Nicotine replacement therapy for smoking cessation (Review)

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[Intervention Review]

Nicotine replacement therapy for smoking cessation

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ABSTRACT

Background

The aim of nicotine replacement therapy (NRT) is temporarily to 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, nasal spray, 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 strategy

We searched the Cochrane Tobacco Addiction Group trials register for papers with 'nicotine' or 'NRT' in the title, abstract or keywords. Date of most recent search July 2007.

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 132 trials; 111 with over 40,000 participants contributed to the primary comparison between any type of NRT and a placebo or non-NRT control group. The RR of abstinence for any form of NRT relative to control was 1.58 (95% confidence interval [CI]: 1.50 to 1.66). The pooled RR for each type were 1.43 (95% CI: 1.33 to 1.53, 53 trials) for nicotine gum; 1.66 (95% CI: 1.53 to 1.81, 41 trials) for nicotine patch; 1.90 (95% CI: 1.36 to 2.67, 4 trials) for nicotine inhaler; 2.00 (95% CI: 1.63 to 2.45, 6 trials) for oral tablets/lozenges; and 2.02 (95% CI: 1.49 to 3.73, 4 trials) for nicotine nasal spray. 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. Only one study directly compared NRT to another pharmacotherapy. In this study quit rates with nicotine patch were lower than with the antidepressant bupropion.

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 50-70%, 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 spray, 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 132 trials of NRT, with over 40,000 people in the main analysis. It 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%. Most of the studies were performed in people smoking more than 15 cigarettes a day. What limited evidence there is suggests no overall difference in effectiveness of different forms of NRT nor a benefit for using patches beyond 8 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. Preliminary data suggests that starting to use NRT 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.

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 mucosa (chewing gum, lozenges, sublingual tablets, inhaler/inhalator) or skin (transdermal patches). Other products are also under development (Park 2002; D'Orlando 2004; Ikinci 2006; Bolliger 2007).

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 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 22 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 intended to be worn for 16 hours each day. Nicotine lozenges and nicotine chewing gum are available in both 2 mg and 4 mg strengths. 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.

Table 1. Nicotine replacement therapies

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

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 (Fiore 2000; West 2000; NZ NACHD 2002; Woolacott 2002; Italy ISS 2004; Zwar 2004; Le Foll 2005). 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 antidepressants such as bupropion 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 (~1mg/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 amongst people who have relapsed after recent use of NRT?
- Is initiating nicotine patch 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?
- 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 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 (Lancaster 2000).

Types of interventions

Comparisons of NRT (including chewing gum, transdermal patches, nasal spray, inhalers and tablets or lozenges) versus placebo or no nicotine replacement therapy control. The terms 'inhaler' and 'inhalator' (a cigarette-like 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 and comparing more than one type of NRT to a single type.

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/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. It also included trials where the support included multi-session group-based counselling, with frequent sessions around the quit date. In the present update of the review we have attempted to provide a more fine-grained analysis and have distinguished between high intensity group-based support and other trials within the high intensity category.

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. 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.

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 2007 for trials with any reference to the use of nicotine replacement therapy of any type, by searching for 'nicotine' or 'NRT' 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 are: the Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library) Issue 4, 2006, MEDLINE (Ovid) update code 20070629, EMBASE (Ovid) week 20 2007, PsycINFO (Ovid) update code 20070709, Science Citation Index (Web of Science) 1/2007. The trials register also includes trials identified by handsearch 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 after 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 did not repeat the exercise for subsequent updates.

Data collection and analysis

Two individuals independently extracted data from the published reports and abstracts. Disagreements were resolved 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. Reports published only in non-English language journals were examined with the assistance of translators.

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.) Following changes to the Cochrane Tobacco Addiction Group's recommended method of data analysis since this review was last updated, we have changed the way in which we summarize the effects of treatment. We now use the risk ratio rather than the odds ratio for summarizing individual trial outcomes and for estimates of pooled effect. Treatment effects will seem smaller when expressed as risk ratios than when expressed as odds ratios, unless the event rates are very low. For example, if 20 out of 100 participants have quit in the intervention group, and 10 out of 100 in the control group, the risk ratio is 2.0 [(20/100)/(10/100)], whilst the odds ratio is 2.25 [(20/80)/(10/90)]. 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). We estimated a pooled weighted average of risk ratios using a Mantel-Haenszel method, with 95% confidence intervals.

To investigate heterogeneity we use the I^2 statistic, given by the formula [(Q - df)/Q] x 100%, where Q is the chi-squared 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 chi-squared test for heterogeneity will be unduly powerful and may identify statistically significant but clinically unimportant heterogeneity

In comparing NRT to placebo, 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, the intensity of behavioural support and the clinical setting of treatment. 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. Where the estimates of effect clearly differed across subgroups we used metaregression 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. To provide a clinical perspective in the Discussion we estimated the number of people who would need to be treated (NNT) 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 NNT as the inverse of the difference between the treated and untreated quit rates (Altman 2002).

We include in this updated review the Cochrane Tobacco Addiction Group's Glossary of smoking-related terms (Table 2).

Table 2. Glossary of terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products, May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence
Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation': A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood.
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence.
Cessation	Also called 'quitting' The goal of treatment to help people achieve abstinence from smoking or other tobacco use, also used to describe the process of changing the behaviour
Continuous abstinence	Also called 'sustained abstinence' A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence
'Cold Turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support.
Craving	A very intense urge or desire [to smoke]. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614
Dopamine	A neurotransmitter in the brain which regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size': The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco.
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to

Table 2. Glossary of terms (*Continued*)

	relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse.
nAChR	[neural nicotinic acetylcholine receptors]: Areas in the brain which are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking.
Nicotine Replacement Therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges.
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial.
Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. NRT, bupropion
Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation which typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes et al 'Measures of abstinence in clinical trials: issues and recommendations'; Nicotine & Tobacco Research, 2003: 5 (1); 13-25
Relapse	A return to regular smoking after a period of abstinence
Secondhand smoke	Also called passive smoking or environmental tobacco smoke [ETS] A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins.
Self-efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively.

Table 2. Glossary of terms (*Continued*)

Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Tar	The toxic chemicals found in cigarettes. In solid form, it is the brown, tacky residue visible in a cigarette filter and deposited in the lungs of smokers.
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects.
Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614

RESULTS

Description of studies

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

The review includes 132 studies. Trials were conducted in North America (66 studies), Europe (55), Australasia (4 studies), Japan (2 studies), South Africa (2 studies), Taiwan, Thailand, and Venezuela, or in multi-region trials (3 studies). The median sample size was around 200 but ranged from less than 50 to over 1500 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. Cooper 2005 and Pirie 1992 recruited only women and Wisborg 2000 recruited only pregnant women. 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. One trial recruited only people who smoked 10 or fewer cigarettes/day (Ahluwalia 2006). 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). Two trials recruited people with a history of alcohol dependence (Hughes 2003; Kalman 2006). One study recruited people with a history of cardiac disease (Joseph 1996).

Type and dose of nicotine replacement therapy

One hundred and eleven studies 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 53 trials of nicotine gum, 41 of transdermal nicotine patch, six of an oral nicotine tablet or lozenge, four of intranasal nicotine spray, four of nicotine inhaler, one providing patch and inhaler (Hand 2002) and two offering a choice of products (Kralikova 2002; Molyneux 2003). 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, and using 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; Tonnesen 1988). In three trials the physician offered nicotine gum but participants did not necessarily accept or use it (Ockene 1991; Page 1986; Russell 1983). Two trials compared a fixed dosage regimen with an ad lib regimen (Killen 1990; Goldstein 1989). The treatment period was typically 2-3 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. Thirty-one studies used a 24-hour formulation and ten a 16-hour product. 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. Seven trials directly compared a higher dose patch to a standard dose (CEASE 1999; Dale 1995; Hughes 1999; Jorenby 1995; Kalman 2006; Killen 1999; Paoletti 1996). 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 31 of the trials. Four trials directly compared two durations of therapy (Bolin 1999; CEASE 1999; Glavas 2003b; Hilleman 1994).

There are five 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). A fifth trial used 2 mg or 4 mg lozenges according to dependence level 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 6 in total. There are four trials of intranasal nicotine spray (Blondal 1997; Hjalmarson 1994; Schneider 1995; Sutherland 1992), and four trials of nicotine inhaler (Hjalmarson 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).

Six trials compared combinations of two forms of nicotine therapy with only one form; patch with gum to patch alone (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 inhaler to either one alone (Tonnesen 2000) and patch with nasal spray to either one alone (Croghan 2003). In addition to these last two trials allowing a direct comparison between two single types, Lerman 2004 compared patch to nasal spray. A factorial trial compared nicotine and bupropion (Zyban) (Jorenby 1999). Two unpublished trials of combination therapies with only three-month follow up are excluded but contribute to a sensitivity analysis in the results (Sutherland 1999; Finland unpublished).

Treatment setting

Twelve of the gum trials and six of the patch trials in the main comparison 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 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. One trial in an antenatal clinic (Wisborg 2000) is kept in a separate category. Six of the gum trials, one of the nasal spray trials and one of the inhaler trials, were carried out in specialized smoking cessation clinics to which participants had usually been referred. Eight trials (three gum, four patch, one giving a choice of products and one giving a combination of products) were undertaken with hospital in- or out-patients, some of who were recruited because they had a coexisting smoking-related illness. Three patch trials were undertaken in settings intended to resemble 'over-the-counter' (OTC) use of NRT (Davidson 1998; Hays 1999; Sonderskov 1997). 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 in a primary care setting evaluated the effect of cost on the use and efficacy of nicotine gum (Hughes 1991). The remaining gum, patch, inhaler and nasal spray 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. One of the patch trials was conducted in relapsed smokers (Gourlay 1995).

Pre-cessation use of NRT

Four trials (Rose 1994; Rose 1998; Rose 2006; Schuurmans 2004) tested the use of nicotine patch compared to placebo initiated two weeks before the quit date. Following the quit date all study arms received active NRT. Three of the studies included other factorial arms testing mecamylamine. We combined the arms with the same pre-quit NRT conditions in our analysis.

Excluded studies are listed with reasons in the Table of Excluded Studies. 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 exclude one trial which included a test of mailed patches (Velicer 2006). This trial proactively recruited people by telephone and those in one intervention group were 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. They did not need to be intending to make a quit attempt.

