 2.17]
1.3 Nasal spray plus patch versus patch alone	1	237	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.37, 4.49]
1.4 Nasal spray plus patch versus either patch or spray alone	1	1384	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.85, 1.78]
1.5 Patch plus inhaler versus inhaler alone	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.89, 2.17]
1.6 Patch plus inhaler versus either patch or inhaler alone	1	337	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.17, 1.52]
1.7 Patch plus lozenge versus either patch or lozenge alone	2	1611	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.09, 1.48]

Comparison 12. Direct comparisons between NRT types

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	6	3201	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.07]
1.1 Inhaler versus patch	1	222	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.22, 1.60]
1.2 Nasal spray versus patch	2	1272	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.64, 1.27]
1.3 Lozenge versus patch	3	1707	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.12]

Comparison 13. Purchased NRT without support versus physician support

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation using physician prescribed NRT versus NRT without support (all NRT purchased)	2	820	Risk Ratio (M-H, Fixed, 95% CI)	4.58 [1.18, 17.88]
1.1 Nicotine patch	1	300	Risk Ratio (M-H, Fixed, 95% CI)	6.91 [0.36, 132.59]
1.2 Nicotine inhaler	1	520	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.86, 18.66]

Comparison 14. Pre-cessation initiation of NRT versus post quit day only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	8	2774	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.98, 1.41]
1.1 Patch	6	1772	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [1.08, 1.65]
1.2 Gum	2	406	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.65, 1.43]
1.3 Lozenge	1	596	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.30, 1.21]

Comparison 15. NRT in pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Abstinence at end of pregnancy	4	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.00, 1.68]
1.2 Abstinence at longest post partum follow-up	3	625	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.80, 1.80]

Comparison 16. NRT and bupropion; direct comparisons and combinations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NRT versus bupropion	5	2544	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.87, 1.18]
1.1 Patch versus bupropion	4	1552	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.79, 1.18]
1.2 Lozenge versus bupropion	2	781	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.40]
1.3 Choice of NRT versus bupropion	1	211	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.62, 1.77]

2 Combination therapy versus bupropion alone	4	1991	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.06, 1.45]
2.1 Patch plus bupropion versus bupropion alone	1	489	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.86, 1.73]
2.2 Gum plus bupropion versus bupropion alone	1	452	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.76, 1.60]
2.3 Lozenge plus bupropion versus bupropion alone	2	1050	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.07, 1.58]
3 Combination therapy versus placebo	2	704	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [1.65, 4.12]
3.1 Patch plus bupropion versus placebo	1	405	Risk Ratio (M-H, Fixed, 95% CI)	3.99 [2.03, 7.85]
3.2 Lozenge plus bupropion versus placebo	1	299	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.81, 2.90]

Comparison 17. Palpitations in NRT vs placebo users

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Palpitations/chest pains	15	11074	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [1.37, 2.57]

ADDITIONAL TABLES

Table 1. Nicotine replacement therapies available in the UK

Type	Available doses
Nicotine transdermal patches	Worn over 16 hours: 5 mg, 10mg, 15 mg, 25 mg doses Worn over 24 hours: 7mg, 14 mg, 20mg, 21 mg, 30mg doses*
Nicotine chewing gum	2 mg and 4 mg doses
Nicotine sublingual tablet	2 mg dose
Nicotine lozenge	1 mg, 1.5 mg, 2 mg and 4 mg doses
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 10mg
Nicotine metered nasal spray	0.5 mg dose/spray
Nicotine oral spray	1 mg dose/spray

Information extracted from British National Formulary

* 35 mg/24hr and 53.5 mg/24hr patches available in other regions.

FEEDBACK

How should efficacy be measured?

Summary

The comment (December 2002) states that NRT is not more effective than abrupt cessation. We summarise the supporting arguments and our response to each below:

Reply

1. Pierce & Gilpin (Pierce JP, Gilpin EA. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA* 2002;288:1260-4) found no difference in long-term cessation rates between those who did and who did not use NRT.

This point is addressed in a letter commenting on the study (Stead LF et al. Effectiveness of over-the-counter nicotine replacement therapy. *JAMA* 2002;288:3109-10). The main limitation of their study is that the comparison between groups of people who chose or did not chose to use NRT. These two groups probably differ in many respects related to their chance of successful quitting, and it is impossible to adjust for these possible confounders. Therefore the conclusions of the study are stronger than the evidence justifies.