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-five studies (28%) reported allocation procedures in sufficient detail to be rated A for their attempts to control selection bias by using a system whereby treatment allocation could not be known or predicted until a participant is enrolled and assigned to a study condition. The majority of studies either did not report how randomization was performed and allocation concealed, or reported it in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made (rated B). A small number of nicotine gum trials randomized to treatment according to day or week of clinic attendance (Page 1986; Richmond 1993; Russell 1983), birth date (Fagerstrom 1984), or smokers' clinic group (McGovern 1992) (rated C). 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 C. The main findings were not sensitive to the exclusion of C, or B and C grade studies from the meta-analysis.

Fifteen gum trials (Gilbert 1989; Gross 1995; Hall 1985; Harackiewicz 1988; Jensen 1991; McGovern 1992; Nakamura 1990; Nebot 1992; Niaura 1994; Niaura 1999; Richmond 1993; Roto 1987; Segnan 1991; Villa 1999; Zelman 1992) and four patch trials (Cinciripini 1996; Otero 2006; Velicer 2006; Wong 1999) did not have a matched placebo control, and a further two had both a placebo and 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. Eighty-six (65%) 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. Thirty-two (24%) reported only the point prevalence of abstinence at the longest follow up. In five studies it was unclear exactly how abstinence was defined. In one trial, participants who smoked up to three cigarettes per week were still classified as abstinent (Abelin 1989). Most studies reported follow up at least 12 months from start of treatment. Thirteen gum trials, 12 patch trials 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.

Biochemical validation of self-reported smoking cessation was used in all but 14 of the trials. Validation of abstinence was carried out by measurement of nicotine metabolites in saliva, urine or blood in 27 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. The main findings were not sensitive to the exclusion of studies that did not attempt to validate abstinence.

Some of the studies involve NRT versus usual care and are inevitably not double-blind in design. We did not assess whether trials reported an assessment of the integrity of blinding, in line with the CONSORT guidelines (CONSORT 1996). 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). Also it is possible that those who believe that they are receiving a placebo may be more likely to stop trying to quit.

Effects of interventions

Each of the five forms of nicotine replacement therapy (NRT) significantly increased the rate of cessation compared to placebo, or no NRT (Comparison 1). This meta-analysis included 111 trials, with over 43,000 participants. For the different types of NRT the risk ratio (RR) was 1.43 (95% confidence interval (CI): 1.33 to 1.53, 53 trials) for nicotine gum, 1.66 (95% CI: 1.53 to 1.81, 41 trials) for nicotine patch, 1.90 (95% CI: 1.36 to 2.67, 4 trials) for nicotine inhaler, 2.00 (95% CI: 1.63 to 2.45, 6 trials) for oral tablets/lozenges, and 2.02 (95% CI: 1.49 to 2.73, 4 trials) for nicotine nasal spray. 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 metaregression with gum as baseline, only the difference with the tablets/lozenges group was statistically significant (P value = .014), whilst the difference with nasal spray was marginally significant (P = .055). The pooled risk ratio for abstinence for any form of NRT relative to control was 1.58 (95% CI: 1.50 to 1.66). The I^2 statistic was 24%, 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 56 (50%) 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 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.

Sensitivity to definition of abstinence

For the nicotine gum and patch trials 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 (Comparison 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 32/53 studies (60%) reported sustained 12-month abstinence and the estimate was almost identical to that for all 53 studies (sustained 12-month RR 1.43, 95% CI 1.31 to 1.56, I^2 = 34%). For nicotine patch, 21/41 studies (51%) reported sustained 12-month abstinence, and the relative risk estimate was lowest in this subgroup (sustained 12-month RR 1.51, 95% CI 1.35 to 1.70, I^2 = 27%). For neither the gum nor patch trials was there evidence from metaregression that the risk ratios differed significantly between subgroups.

Sensitivity to intensity of behavioural support

Each trial 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. We conducted subgroup analyses by intensity of support for gum and patch trials separately (Comparison 3). For nicotine gum the relative risk estimate was similar across all three subgroups. The control group quit rates did vary as expected, averaging 5.9% with low intensity support, 9.8% 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, 6.7% with high intensity individual support and 14.8% with group-based support. Using metaregression 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 (Comparison 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 did a further subgroup analysis based on the setting in which smokers were recruited or treated, for each type of NRT (Comparison 4). For nicotine gum there was no evidence that the relative effect differed substantially across the main subgroups. The subgroup of three trials recruiting hospital in- or outpatients had a lower and non-significant estimated effect. As expected the average control group quit rate was highest amongst smokers recruited and treated in specialist smoking clinics (16%), lower in community volunteers (11%) and lowest in people recruited and treated in primary care settings (5%).

For nicotine patch, effects in subgroups were again generally similar. We did not think that any of the patch trials recruited people attending smoking cessation clinics, but it is possible that some trials in community volunteers provided treatment in specialist clinics. For patches used in hospital settings the results, based on four trials, are consistent with those seen in other settings. In the single trial of a nicotine patch for women trying to quit during pregnancy no benefit of the patch was detected (Wisborg 2000). Nasal spray and inhaler trials did not show differences in effect by setting, and all lozenge trials involved community volunteers. Two other trials of other types of NRT involved hospital patients; Molyneux 2003 offered a choice of type of NRT to hospital inpatients, in which 63% chose patch; the use of NRT increased quit rates but the difference was not significant. Hand 2002 provided a combination of patch and inhaler to hospital in- or outpatients for three weeks, compared to individual counselling alone, and quit rates were similar at 12 months. Three patch studies have assessed the effect of patch amongst community volunteers treated in an 'Over the Counter' (OTC) setting offering low levels of support and little or no contact with healthcare professionals. The effect estimate was similar to that in other settings (RR 1.98, 95% CI 1.40 to 2.79, Comparison 04.02.02).

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 of the physician support compared to no support (RR 4.58, 95% CI: 1.18 to 17.88) (Comparison 13).

Nicotine gum - effects of dose and scheduling

Most trials used the 2 mg dose so we did not do 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. Comparison 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. Comparison 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, Comparison 6).

Nicotine patch - effects of dose and scheduling

Seven trials have compared a high dose patch to standard dose (Comparison 7). 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). 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 seven studies gives an estimated RR of 1.15 (95% CI: 1.01 to 1.30) providing only marginal evidence of a small benefit from higher doses. Three studies had point estimates favouring the lower dose group but there was 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 10 trials that used a 16-hour patch (I^2= 54%) (Comparison 8). 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 difference in treatment effect between 15 trials providing up to eight weeks of pharmacotherapy and 26 offering a longer period. (Comparison 9). 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). Smaller trials comparing a three-week to a 12-week course (Bolin 1999) and a three-week to a six-week course (Glavas 2003b) also found no evidence for a difference.

Indirect comparison did not detect a difference in effect between 31 trials where participants were weaned from patch use by gradually tapering the dose and eight trials where withdrawal was abrupt (Comparison 10). Similarly, no difference was detected in the two trials that directly compared weaning with abrupt withdrawal, (Hilleman 1994; Stapleton 1995).

Combinations of different forms of nicotine therapy

Six trials compared the use of two types of NRT with using a single type only, and one compared two types to no NRT (Hand 2002). Pooling all seven trials suggests a statistically significant benefit (Comparison 11, RR 1.35, 95% CI: 1.11 to 1.63), with little statistical heterogeneity (I^2=25%), but the trials are relatively clinically heterogeneous in the combinations and comparison therapies used. The effect was similar when excluding the trial with a no-NRT control. Only one of the trials, comparing nasal spray and patch with patch alone, showed a significantly higher rate of sustained abstinence at one year with the combined therapy (Blondal 1999). We are aware of two unpublished studies that failed to detect significant short-term effects and did not have longer-term follow up (Sutherland 1999; Finland unpublished). Brief details in Table of Excluded Study). 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 just significant, with or without the relevant unpublished study.

Direct comparison between different types of NRT

Three trials have directly compared types (Comparison 12). None detected significant differences. Pooling the two that compared nasal spray with patch also failed to detect a significant difference (Nasal spray versus patch RR 0.90, 95% CI 0.64 to 1.27). 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.

Pre-cessation use of NRT

The pooled estimate from four trials suggests that using a nicotine patch for a brief period before the target quit day significantly increases the rate of cessation compared with initiating active patch use on the quit day (Comparison 14, RR 1.79, 95% CI 1.17 to 2.72). One other trial included groups who began using nicotine gum or placebo gum before quit day (Herrera 1995). This procedure did not significantly increase quitting at six weeks and long-term outcomes were not reported, but when we tested the inclusion of short-term outcomes in the meta-analysis with the four patch trials a significant effect remained.

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), 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 with bupropion

In one study the cessation rate was significantly lower for nicotine patch and placebo tablet than bupropion and placebo patch (Jorenby 1999). The combination of bupropion and nicotine patch significantly increased the rate over placebo alone or patch alone, but not over bupropion alone (Comparison 15). Another trial compared nicotine gum and bupropion to bupropion alone (Piper 2007); pooling this and the patch+bupropion combination trial also failed to detect a significant additional benefit from NRT.

Adverse Effects

No attempt was made in this overview 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 spray 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. 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). There has been 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).

DISCUSSION

This overview provides reliable evidence from trials including over 40,000 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 3-5% (Hughes 2004a). Use of NRT might be expected to increase the rate by 2-3%, giving a number needed to treat (NNT) of 33-50. 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 NNT of 12.

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 spray the confidence intervals are wide. In a metaregression the estimated difference in effect between gum and the tablet/lozenge subgroup was statistically significant. 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. 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. Three studies have directly compared different types, and differences between them were non-significant individually and when pooled. 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 difference 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 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 from use of the nicotine patch at doses higher than 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).

Combinations of NRT products

The evidence suggests that using a combination of NRT products is better than one product 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. The 2000 US clinical practice guidelines (Fiore 2000) recommended the use of nicotine patch with another form of NRT as a second-line therapy for patients unable to quit on a single type of NRT or bupropion. At that time the strength of evidence was recognized as less than optimal due to the clinical heterogeneity of the studies in the meta-analysis. Two further trials have been published since then, strengthening the evidence. 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).

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 recent letter (Walsh 2007) identified inconsistencies in the classification of low and high intensity support in this review. In response we have changed the classification of a small number of trials. This has not altered 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' use of NRT and use with support from healthcare providers. We did 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, and one interpretation of this is that although the latter group typically had more frequent contact with study co-ordinators, this was not markedly increasing quitting or preventing 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 within patch or gum studies according to the setting of recruitment and treatment. These subgroup analyses 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%. This was similar to the rate amongst community volunteers who were treated in 'OTC' settings. 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, in the subgroup of four studies of nicotine patch amongst people recruited in inpatient and outpatient settings there was evidence of benefit.

There has been continuing debate about the amount of evidence for efficacy of NRT when obtained OTC without advice or support 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 paper 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.

It has been suggested that the 'real world' effectiveness of NRT declines or disappears once it becomes available to purchase without a requirement for contact with a health professional who can offer behavioural support and guidance on appropriate use (Pierce 2002). This was based on a comparison of two cross sectional surveys in California. Before 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). One source of confounding which may have been incompletely controlled is the level of addiction of people who chose to use NRT compared to those who did not (Shiffman 2005). People who have used NRT may also be more likely to recall quit attempts. A second 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. A more recent multicountry 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. Although no study in which participants self-select treatment can be free from the possibility of bias due to unmeasured confounders, the results of this study provide additional reassurance. A review on the impact of NRT on population trends in smoking behaviour concluded that at the moment not enough smokers are using NRT during quit attempts for there to have been a measurable effect (Cummings 2005).

Trials in special populations

One trial of nicotine patch in pregnant women is now included in the review. Women still smoking after their first trimester were recruited, and they were followed up until one year post partum. No significant benefit of treatment was detected, although the confidence interval does not exclude the possibility of benefit. Quit rates one year after delivery were 15% in the patch group and 14% in the placebo group. Using quit rates at the final prenatal follow up did not alter the conclusions, with rates of 28% versus 25%. Possible explanations for the lack of relative benefit may have been low compliance with patch use, and the intensive cessation counselling offered to all participants. We excluded two other 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. Another trial was published too late to be included in this update (Pollak 2007). A recent 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). A large trial is now underway in the UK (Coleman 2007)

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 is now included (Moolchan 2005). This compared nicotine patch, gum, and double placebo. Two trials 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. No significant difference was detected at this 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). Compliance with 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. Munafo and colleagues have reported the results of a meta-analysis of nicotine patch by sex (Munafo 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 there was a non-significant trend in that direction for outcomes at 12 months. 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 (Munafo 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 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.

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 the nicotine patch for a short period before an abrupt 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). Based on meta-analysis of four trials included in this review there appears to be evidence that this increases quit rates over that achieved by post-quitting NRT alone. A large trial of pre-cessation NRT use is now underway in New Zealand.

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.

Retreating 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

There is evidence from one large study (Jorenby 1999) that bupropion is more effective than nicotine patch. A combination of NRT and bupropion has not been found to be significantly more effective than bupropion alone. No trial of a direct comparison between NRT and varenicline has yet been published.

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 whilst 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 overview, which need to be borne in mind: use of tabulated 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 tabulated 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, Egger personal communication) suggests that this is the case. A regression method to assess the symmetry of funnel plots showed evidence of asymmetry, and hence possible publication bias, for both nicotine gum and transdermal patches in an earlier version of this review. For the nicotine inhaler we are aware of one unpublished trial with a non-significant result. A recent 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 nicotine replacement may be smaller than our estimates suggest.

This review excludes studies with less than six months 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, 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 less 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 or 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 only during waking hours (16 hours a day) is as effective as wearing it 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. It should be noted though 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. Nicotine patch was less effective than bupropion in one trial, but further trials are needed to confirm this. Any decision about which pharmacotherapies to use should take into account potential adverse effects as well as benefits.

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. The effect of starting NRT use before the quit date.

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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 Randomization: method not stated
Participants	199 primary care patients 40% F, av.age 41, av.cpd 27
Interventions	1. Nicotine patch, 24hr, 12 wk with weaning; 21mg 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ahluwalia 1998

Methods	Country: USA Recruitment: hospital in- and outpatients Randomization: computer-generated random number table
Participants	410 African American smokers Av.age 47, FTND 6
Interventions	1. Nicotine patch (21mg 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	

Risk of bias

Item	Authors' judgement	Description

Ahluwalia 1998 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Ahluwalia 2006

Methods	Country: USA Recruitment: community volunteers Randomization: central blocked scheme, sequential envelopes
Participants	755 African American light smokers (<= 10 cpd) 67% F, av.age 45, av.cpd 8
Interventions	Factorial trial, behavioural interventions collapsed for this review 1. Nicotine gum (2mg), recommended use tailored to cpd. Highest 10/day for 4wks, tapering for 4wks 2. Placebo gum, 8wks Level of support: high (3 in-person visits at randomization, wk1, wk8, and phone contact at wk3, wk6, wk16, 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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Areechon 1988

Methods	Country: Thailand Recruitment: community volunteers Randomization: method not stated
Participants	200 smokers (>=15 cpd) 6% F, av.age 39, av.cpd 24
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
Notes	Support level reclassified as high, 2008

Areechon 1988 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Blondal 1989

Methods	Country: Iceland Recruitment: community volunteers invited to attend a smoking cessation clinic Randomization: method not stated
Participants	182 smokers (included pipe & cigar users, smoked at least once a day) 57% F, av.age 42, av. tobacco use 21g/day
Interventions	1. Gum (4mg) for at least 1m 2. Placebo gum (containing pepper) for 1m or more Level of support: high (group therapy, 5 1hr 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

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Blondal 1997

Methods	Country: Iceland Recruitment: community volunteers Randomization: computer-generated code, dispensed by pharmacy. Double blind.
Participants	159 smokers (>=1 cpd) 44% F, av.age 42, av. tobacco use 25g/day
Interventions	1. Nicotine nasal spray (NNS) ad lib use. Each dose (2 squirts) delivered 1mg 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 x 6 1hr sessions)
Outcomes	Sustained abstinence at 1 yr (continuous abstinence from quit day, follow up also at 2 yrs) Validation: CO<10ppm at each of 5 follow ups

Blondal 1997 (*Continued*)

Notes	Abstinence at 24m 15/79 vs 11/78. OR 1.4	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Blondal 1999

Methods	Country: Iceland Recruitment: community volunteers Randomization: computer-generated code at pharmacy
Participants	237 smokers (>=1 cpd) 67% F, av.age 41-43, av. tobacco use 25g/day
Interventions	1. Nicotine nasal spray (NNS) (0.5mg/dose) + 15mg 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

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

Bohadana 2000

Methods	Country: France Recruitment: community volunteers Randomization: computer-generated code
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
Interventions	1: Nicotine inhaler, 26wks, combined with nicotine patch (15 mg/16hr) for first 6wks, placebo patch for next 6wks 2: Nicotine inhaler, 26wks, placebo patch for first 12wks

Bohadana 2000 (*Continued*)

	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 (2wks, 6wks, 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Bolin 1999

Methods	Country: USA Recruitment: smoking cessation clinic Randomization: method not stated. Assignment on first day of patch use.	
Participants	98 smokers 16% F, av.age 54, av.cpd 20	
Interventions	1. Nicotine patch for 12wks (21 mg/3wks, 14 mg/3wks, 7 mg/3wks) 2. Nicotine patch for 3wks (21 mg/1wk, 14 mg/1wk, 7 mg/1wk) 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 - 20wks from beginning of programme, 16wks since start of NRT	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Br Thor Society 1983

Methods	Country: UK (95 centres) Recruitment: hospital chest clinics (80%) and inpatient wards Randomization: by numbered envelope
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 (2mg 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Buchkremer 1988

Methods	Country: Germany Recruitment: community volunteers Randomization: method not stated
Participants	131 smokers 50% F, av.age 35, av.cpd 29
Interventions	1. Nicotine Patch (24hr/day, 8wks, 15cm2 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

Risk of bias

Item	Authors' judgement	Description

Buchkremer 1988 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Campbell 1987

Methods	Country: UK Recruitment: primary care (45 GPs in 11 centres) Randomization: method not stated
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 (2mg) 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	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Campbell 1991

Methods	Country: UK Recruitment: hospital inpatients Randomization: not stated
Participants	212 patients with smoking-related diseases 44% F, 53% 50+, 61% smoked >15 cpd
Interventions	1. Nicotine gum 2-4mg (3m) 2. Placebo gum Level of support: high (support at 2, 3, 5wks, 3m, 6m)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Campbell 1991 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Campbell 1996

Methods	Country: UK Recruitment: hospital inpatients and outpatients Randomization: method not stated
Participants	234 adult smokers (>1 cpd in previous wk) (172 outpatients, 62 inpatients) Stratified on FTND 54% F, av.age 49
Interventions	1. Nicotine patch (21mg, 24hr, 12wks 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.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

CEASE 1999

Methods	Country: Multicentre - 36 clinic centres in 17 European countries Recruitment: community volunteers Randomization: central computer-generated allocation list, stratified by centre
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 15mg or 25mg (16hr), duration of active treatment 28 wks (incl 4 wk fading) or 12 wks (incl 4 wk fading). 1. 25mg patch for 28 wks (L-25) 2. 25mg patch for 12 wks (S-25) 3. 15mg patch for 28 wks (L-15) 4. 15mg patch for 12 wks (S-15) 5. Placebo Level of support: high (brief advice & self help brochure, visits at enrolment, TQD, wk 1, 2, 4, 8, 12, 22, 26)

CEASE 1999 (*Continued*)

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 comparison 4, dosages in comparison 8. Level of support reclassified to high for 2007 because of repeated visits. Limited support at these visits	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Cinciripini 1996

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
Participants	64 smokers (>15 cpd) 70% F, av.cpd 29/22	
Interventions	1. Nicotine patch (21mg, 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 64 followed up for 1 yr. 6m quit rates were approx 53% vs 30% (personal communication 2004)	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Clavel 1985

Methods	Country: France Recruitment: community volunteers Randomization: method not stated
Participants	427 smokers (>=5 cpd) 51% F, av.age 34, av.cpd 22 for intermediate group (Clavel 1984)

Clavel 1985 (*Continued*)

Interventions	1. Nicotine gum (2mg) x 1 box 2. Control group (time lock controlled cigarette case) (Acupuncture arm not included in this review) Level of support: High (3 1hr 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Clavel-Chapelon 1992

Methods	Country: France Recruitment: community volunteers Randomization: method not stated
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 (2mg) for up to 6m, max 30/day 2. Placebo gum (contained 1mg unbuffered nicotine) Level of support: high (3 acupuncture session at 0, 7, 28 days)
Outcomes	Abstinence at 13m (1m quitters followed up). 4-yr follow up reported in 1997 with different 1 yr results Validation: none at 1 yr
Notes	First included in 2008 update. Question over inclusion because placebo contained small amount of nicotine Abstinence at 4y 30/481 vs 32/515