The criticism authors also cite the Minnesota insurance review (Boyle RG et al. Does insurance coverage for drug therapy affect smoking cessation? *Health Affairs* 2002 Nov-Dec;21:162-8) but it does not seem to give further support to the point made. The main finding of Boyle et al was that introducing an insurance benefit did not increase use of NRT.

2. In the real-world those relying exclusively upon NRT are relapsing and dying at pre-NRT rates.

This is an assertion which is not supported by evidence.

3. NRT study instruction is designed and sequenced in order to foster device transfer. In fact the placebo group must be deprived of critical abrupt cessation instructional tips because if given and followed many could have a negative impact upon the active group.

The review does not make the assertion or implication attributed to it. In the studies involving behavioural support as well as active versus placebo NRT, both active and placebo groups are typically given instructions designed to maximise their chances of success. In these circumstances NRT if anything shows a larger advantage over placebo than it does in minimal support settings. If it is being asserted that placebo groups are being deprived of progressive cigarette weaning or some form of lapse management strategy, there is no evidence to suggest that this approach is effective.

4. The duration of abstinence for NRT groups should begin from the time they stop using NRT.

In response to this it should be noted that it is cigarettes which are causing the harm to health and the aim is to help people stop smoking. Secondly, studies that have followed up smokers long-term show that the medication genuinely improves long-term cessation rates and does not simply set the relapse clock back by the time period when nicotine replacement is being used.

5. There are clinic programmes achieving success rates at least as good as those using NRT.

It is necessary to make direct comparisons ensuring that the same criteria are applied to both groups to be able to draw conclusions.

Finally it must be noted that the Cochrane review shows that NRT is estimated to help some 7% smokers to stop long-term who would not have stopped had they used a similar approach but without NRT. This effect is small but given the health benefits from stopping smoking it is a highly cost-effective life-preserving medication. That is not to say that other interventions, including a different kind of behavioural intervention that was incompatible with NRT could not get better results. However, it is not enough just to assert the possibility; with so many lives at stake it would be imperative to demonstrate the effectiveness of such approaches.

Contributors

Comment by John R. Polito. Response by Tim Lancaster & Lindsay Stead on behalf of review authors. Criticism editor Robert West.

How should effectiveness be measured

Summary

The comment (October 2003) suggests that randomised controlled trials (RCTs) alone cannot establish the effectiveness of an intervention in a population.

Reply

RCTs establish the size of effect of an intervention in a particular context in a sample who are eligible and willing to receive the intervention. It always remains possible that the effect size would be different in a different population under different conditions which is why it is important to assess in RCTs how representative the samples are, and how far the context of the trial represents the likely clinical scenarios in which the intervention will be applied. In other words an RCT seeks to achieve internal validity (corresponding to efficacy) and aspires to maximise external validity (corresponding to effectiveness). A 'real-world' comparison of two groups that are not comparable, and where the differences are not adequately controlled for by design or analysis, does not permit attribution of differences or similarities in outcome to the intervention under investigation.

Contributors

Comment by John Pierce. Reply by Lindsay Stead & Tim Lancaster on behalf of review authors.
Criticism Editors: Robert West (internal), Lisa Bero (external).

Impact of failure to assess blinding on validity

Summary

The comment (May 2004) drew attention to a recent paper (Mooney M, White T, Hatsukami D. The blind spot in the nicotine replacement therapy literature: assessment of the double-blind in clinical trials. *Addictive Behaviors* 2004; 29(4):673-684) that notes that most NRT trials do not report whether blinding was maintained, and of those that did, blinding failure was common. The comment also suggests that smokers failing to quit with an NRT-assisted attempt will not benefit from NRT use in subsequent attempts, and questions whether people who quit smoking but continue to use NRT should be regarded as having quit or not.

Reply

The issue of possible failure of blinding, and hence of possible bias in estimates of treatment effect, is a potential problem in many areas of medicine. Failure to report whether the success of blinding has been tested is widespread (1). There are problems with how best to test the effectiveness of blinding. If participants' guesses are influenced by their success in quitting, then apparent breaking of the blind might be more common where treatment was effective (2).