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Cooper 2005

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	439 female smokers (>= 10 cpd) Av.age 38, av.cpd 23
Interventions	1. Nicotine gum (2mg), 10-12 pieces/day recommended, for 9 wks, weaning last 3 wks. 2. Placebo gum Level of support: high. x13 1hr weekly cognitive behavioural group sessions. Reduction 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Croghan 2003

Methods	Country: USA, multicentre Recruitment: community volunteers Randomization: central, controlling for cpd, yrs smoked, gender, site
Participants	1384 smokers (>=15 cpd) 58% F, av.age 42, av.cpd 26
Interventions	1. 15mg/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

Risk of bias

Item	Authors' judgement	Description

Croghan 2003 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Dale 1995

Methods	Country: USA Recruitment: community volunteers and smoking clinic attenders. Randomization: method not stated
Participants	71 smokers stratified according to light, moderate and heavy smoking rates. 56% F, av.age 48, av.cpd 26
Interventions	1. 11mg/24hr nicotine patch 2. 22mg/24hr nicotine patch 3. 44mg/24hr nicotine patch 4. Placebo patch for 1 wk followed by 11 or 22mg 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.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Daughton 1991

Methods	Country: USA Recruitment: community volunteers at 2 sites Randomization: method not stated
Participants	158 smokers (at least 1 pack of cpd) 53% F, av.age 42, av.cpd 33
Interventions	1. Nicotine patch (15cm2, 4 wks) worn for 16hr/day 2. Nicotine patch (15cm2, 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
Notes	1 +2 vs 3 in comparison 1. 16 vs 24 hr in comparison 6. Not used in support intensity subgroup analysis

Daughton 1991 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Daughton 1998

Methods	Country: USA (21 sites) Recruitment: catients at family practices - self-referred to study or recruited by physician. Randomization: centrally generated
Participants	369 smokers (> 20 cpd) Av.age 37, av.cpd 27-30
Interventions	1. Nicotine patch (21mg, 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 <= 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.

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

Dautzenberg 2001

Methods	Country: France Recruitment: community volunteers Randomization: method not stated
Participants	433 smokers (excludes 25 from ITT population) 52% F, av.age 39, av.cpd 21
Interventions	1. Nicotine lozenge (1mg, 8-24/day, 6 wks + 6 wks weaning for quitters) 2. Placebo lozenge Level of support: not stated

Dautzenberg 2001 (*Continued*)

Outcomes	PP abstinence at 26 wks Validation: CO<10ppm	
Notes	Based on published abstract	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Davidson 1998

Methods	Country: USA (4 centres) Recruitment: community volunteers in shopping malls (OTC setting) Randomization: central computer-generated schedule	
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 (22mg, 24 hr, 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Ehrsam 1991

Methods	Country: Switzerland Recruitment: university (primary care) Randomization: method not stated
Participants	112 smokers at 2 universities Av.age 26, av.cpd 23

Ehrsam 1991 (*Continued*)

Interventions	1. Nicotine patch (21 or 14mg/24hr, 9 wks, tapered) 2. Placebo patch Level of support: high (no counselling)	
Outcomes	Sustained abstinence at 12m Validation: urinary cotinine	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Fagerstrom 1982

Methods	Country: Sweden Recruitment: smoking cessation clinic Randomization: method not stated	
Participants	100 smokers 59% F	
Interventions	1. Nicotine gum (2mg) 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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Fagerstrom 1984

Methods	Country: Sweden Recruitment: general practices and industrial clinics (primary care) Randomization: by birthdate

Fagerstrom 1984 (*Continued*)

Participants	145 motivated smokers 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 4mg) 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Fee 1982

Methods	Country: UK Recruitment: smoking cessation clinic Randomization: method not stated	
Participants	352 smokers, no other demographic data	
Interventions	1. Gum (2mg) 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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Fiore 1994A

Methods	Country: USA Recruitment: community volunteers Randomization: pregenerated computer sequence	
Participants	88 smokers (>15 cpd)	
Interventions	1. Nicotine patch (22mg/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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Fiore 1994B

Methods	Country: USA Recruitment: community volunteers Randomization: pregenerated computer sequence	
Participants	112 smokers (>15 cpd)	
Interventions	1. Nicotine patch (22mg/24hr, 6 wks incl weaning) 2. Placebo patch Level of support: high (x8 weekly 10-20 min individual counselling)	
Outcomes	PP abstinence at 6m (7 days PP) Validation: CO	
Notes	Reported in same paper as Fiore 1994A	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Fortmann 1995

Methods	Country: USA Setting: community volunteers (telephone recruitment) Randomization: method not stated	
Participants	1044 smokers aged 18-65, able to quit for 24 hr, and without serious illness 42% F, av.age 40, av.cpd 20	
Interventions	1. Nicotine gum (2mg, 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 OR is unaltered but CIs narrow.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Garcia 1989

Methods	Country: Spain Recruitment: primary care Randomization: method not stated	
Participants	106 adult smokers (excludes 81 not beginning treatment) 65% F, av.age 36, av.cpd 25	
Interventions	1. Gum (2mg) 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<=7ppm	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

Garcia 1989 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Garvey 2000

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated, stratified by high- and low-dependence
Participants	608 smokers, aged>20, smoking>5 cpd. 51% F, av.cpd 23
Interventions	1. 4mg nicotine gum (recommended 9-15 pieces), weaning from 2m 2. 2mg 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 + 2mg doses combined in main comparison. 4mg compared to 2mg in comparison of doses

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gilbert 1989

Methods	Country: Canada Recruitment: primary care Randomization: sealed envelopes
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 (2mg) 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

Gilbert 1989 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Glavas 2003a

Methods	Country: Croatia Recruitment: hospital health professionals Randomization: random numbers and sealed envelopes.
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/8 mg 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 1 yr (5-yr abstinence also reported, not used in MA) Validation: CO<11ppm
Notes	

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

Glavas 2003b

Methods	Country: Croatia Recruitment: community volunteers Randomization: sealed numbered envelopes independently prepared
Participants	160 smokers
Interventions	1. Nicotine patch, 24hr, 25mg/15mg/8mg starting dose depending on baseline cpd. 6 wks 2. Nicotine patch, 24hr, 25mg/15mg 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

Glavas 2003b (*Continued*)

Notes	Both durations pooled for main comparison.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Glover 2002

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	241 smokers (>=10 cpd) 54%F, av.age 42, av.cpd 29
Interventions	1. Nicotine sublingual tablet (2mg). 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<10ppm
Notes	
Risk of bias	

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Goldstein 1989

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
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 (2mg); 1 piece/hr for 1st week with tapering over 10 wks 2. Ad lib nicotine gum; to be used when urge to smoke, max 30/day Level of support: high (10x 1hr 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.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gourlay 1995

Methods	Country: Australia Recruitment: community volunteers Randomization: method not stated	
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 30cm2 (21mg/24 hr) for 4 wks, 20cm2 (14mg/24 hr) for 4 wks, 10cm2 (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.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gross 1995

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated, stratified on measures of addiction, no blinding
Participants	177 smokers 51% F, av. age 42, av.cpd 33, av. FTND score 7.8

Gross 1995 (*Continued*)

Interventions	1. Nicotine gum (2mg), 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hall 1985

Methods	Country: USA Recruitment: community volunteers and physician referrals Randomization: 'randomly assigned within time constraints' method not stated
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 - 2mg nicotine gum (period of use not specified) and intensive behavioural treatment 3. Low contact behavioural treatment (4 meetings over 3 wks) and 2mg 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hall 1987

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
Participants	139 adult smokers 47% F, av.age 39, av. cpd 30	
Interventions	2x2 factorial trial of gum and behavioural support 1. Nicotine gum (2mg) up to 12m 2. Placebo gum up to 12m Both levels of behavioural support classified as high intensity & collapsed in analysis (both group-based, x14 75 min sessions, or x5 60min sessions)	
Outcomes	PP abstinence at 12m Validation: CO<8ppm & serum thiocyanate<95 mm/l	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hall 1996

Methods	Country: USA Recruitment: community volunteers Randomization: stratified by history of depression and no. of cpd. Method not stated	
Participants	207 smokers of which 6 excluded from analyses because of protocol breaches 52% F, av.age 40, av.cpd 24	
Interventions	2x2 factorial trial of gum and psychological treatment 1. Nicotine gum (2mg) 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<=10ppm at 8, 12, 26 wks and urinary cotinine<=60ng/ml at 52 wks	
Notes	Psychological treatment arms collapsed, no evidence of a significant interaction	
Risk of bias		
Item	**Authors' judgement**	**Description**

Hall 1996 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Hand 2002

Methods	Country: UK Recruitment: hospital in- or outpatients referred by hospital doctor Randomization: alternation by month of recruitment
Participants	245 patients with smoking-related disease. 46% M, typically aged 50+, smoking 15+ cpd
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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Harackiewicz 1988

Methods	Country: USA Recruitment: primary care (University Health Centre) Randomization: method not stated
Participants	197 smokers (151 used in MA) 63% F, av.age 36, av.cpd 26
Interventions	1. Nicotine gum (2mg, 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 sub-sample of subjects

Harackiewicz 1988 (*Continued*)

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		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hays 1999

Methods	Country: USA (3 sites) Recruitment: community volunteers Randomization: in 2 stages - first to open label or double-blind study, then to active or placebo patch. At stage 1 participants told about their assigned arm and could decline enrolment but could not cross over. No information given on numbers not enrolling but baseline characteristics similar across groups. For stage 2 of randomization both participants and investigators blinded.	
Participants	958 smokers, >15 cpd 50% F, av.age 44, typically smoked 21-40/day	
Interventions	1. Nicotine patches (22mg, 24 hr for 6 wks) purchased by participants, open label 2. Nicotine patches (22mg, 24 hr 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)	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Herrera 1995

Methods	Country: Venezuela Recruitment: community volunteers Randomization: method not stated. Stratified into high and low dependence groups, who were randomized to different treatments.
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. 2mg nicotine gum 2. Placebo gum High dependence smokers (FTND 7-11): 1. 4mg nicotine gum plus 2. 2mg 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 2 yrs (1 yr also reported) Validation: expired CO<6ppm
Notes	Low dependence smokers included in comparison 1. High dependence smokers in comparison 2, 4mg vs 2mg gum. Relapse between 1 & 2 yrs similar between low dependence groups. Higher relapse in 4mg high dependence than 2mg

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hilleman 1994

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated, open label
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 (21mg/24 hr) for 6 wks, no weaning 2. Nicotine patch, 21mg 4 wks, weaning to 14mg 4 wks, 7mg 4 wks Level of support: high (12 weekly behaviour therapy sessions), does not contribute to intensity subgroup comparison

Hilleman 1994 (*Continued*)

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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hjalmarson 1984

Methods	Country: Sweden Recruitment: smoking cessation clinic Randomization: randomized by therapy group (26). Unclear if enroller blind, but therapists blind	
Participants	206 smokers 56% F, av.age 42, av. cpd 24	
Interventions	1. Nicotine gum (2mg) (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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hjalmarson 1994

Methods	Country: Sweden Recruitment: smoking cessation clinic Randomization: all participants attending first treatment clinic session randomized so recruitment bias unlikely, but treatment allocater not blinded, so that household members could be given same medication. Therapist and subjects were blinded
Participants	248 smokers 57% F, av.age 45, av. cpd 22

Hjalmarson 1994 (*Continued*)

Interventions	1. Nicotine nasal spray (0.5 mg/spray) used as required up to 40 mg/day for up to 1 yr. 2. Placebo spray Level of support: high (x8 45-60 min group sessions over 6 wks with clinical psychologist)
Outcomes	Sustained abstinence at 12m Validation: CO<10ppm
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hjalmarson 1997

Methods	Country: Sweden Recruitment: smoking cessation clinic Randomization: participants assigned a number on attending first group session. Numbers on a list randomizing to medication. Participants from the same household randomized to same treatment.
Participants	247 smokers (>10 cpd) who had previously made a serious attempt to stop using nicotine gum 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 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	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Huber 1988

Methods	Country: Germany Recruitment: community volunteers Randomization: method not stated
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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hughes 1989

Methods	Country: USA Recruitment: primary care Randomization: a random digit entered to their subject number used to dispense gum
Participants	315 daily smokers 56% F, av. age 37, av. cpd 29
Interventions	1. Nicotine gum (2mg 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.

Risk of bias

Item	Authors' judgement	Description

Hughes 1989 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Hughes 1990

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	78 smokers 54% F, av.age 34-44, av. cpd 24-30
Interventions	1. Placebo gum 2. 1mg nicotine gum (unbuffered formula, available dose approx 0.5mg) 3. 2mg nicotine gum 4. 4mg 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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hughes 1991

Methods	Country: USA Recruitment: primary care patients Randomization: sealed envelopes
Participants	106 smokers 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 2mg) 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

Hughes 1991 (*Continued*)

Notes	Tested effect of price on gum use and efficacy. Results given in text, not included in any MA	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Hughes 1999

Methods	Country: USA (12 sites), Australia (1 site) Recruitment: community volunteers & referrals Randomization: method not stated
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. 42mg nicotine patch (24 hr, 6 wks + 10 wks tapering) 2. 35mg nicotine patch 3. 21mg 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 post-quit) verified at each follow-up visit. (12m follow up only completed for 11 of 13 sites) Validation: CO=<10ppm
Notes	All doses pooled in comparison 1 against placebo. 44mg vs 22mg in dose-response comparison 6m abstinence rates used in analyses since not all centres completed 12m follow up due to sponsor termination of study. Denominators confirmed by author.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hughes 2003

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	115 smokers with a history of alcohol dependence, >=30 cpd 68% M, av.cpd 30

Hughes 2003 (*Continued*)

Interventions	1.Nicotine patch (21mg, 24 hr, 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 post-quit) Validation: CO=<10ppm at each follow-up visit	
Notes	Unadjusted ORs used in MA not significant, significant when adjusted for smoking variables.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hurt 1990

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
Participants	62 adult smokers (>20 cpd) 53% F, av.age 39, av. cpd 30	
Interventions	1. Nicotine patch (30mg 24 hrs, 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 x 6 weekly visits)	
Outcomes	Sustained abstinence at 12m (quit by wk 6, & all subsequent visits) Validation: CO<=8ppm	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Hurt 1994

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	240 adult smokers (>20 cpd) 53% F, av.age 43, av. cpd 30

Hurt 1994 (*Continued*)

Interventions	1. Nicotine patch (22mg/24 hr, 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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

ICRF 1994

Methods	Country: UK Setting: primary care (19 general practices) Randomization: random allocation of study numbers to treatment group and sequential allocation of study numbers.	
Participants	1686 smokers (>15 cpd) 55% F, av.age 43, av. cpd 24	
Interventions	1. Nicotine patch (21mg/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	8 year follow up in Yudkin 2003, OR remained similar.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Jamrozik 1984

Methods	Country: UK Recruitment: primary care (6 general practices) Randomization: alphabetical code list, doctors & patients blind
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 (2mg) 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<=12ppm
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Jarvis 1982

Methods	Country: UK Recruitment: smoking cessation clinic Randomization: in groups of 10 taken in order from waiting list, sequence generation & concealment not described
Participants	116 clinic attenders 55% F, av.age 41/38, av. cpd 31/27 (P<0.05)
Interventions	1. Nicotine gum (2mg) unrestricted amount for at least 3m 2. Placebo gum (1mg unbuffered nicotine) Level of support: high (group therapy x6 1 hr 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jensen 1991

Methods	Country: Denmark Recruitment: smoking cessation clinic Randomization: smokers randomized to groups and groups to treatment. No information on sequence generation or allocation concealment. Participants not blind
Participants	293 adult smokers (>10 cpd) in relevant arms 54% F, av. age 42, av. cpd 21-22
Interventions	1. Nicotine gum (2mg for 3m) 2. Silver acetate chewing gum (not used in MA) 3. Standard chewing gum 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jorenby 1995

Methods	Country: USA Recruitment: community volunteers Randomization: double-blind, no further details
Participants	504 adult smokers (>=15 cpd) 53% F, av.age 44, av. cpd ~27
Interventions	1. Nicotine patch 22mg for 6 wks then 2 wks 11mg with minimal counselling 2. Same patch, individual counselling 3. Same patch, group counselling. 4. 44mg patch for 4 wks then 2 wks 22mg then 2 wks 11mg with minimal counselling 5. Same patch, individual counselling 6. Same patch, group counselling.
Outcomes	Abstinence (>1 wk) at 6m Validation: CO<10ppm
Notes	Does not contribute to comparison 1. Support levels collapsed in comparison 8 between high and standard dose

Risk of bias

Jorenby 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Jorenby 1999

Methods	Country: USA (4 sites) Recruitment: community volunteers Randomization: method not stated. Unequal cell design, not balanced within sites
Participants	893 smokers, (>15 cpd) 52% F, av.age 42-44, av. cpd 25-28
Interventions	1. Nicotine patch (21mg/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 telephone 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 comparisons. Combinations compared in Comparison 9

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Joseph 1996

Methods	Country: USA, multicentre trial Recruitment: 10 Veterans Affairs Medical Centers Randomization: Co-ordinating centre used computer-generated schedule to randomly assign in blocks of 10
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, (21mg/24hr for 6 wks, 14mg for 2 wks, 7mg for 2 wks) 2. Placebo patch Level of support: High (self-help pamphlets and brief behavioural counselling on 3 occasions)

Joseph 1996 (*Continued*)

Outcomes	PP abstinence at 6m (Joseph 1996), 12m (Joseph 1999) Validation: CO<=10ppm	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Kalman 2006

Methods	Country: USA Recruitment: Veterans Admin Medical Centre and community-based substance abuse treatment facility Randomization: method not stated. (unblinded during dose tapering)
Participants	130 smokers (>=20 cpd with history of alcohol dependence & >=2m abstinence from alcohol & illicit drugs) 84%M, av.age 47, Av. cpd 32
Interventions	Dose response trial 1. Nicotine patch (42mg (2x21mg)) 4 wks, then tapered for 8 wks 2. Nicotine patch (21mg & placebo) for 4 wks then same tapering as 1. (Level of support: high (x5 1 hr 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
Risk of bias	
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Killen 1984

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	64 adult smokers 72% F, av.age 44, av. cpd 32

Killen 1984 (*Continued*)

Interventions	1. Nicotine gum (2mg) 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Killen 1990

Methods	Country: USA Recruitment: community volunteers who had abstained from smoking for 48 hrs Randomization: method not stated	
Participants	1218 adult smokers 52% F, av.age 43, av. cpd 25.	
Interventions	1. Nicotine gum (2mg, 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Killen 1997

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
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 (21mg/24hr) for 8 wks, 14mg 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 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Killen 1999

Methods	Country: USA Recruitment: community volunteers responding to advertisements - heavy smokers selected from responders Randomization: method not stated
Participants	408 heavy smokers (> 25 cpd) 59% M, av.age 47, av. cpd 36, Modified FTND score 18
Interventions	1. 25mg nicotine patch for 6 wks (16 hr, no tapering) 2. 15mg 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)
Notes	Does not contribute to comparison 1. 85% of self-reported quitters provided samples for validation at 12m

Killen 1999 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kornitzer 1987

Methods	Country: Belgium Recruitment: worksite primary care clinic Randomization: method not stated
Participants	199 smokers (av cpd 24-5)
Interventions	1. Nicotine gum (4mg) for at least 3m 2. Nicotine gum (2mg) for same time period Level of support: low
Outcomes	PP abstinence at 12m Validation: cotinine and carboxyhemaglobin in a sub-sample of subjects
Notes	Contributes data only to 4mg vs 2mg Comparison 2

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Kornitzer 1995

Methods	Country: Belgium Recruitment: worksite volunteers Randomization: computer-generated list, blinded
Participants	374 healthy smokers (>10 cpd for >3 yrs) 61% M, av. age 40, av. cpd 25
Interventions	1. Nicotine patch (12 wks 15mg/16hr, 6 wks 10mg, 6 wks 5mg) and nicotine gum (2mg, 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.