Where there is evidence that blinding has failed, there still needs to be an assessment of whether this has led to bias in effect estimates. Mooney's paper makes it clear that there are insufficient data to try to assess whether there was evidence of a bias in treatment estimates in the existing trials. There are many potential sources of bias in trials, and we don't have any evidence to suggest that failure of blinding is more of a problem in trials of NRT. We focus on outcomes at least six months after the quit attempt, so that any differential effect of guessing the treatment assignment on the likelihood of successful quitting would need to be long lasting.

Small amounts of nicotine have been used in placebo products in attempts to improve maintenance of the blind by giving a characteristic taste or smell. In most cases the amounts are small. If there were sufficient nicotine to be pharmacologically active it would seem more likely to decrease the effect of active NRT than inflate the treatment effect.

We do not think there is evidence to state that an initial failure with NRT means that subsequent attempts will also fail. People who have a failed quit attempt in a trial seem to have a low chance of success if they immediately try again, as noted in the studies by Gourlay, and Tonnesen (which was uncontrolled). A recent study found a similar poor outcome when people who had failed to quit using nicotine patch were randomized to second line therapy with bupropion or placebo (5). In contrast, two recent studies have found that people who reported failed quit attempts using NRT do at least as well when enrolled in trials and treated with NRT as do NRT-naïve participants. (6,7).

It is important that smokers realise that their chance of a successful long-term quit from each attempt is low and that NRT, although increasing the likelihood of success, is not a 'magic bullet', and this point is made in the review.

We do not agree that people who give up smoking cannot regard themselves as quitters whilst they are using NRT. In the context of a history of chronic smoking over a period of years we do not think that it is a major concern that 6.7% of new gum users may be still using it after six months. The rate of persistent use appears to fall rapidly, with the same study noting a rate of 2.8% for use after a year or more. Rates of persistent patch use are lower.

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- (6) Durcan MJ, White J, Jorenby DE, Fiore MC, Rennard SI, Leischow SJ et al. Impact of prior nicotine replacement therapy on smoking cessation efficacy. *Am J Health Behav* 2002; 26(3):213-220.
- (7) Shiffman S, Dresler CM, Rohay JM. Successful treatment with a nicotine lozenge of smokers with prior failure in pharmacological therapy. *Addiction* 2004; 99(1):83-92.

Contributors

Comment by John R. Polito. Reply by Lindsay Stead, Tim Lancaster
Criticism editor Robert West

WHAT'S NEW

Last assessed as up-to-date: 19 September 2012.

Date	Event	Description
19 September 2012	New search has been performed	Searches updated, 18 new studies added. Table of adverse events added
19 September 2012	New citation required but conclusions have not changed	Additional author. No major changes to conclusions.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 2, 1996

Date	Event	Description
22 June 2011	Amended	Additional table converted to appendix to correct pdf format
16 April 2008	Amended	Converted to new review format.
1 November 2007	New citation required and conclusions have changed	New studies added, some comparisons reorganised, effect measure changed from odds ratio to risk ratio. Minor changes made to the conclusions about the evidence for combinations of NRT types. Authors changed
7 April 2004	New citation required and minor changes	Twelve new studies added, no changes to main conclusions.

CONTRIBUTIONS OF AUTHORS

JHB and LS have extracted data for the most recent update. The review text was updated by LS and JHB with review and suggestions from all other authors. KC extracted data on adverse effects for the most recent update, and completed risk of bias assessments for all included studies. CB contributed in particular to the sections on pre-cessation use of NRT. We thank Annette Pluddemann for help in translating study reports.

DECLARATIONS OF INTEREST

Chris Bullen was involved in a trial on pre-cessation use of NRT ([Bullen 2010](#)) and David Mant was involved in a trial of transdermal nicotine ([ICRF 1994](#)). Chris Silagy, an original author, received funds for consultancy work undertaken (at various times) on behalf of Pharmacia and Upjohn, Marion Merrell Dow, Glaxo Wellcome and SmithKline Beecham.

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NOTES

Prof Chris Silagy died in December 2001. In recognition of his major contribution he remained as first author until 2007. The authorship changed from 2008 issue 1.

INDEX TERMS

Medical Subject Headings (MeSH)

*Tobacco Use Cessation Products; Administration, Cutaneous; Administration, Inhalation; Chewing Gum; Nicotine [administration & dosage]; Nicotinic Agonists [administration & dosage]; Randomized Controlled Trials as Topic; Smoking [prevention & control]; Smoking Cessation [*methods]; Tablets

MeSH check words

Humans