Kornitzer 1995 (*Continued*)

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

Kralikova 2002

Methods	Country: Czech Republic Recruitment: community volunteers 'wanting to reduce' Randomization: method not stated
Participants	314 smokers (>=15 cpd) 58% F, av.age 46, av. cpd 25
Interventions	1. Choice of 4mg 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

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Leischow 1996

Methods	Country: USA Recruitment: community volunteers Randomization: computer-generated code
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, 10 in all)

Leischow 1996 (*Continued*)

Outcomes	Sustained abstinence at 12m Validation: CO<10ppm at each follow up	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Leischow 1999

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
Participants	300 smokers prepared to purchase patch and make a quit attempt 45% F, av.age 43, av. cpd 26	
Interventions	1. Nicotine patch (15mg/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.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Leischow 2004

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	520 smokers prepared to purchase inhaler and make a quit attempt 51% F, av.age 48, av. cpd 26

Leischow 2004 (*Continued*)

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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Lerman 2004

Methods	Country: USA Recruitment: community volunteers and referrals Randomization: computer-generated, operated by data manager. Allocation concealment judged adequate, after allocation only outcome assessors blind
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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Lewis 1998

Methods	Country: USA Recruitment: hospitalised patients willing to make a quit attempt Randomization: predetermined computer-generated code
Participants	185 smokers (>=10 cpd) 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 (22mg/ 24hrs for 3 wks, tapered to 11mg 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<=10ppm
Notes	3 vs 1+2 used in MAs (Restricting control to 2 only would reduce the OR to 1.6)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Llivina 1988

Methods	Country: Spain Recruitment: smoking cessation clinic Randomization: method not stated
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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Malcolm 1980

Methods	Country: UK Recruitment: community volunteers Randomization: method not stated	
Participants	194 smokers 40-43% F, av.age 44-46, av. cpd 25-26	
Interventions	1. Nicotine gum (2mg) 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<=1.6%	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Marshall 1985

Methods	Country: UK Setting: primary care - patients responding to a postcard from a GP (i.e. selected by motivation) Randomization: method not stated, married couples allocated to same group	
Participants	200 smokers, 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: expired CO.	
Notes	Does not contribute to comparison 1. Test of different intensity of support.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

McGovern 1992

Methods	Country: USA Recruitment: community volunteers Randomization: by clinic group	
Participants	293 adult smokers. Av. cpd not stated. 58% smoked >25 cpd.	
Interventions	1. ALA Freedom from Smoking clinic program plus nicotine gum (2mg 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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Molyneux 2003

Methods	Country: UK Recruitment: hospital Randomization: in blocks of 9, concealment not described	
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 (15mg 16 hr patch/ 2mg or 4mg gum, 10mg inhalator/ 2mg sublingual tablet, 0.5mg 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Moolchan 2005

Methods	Country: USA Recruitment: community volunteers Randomization: central pharmacy, with replacement of non-completer
Participants	120 adolescent (age 13-17) smokers (>=10 cpd) 70% F, av.age 15, av. cpd 19
Interventions	1. Nicotine patch (21mg, or 14mg for <20 cpd) for 6 wks +placebo gum 2. Nicotine gum (4mg, or 2mg for <24 cpd) for 6 wks + placebo patch 3. Double placebo Level of support: high (x11 45-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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Mori 1992

Methods	Country: Japan Recruitment: hospital Randomization: method not stated
Participants	264 smokers with smoking-related illness. Number of cpd not stated.
Interventions	1. Nicotine gum 2mg for 3m 2. Placebo gum Level of support: low
Outcomes	Abstinence (not defined) at 6m Validation: serum thiocyanate
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Nakamura 1990

Methods	Country: Japan Recruitment: community volunteers Randomization: by number in screening programme, and by worksite	
Participants	60 adult smokers. Av. cpd 31	
Interventions	1. Nicotine gum (2mg, 2m or longer) 2. Non-placebo control group received counselling Level of support: high	
Outcomes	Sustained abstinence at 6m Validation: CO	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Nebot 1992

Methods	Country: Spain Recruitment: primary care Randomization: physicians randomized to treatment, method not stated. No information about avoidance of selection bias in recruitment of smokers so rated C	
Participants	425 unselected smokers. 60-70% smoking > 15 cigs/day	
Interventions	1. Brief counselling from physician 2. Physician counselling plus nicotine gum 3. Health education from nurse Level of support: low	
Outcomes	PP abstinence at 12m Validation: CO	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Niaura 1994

Methods	Country: USA Recruitment: outpatient settings and physician referrals (primary care subgroup) Randomization: method not stated. Stratified by nicotine dependence
Participants	77 low dependence (FTND<=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 2mg, 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Niaura 1999

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated, no placebo
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 (2mg) 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.

Risk of bias

Item	Authors' judgement	Description

Allocation concealment?	Unclear	B - Unclear

Ockene 1991

Methods	Country: USA Recruitment: primary care Randomization: Each physician delivered 1 of the 3 interventions according to instructions in a packet for each patient.
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 (2mg) 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.

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Oncken 2007

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated, 3:5 ratio
Participants	152 postmenopausal women (<=10 cpd) Av.cigs/day 22, av.age 54/56.6
Interventions	1. Nicotine patch (21mg for 13 wks incl 4 wks tapering) 2. Placebo patch Level of support: high (7 visits incl 4 x 2 hr group counselling, 1 pre-TQD)
Outcomes	PP abstinence at 16m (12m post-EOT) Validation: CO<8ppm
Notes	New for 2008 update

Oncken 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Otero 2006

Methods	Country: Brazil Recruitment: community volunteers Randomization: method not stated
Participants	1199 smokers (includes 254 non-attenders) 63%F, av.age 42, 46% smoked >20 cpd
Interventions	Factorial design with multiple levels of behavioural support 1. Nicotine patch (21mg, 14mg 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	New for 2008 update. Contributes to both high & low support subgroups. No placebo. 29% of control group participants asked for nicotine patch after the 3m follow up which might have increase control group quit rates at 12m

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Page 1986

Methods	Country: Canada Recruitment: primary care (5 family practices in Ontario) Randomization: by day of attendance
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 (2mg) Level of support: low

Outcomes	Sustained abstinence at 6m Validation: none	
Notes	3 vs 1+2 No placebo	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Paoletti 1996

Methods	Country: Italy Recruitment: community volunteers Randomization: method not stated, parallel group design	
Participants	297 smokers (>=10 cpd) 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<250ng/ml) 1. Nicotine patch (15mg/16hr, 18 wks incl taper) 2. Placebo patch Stratum B (Baseline cotinine>250ng/ml) 3. Nicotine patch 15mg 4. Nicotine patch 25mg 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)	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Perng 1998

Methods	Country: Taiwan Recruitment: outpatient chest clinics, volunteers Randomization: performed by an independent facility
Participants	62 smokers (>20 cpd) 94% M, av.age 62, av. cpd 26
Interventions	1. Nicotine patch (24mg/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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Piper 2007

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	608 smokers 58% F, av.age 42, av cpd 22, no details of depression history
Interventions	1. Nicotine gum (4mg, 8 wks) and bupropion (300mg, 9 wks) 2. Placebo gum and bupropion 3. Double placebo (Not used in MA) All arms: 3x 10 min counselling
Outcomes	PP abstinence at 12m Validation: CO & cotinine
Notes	New for 2008 update. Identified from conference abstracts, we use data from paper published after date of search. Contributes to comparison of NRT + bupropion versus bupropion alone

Risk of bias

Item	Authors' judgement	Description

Piper 2007 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Pirie 1992

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	417 women smokers. Av cpd 25-27.
Interventions	1. Group therapy 2. Group therapy plus weight control programme 3. Group therapy plus nicotine gum 4. Group therapy plus weight control programme and nicotine gum. Gum type: 2mg ad lib Level of support: high
Outcomes	Sustained abstinence at 12m Validation: expired CO
Notes	3 & 4 compared to 1 & 2

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Prapavessis 2007

Methods	Country: New Zealand Recruitment: community volunteers Randomization: computer-generated but no information on concealment
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 (21mg/24hr for 10 wks, no weaning) 2. No patch Level of support: High (36 45 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 <10 ng/mL
Notes	New for 2008 update No placebo

Prapavessis 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Puska 1979

Methods	Country: Finland Recruitment: community volunteers Randomization: method not stated
Participants	229 adult smokers, 80% smoking>5 cpd
Interventions	1. Nicotine gum (4mg) for 3 wks 2. Placebo gum for 3 wks Level of support: high (group therapy)
Outcomes	PP abstinence at 6m. Validation: none
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Puska 1995

Methods	Country: Finland Recruitment: community volunteers Randomization: method not stated
Participants	300 volunteers aged 20-65, smoking >10 cpd for >3 yrs, no serious illness
Interventions	1. Nicotine patch (15mg/16hrs, 12 wks+ 6 wks taper) plus nicotine gum (2mg 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

Risk of bias

Puska 1995 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Richmond 1993

Methods	Country: Australia Recruitment: primary care Randomization: by week of attendance
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
Notes	No placebo Continuous abstinence rates from Richmond 1993 paper used from 2007. Group 3 not included.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Richmond 1994

Methods	Country: Australia Recruitment: community volunteers Randomization: central pharmacy generation
Participants	315 smokers, av. cpd 29.
Interventions	1. Nicotine patch (24 hr, 22mg/24 hr, 10 wks incl tapering) 2. Placebo patch Level of support: high (group therapy)
Outcomes	Sustained abstinence at 12m (reported in Richmond 1997, which also reports 3 yr follow up, not used in MA) Validation: expired CO
Notes	3 yr abstinence 21/153 vs 8/152, OR 2.9 - higher than at 12m

Richmond 1994 (*Continued*)

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

Rose 1994

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	48 smokers (>=20 cpd) 60% F, av.age 34, av. cpd 27-29
Interventions	2x2 factorial trial. Mecamylamine arms collapsed. 1. Nicotine patch (21mg/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<=8ppm
Notes	Contributes only to pre-cessation comparison.

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Rose 1998

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	80 smokers (>=20 cpd) 49% F, av.age 41, av. cpd 30
Interventions	2x2 factorial trial. Mecamylamine pretreatment arms collapsed. 1. Nicotine patch (21mg/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

Rose 1998 (*Continued*)

Outcomes	Sustained abstinence at 6m Validation: CO<=8ppm	
Notes	Contributes only to pre-cessation comparison.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Rose 2006

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	96 smokers (>=20 cpd) 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 (21mg/24 hr for 2 wks before TQD) 2. Placebo All participants received mecamylamine 2.5mg bid for 4 wks post-TQD, and either 0, 21 or 42mg patch.
Outcomes	PP abstinence at 6m Validation: CO<=8ppm
Notes	Contributes only to pre-cessation comparison. Post-quit conditions did not affect cessation, data not reported in paper
Risk of bias	

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Roto 1987

Methods	Country: Finland Recruitment: primary care (occupational health centres) Randomization: method not stated
Participants	121 smokers (>10 cpd, >1 yr) 43% F

Roto 1987 (*Continued*)

Interventions	1. Nicotine gum (2mg and 4mg), + advice 2. Advice only (no placebo) Level of support: low	
Outcomes	Abstinence at 6m (not defined) Validation: not described	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Russell 1983

Methods	Country: UK Recruitment: primary care - consecutive attenders admitting to being cigarette smokers and consenting to participate at 6 general practices Randomization: according to week of attendance	
Participants	2106 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.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Sachs 1993

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	220 adult smokers. Av. cpd 28-9.
Interventions	1. Nicotine patch (15mg/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	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schneider 1985A

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
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, (2mg 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.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Schneider 1985B

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
Participants	36 heavy smokers (>1 pack/day) no demographic details	
Interventions	Study B (pilot dispensary study): 1. Nicotine gum, (2mg duration not stated) 2. Placebo gum 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.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Schneider 1995

Methods	Country: USA Recruitment: community volunteers (radio and newspaper ads) Randomization: method not stated	
Participants	255 adults with no serious illness, 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: 0.5mg of nicotine per spray. Not less than 8 doses/day and not 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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Schneider 1996

Methods	Country: USA Recruitment: community volunteers Randomization: centralized computer-generated by a 3rd party	
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		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Schuurmans 2004

Methods	Country: South Africa Recruitment: community volunteers Randomization: computer-generated, independent, blinding maintained	
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 (15mg) 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Segnan 1991

Methods	Country: Italy Recruitment: primary care - consecutive patients attending 44 general practices Randomization: sequential, sealed envelopes
Participants	923 practice attenders aged 20-60. Av. cpd not stated. Therapists: GPs who had undergone a 3 hr training session
Interventions	1. Advice and leaflet 2. Repeated counselling (followup 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

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Shiffman 2002 (2mg)

Methods	Country: USA & UK (15 sites) Recruitment: community volunteers Randomization: method not stated
Participants	917 smokers, time to first cigarette >30 mins. 58% F, Av age 41, cpd 17
Interventions	1. Nicotine lozenge, 2mg. Recommended dose 1 every 1-2 hrs, 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<=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 (4mg)

Risk of bias

Item	Authors' judgement	Description

Shiffman 2002 (2mg) (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Shiffman 2002 (4mg)

Methods	Country: USA & UK (15 sites) Recruitment: community volunteers Randomization: method not stated
Participants	901 smokers, time to first cigarette <30 mins 55% F, Av age 44, cpd 26
Interventions	1. Nicotine lozenge, 4mg. Recommended dose 1 every 1-2 hrs, 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<=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 (2mg)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Sonderskov 1997

Methods	Country: Denmark Recruitment: customers seeking to buy nicotine patches over the counter at 42 pharmacies Randomization: sequential treatment packages, stratified by smoking level
Participants	522 smokers of >10 cpd. Smokers of >20 cpd used a higher dose patch than lower rate smokers. 50% F, av.age 39
Interventions	1. Nicotine patch (24 hr). >20/day smokers used 21mg for 4 wks, 14mg for 4 wks, 7mg for 4 wks. Smokers of <20/day used 14mg 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	

Sonderskov 1997 (*Continued*)

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

Stapleton 1995

Methods	Country: UK Setting: primary care Randomization: computer-generated list
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 (15mg/16 hr for 18 wks) 2. Nicotine patch with dose increase to 25mg 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
Notes	The dose increase after 1 wk did not affect cessation, 1+2 vs 3 in comparison 1.

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

Sutherland 1992

Methods	Country: UK Recruitment: smoking cessation clinic Randomization: drew card with A or P for active or placebo allocation
Participants	227 smokers. Av. cpd 25-27
Interventions	1. Nicotine nasal spray, maximum 40 mg/day 2. Placebo spray Level of support: High (4 wks group support)
Outcomes	Sustained abstinence at 12m Validation: CO

Sutherland 1992 (*Continued*)

Notes	Follow up beyond 1 yr reported in Stapleton 1998 Abstinence for 3 yrs 19/116 vs 7/111, OR 2.9	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

TNSG 1991

Methods	Country: USA (9 sites) Recruitment: community volunteers (treated at smoking cessation clinics) Randomization: method not stated	
Participants	808 smokers 60% F, av.age 43, av. cpd 31	
Interventions	1. Nicotine patch (21mg /24 hr, 6 wks+) 2. Nicotine patch 14mg 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Tonnesen 1988

Methods	Country: Denmark Recruitment: primary care Randomization: by numbered envelope
Participants	113 low to medium dependence smokers (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

Tonnesen 1988 (*Continued*)

Interventions	Group A: Low/medium dependence 1. Nicotine Gum (2mg) for 16 wks 2. Placebo Group B: High dependence 1. Nicotine gum 4mg for 6 wks then 2mg 2. Nicotine gum 2mg Level of support: high (informal group support, 6 sessions)	
Outcomes	Sustained abstinence at 12m (24m also reported) Validation: expired 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Tonnesen 1991

Methods	Country: Denmark Recruitment: community volunteers Randomization: packages labelled with consecutive numbers from computer-generated random code	
Participants	289 smokers (>=10 cpd) 70% F, av.age 45, av. cpd 22	
Interventions	1. Nicotine patch (15mg/16 hr 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: expired 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Tonnesen 1993

Methods	Country: Denmark Recruitment: community volunteers Randomization: computer-generated randomization code
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: expired CO
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Tonnesen 2000

Methods	Country: Denmark Recruitment: referrals to lung clinic Randomization: computer-generated list of random numbers, unclear whether allocation concealed (open label)
Participants	446 smokers (>=10 cpd) 52% F, av.age 49, av. cpd 18
Interventions	1. 5mg nicotine patch (placebo) 2. 15mg (16 hr) nicotine patch for 12 wks (up to 9m on request) 3. Nicotine inhaler (4-12/day ad lib) 4. Combination, 15mg patch and inhaler 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.

Risk of bias

Item	Authors' judgement	Description

Tonnesen 2000 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Tonnesen 2006

Methods	Country: Denmark Recruitment: lung clinic patients & newspaper adverts Randomization: blocked list, no information on concealment
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 (2mg), 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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Villa 1999

Methods	Country: Spain Recruitment: volunteers working in a university health and safety department Randomization: method not described, randomized by group
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 (2mg) 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

Villa 1999 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Wallstrom 2000

Methods	Country: Sweden Recruitment: community volunteers Randomization: computer assignment
Participants	247 smokers (>= 10 cpd) 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<10ppm
Notes	

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

Westman 1993

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated
Participants	158 smokers (excludes 1 participant who used nicotine gum throughout) 57% F, av.age 41, av. cpd 30
Interventions	1. Nicotine patch (25mg/24 hr, 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

Westman 1993 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Wisborg 2000

Methods	Country: Denmark Recruitment: volunteers, antenatal clinic Randomization: centrally held list
Participants	250 pregnant women who continued to smoke after 1st trimester Av.age 28, av. cpd 14; 43% primiparous
Interventions	1. Nicotine patch (15mg/16 hr, tapering to 10mg, 11 wks total) 2. Placebo patch Level of support: high. 4x 15-20 min sessions of midwife counselling at 0, 4,11 wks from enrolment, and 4 wks before expected delivery
Outcomes	Abstinence at 1 yr post partum (telephone interview). (Rates at 3m post partum and 4 wks prior to delivery 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.
Risk of bias	
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Wong 1999

Methods	Country: USA Recruitment: community volunteers Randomization: computer-generated schedules, stratified by gender
Participants	100 smokers (>10 cpd for > 1 yr) 53% F, av.age 42, av. cpd 28
Interventions	Factorial study of nicotine patch and naltrexone, no placebo patch Nicotine patch: 21mg (24 hr) for 8 wks, tapering to 14mg for 4 wks

Wong 1999 (*Continued*)

	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<=8ppm	
Notes	One site from a multicentre trial. No significant main effects of naltrexone, so arms collapsed.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Zelman 1992

Methods	Country: USA Recruitment: community volunteers Randomization: method not stated	
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 2mg, average 10 pieces/day, duration not stated + skills training 4. Nicotine gum + support counselling. Level of support: high (6 x 60-75 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	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

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; OTC=over the counter; PP=point prevalence; TQD=target quit date; wk=week

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

Allen 2005	Short-term study of effect of nicotine patch on weight change during early abstinence
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
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.
Chou 2004	Only 3m follow up
Christen 1984	Only 15 wk follow up
Cohen 1989a	Primarily a trial of training dentists. Included in Cochrane review of training of health professionals (Lancaster 1996)
Cohen 1989b	Primarily a trial of training doctors. Included in Cochrane review of training of health professionals (Lancaster 1996)
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.
Dey 1999	Compared free and paid prescription for nicotine patch. Only 14 wk follow up
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 1994 (Study 1)
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

(*Continued)*

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
Glover 1992	Follow up less than 6m
Hajek 1999	Follow up less than 6m. There were no significant differences in 12 wk abstinence rates between gum, patch, spray or inhaler groups.
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
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.
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
Krumpe 1989	Only 10 wks follow up
Kupecz 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

(*Continued)*

Marsh 2005	Only 3m follow up, safety study comparing 4mg lozenge to 4mg gum
McCarthy 2006	Only 3m follow up, study of withdrawal symptoms
Meier 1990	Short-term follow up. Compared dependence individualized to standard dose patch.
Merz 1993	Only 3m follow up
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
Okuyemi 2007	Intervention combined nicotine gum and multiple sessions of motivational interviewing
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
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 1 wk).
Rose 1990	Only 3 wks follow up
Sachs 1995	Only 6 wks follow up
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 16 hr 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 (35mg) patch.

(*Continued)*

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
Tzivoni 1998	Follow up less than 6m
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
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
Wiseman 2005	2-week crossover study
Working Group 1994	Follow up less than 6m

OTC=over the counter

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

Coleman 2007

Trial name or title	Smoking, Nicotine and Pregnancy (SNAP)
Methods	
Participants	1050 pregnant women
Interventions	Nicotine or placebo transdermal patches with behavioural support
Outcomes	Smoking status 6m after childbirth

Coleman 2007 (*Continued*)

Starting date	2007
Contact information	tim.coleman@nottingham.ac.uk
Notes	

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	110	43040	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.50, 1.66]
1.1 Gum	53	19090	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.33, 1.53]
1.2 Patch	41	18237	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.53, 1.81]
1.3 Inhaler/ Inhalator	4	976	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.36, 2.67]
1.4 Tablets/ Lozenges	6	3109	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.63, 2.45]
1.5 Intranasal Spray	4	887	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.49, 2.73]
1.6 Patch and inhaler	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]
1.7 Choice of NRT product	2	496	Risk Ratio (M-H, Fixed, 95% CI)	2.26 [1.26, 4.05]

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	53	19090	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.33, 1.53]
1.1 Sustained 12m	32	13737	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.31, 1.56]
1.2 Sustained 6m	6	890	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.32, 2.73]
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	7	1962	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.21, 1.71]
2 Nicotine patch: Smoking cessation	41	18237	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.53, 1.81]
2.1 Sustained 12m	21	10928	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.35, 1.70]
2.2 Sustained 6m	8	3590	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.57, 2.30]
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	6	1137	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [1.47, 2.83]

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	52	18268	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.34, 1.54]
1.1 Low intensity support	15	7960	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.24, 1.63]
1.2 High intensity individual support	17	6697	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [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	41	18236	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.53, 1.81]
2.1 Low intensity support	12	4388	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.49, 2.12]
2.2 High intensity support	20	10210	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.43, 1.84]
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 Nicotine gum. Smoking cessation	53	19090	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.33, 1.53]
1.1 Community volunteer	28	8336	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.28, 1.53]
1.2 Smoking Clinic	6	1283	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.30, 1.91]
1.3 Primary Care	16	7277	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.35, 1.85]
1.4 Hospitals	3	2194	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.86, 1.43]
2 Nicotine patch. Smoking cessation	41	18237	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.53, 1.81]
2.1 Community volunteer (treatment provided in medical setting)	27	10517	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.56, 1.90]
2.2 Community volunteer (treatment provided in 'Over the Counter' setting)	3	2278	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.40, 2.79]
2.3 Primary Care	6	4150	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.17, 1.77]
2.4 Hospitals	4	1042	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.16, 2.26]
2.5 Antenatal clinic (pregnant women)	1	250	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.59, 1.94]
3 Nicotine Inhaler/inhalator. Smoking cessation	4	976	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.36, 2.67]
3.1 Community volunteer	2	443	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.98, 3.27]
3.2 Smoking Clinic	2	533	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.30, 2.95]
4 Nicotine tablet/lozenge. Smoking cessation	6	3109	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.63, 2.45]
4.1 Community volunteer	6	3109	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.63, 2.45]
5 Nicotine Intranasal spray. Smoking cessation	4	887	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.49, 2.73]
5.1 Community volunteer	2	412	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.16, 2.95]
5.2 Smoking Clinic	2	475	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.44, 3.20]
6 Combination of NRT. Smoking cessation	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]
6.1 Hospitals	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]

7 Choice of NRT. Smoking cessation	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.81, 7.68]
7.1 Hospitals	1	182	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.81, 7.68]

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	7	4634	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.01, 1.30]
1.1 44mg vs 22mg (Intensive counselling)	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.32]
1.2 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	40		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 16 hour patch, active versus placebo	10	6568	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.44, 2.01]
1.2 24 hour patch, active versus placebo	31	10521	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	43		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Patch provided for 8 weeks or less	15	4842	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.64, 2.18]
1.2 Patch provided for more than 8 weeks	26	9906	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.43, 1.79]
1.3 28 weeks versus 12 weeks	1	2861	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.88, 1.26]
1.4 12 weeks versus 3 weeks	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.26, 1.41]
1.5 12 weeks versus 6 weeks	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.62, 1.71]
1.6 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	41	16342	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.47, 1.73]
1.1 Nicotine patch versus placebo. With Weaning	31	14321	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.44, 1.72]
1.2 Nicotine patch versus placebo. No weaning	8	1757	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [1.74, 3.06]
1.3 Nicotine patch. Abrupt withdrawal versus weaning	2	264	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.32]

Comparison 11. Combinations of different types of NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Long-term smoking cessation	7	3202	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.11, 1.63]
1.1 Patch plus gum versus patch alone	1	299	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.83, 2.46]
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 inhaler versus nothing	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]

Comparison 12. 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 13. Direct comparisons between NRT types

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	3	1494	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.18]
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]

Comparison 14. Precessation treatment with nicotine patch

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	4	424	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.17, 2.72]

Comparison 15. Nicotine patch and bupropion; direct comparisons and combinations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation at longest follow up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Direct comparison of nicotine patch versus bupropion	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.34, 0.85]
1.2 Effect of combined nicotine patch and bupropion vs placebo	1	405	Risk Ratio (M-H, Fixed, 95% CI)	3.99 [2.03, 7.85]
1.3 Effect of adding bupropion to nicotine (patch + bupropion vs patch alone)	1	489	Risk Ratio (M-H, Fixed, 95% CI)	2.28 [1.46, 3.56]
1.4 Effect of adding nicotine to bupropion (patch or gum + bupropion vs bupropion alone)	2	941	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.90, 1.50]

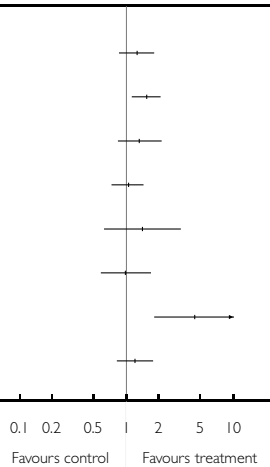
Analysis 1.1. Comparison 1 Any type of NRT versus placebo/ no NRT control, Outcome 1 Smoking cessation at 6+ months follow up.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking cessation at 6+ months follow up

Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Gum					
Ahluwalia 2006	53/378	42/377		2.0 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		1.7 %	1.54 [1.13, 2.10]
Blondal 1989	30/92	22/90		1.0 %	1.33 [0.84, 2.13]
Br Thor Society 1983	39/410	111/1208		2.6 %	1.04 [0.73, 1.46]
Campbell 1987	13/424	9/412		0.4 %	1.40 [0.61, 3.25]
Campbell 1991	21/107	21/105		1.0 %	0.98 [0.57, 1.69]
Clavel 1985	24/205	6/222		0.3 %	4.33 [1.81, 10.38]
Clavel-Chapelon 1992	47/481	42/515		1.9 %	1.20 [0.81, 1.78]



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Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cooper 2005	17/146	15/147		0.7 %	1.14 [0.59, 2.20]
Fagerstrom 1982	30/50	23/50		1.1 %	1.30 [0.90, 1.90]
Fagerstrom 1984	28/96	5/49		0.3 %	2.86 [1.18, 6.94]
Fee 1982	23/180	15/172		0.7 %	1.47 [0.79, 2.71]
Fortmann 1995	110/552	84/522		4.1 %	1.24 [0.96, 1.60]
Garcia 1989	21/68	5/38		0.3 %	2.35 [0.96, 5.72]
Garvey 2000	75/405	17/203		1.1 %	2.21 [1.34, 3.64]
Gilbert 1989	11/112	9/111		0.4 %	1.21 [0.52, 2.81]
Gross 1995	37/131	6/46		0.4 %	2.17 [0.98, 4.79]
Hall 1985	18/41	10/36		0.5 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		0.7 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		1.3 %	0.90 [0.56, 1.44]
Harackiewicz 1988	12/99	7/52		0.4 %	0.90 [0.38, 2.15]
Herrera 1995	30/76	13/78		0.6 %	2.37 [1.34, 4.18]
Hjalmarson 1984	31/106	16/100		0.8 %	1.83 [1.07, 3.13]
Huber 1988	13/54	11/60		0.5 %	1.31 [0.64, 2.68]
Hughes 1989	23/210	6/105		0.4 %	1.92 [0.81, 4.56]
Hughes 1990	15/59	5/19		0.4 %	0.97 [0.40, 2.31]
Jamrozik 1984	10/101	8/99		0.4 %	1.23 [0.50, 2.98]
Jarvis 1982	22/58	9/58		0.4 %	2.44 [1.23, 4.85]
Jensen 1991	49/211	19/82		1.3 %	1.00 [0.63, 1.59]
Killen 1984	16/44	6/20		0.4 %	1.21 [0.56, 2.63]
Killen 1990	129/600	112/617		5.2 %	1.18 [0.94, 1.49]
Llivina 1988	61/113	28/103		1.4 %	1.99 [1.39, 2.84]
Malcolm 1980	6/73	3/121		0.1 %	3.32 [0.86, 12.85]
McGovern 1992	51/146	40/127		2.0 %	1.11 [0.79, 1.56]
Moolchan 2005	8/46	2/40		0.1 %	3.48 [0.78, 15.44]
Mori 1992	30/178	22/186		1.0 %	1.42 [0.86, 2.37]
Nakamura 1990	13/30	5/30		0.2 %	2.60 [1.06, 6.39]
Nebot 1992	5/106	13/319		0.3 %	1.16 [0.42, 3.17]
Niaura 1994	5/84	4/89		0.2 %	1.32 [0.37, 4.77]

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Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Niaura 1999	1/31	2/31		0.1 %	0.50 [0.05, 5.23]
Ockene 1991	40/402	33/420		1.5 %	1.27 [0.82, 1.97]
Page 1986	9/93	13/182		0.4 %	1.35 [0.60, 3.05]
Pirie 1992	75/206	50/211		2.3 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		1.0 %	1.35 [0.82, 2.21]
Richmond 1993	17/200	14/150		0.8 %	0.91 [0.46, 1.79]
Roto 1987	19/54	7/60		0.3 %	3.02 [1.38, 6.61]
Russell 1983	81/729	78/1377		2.5 %	1.96 [1.46, 2.64]
Schneider 1985A	9/30	6/30		0.3 %	1.50 [0.61, 3.69]
Schneider 1985B	1/13	3/23		0.1 %	0.59 [0.07, 5.11]
Segnan 1991	22/294	37/629		1.1 %	1.27 [0.76, 2.12]
Tonnesen 1988	23/60	12/53		0.6 %	1.69 [0.94, 3.06]
Villa 1999	11/21	10/26		0.4 %	1.36 [0.72, 2.57]
Zelman 1992	23/58	18/58		0.8 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**8847**	**10243**		**50.9 %**	**1.43 [1.33, 1.53]**
Total events: 1596 (NRT), 1154 (Control)					
Heterogeneity: Chi^2 = 64.01, df = 52 (P = 0.12); I^2 =19%					
Test for overall effect: Z = 10.01 (P < 0.00001)					
2 Patch					
Abelin 1989	17/100	11/99		0.5 %	1.53 [0.76, 3.10]
Ahluwalia 1998	35/205	24/205		1.1 %	1.46 [0.90, 2.36]
Buchkremer 1988	11/42	16/89		0.5 %	1.46 [0.74, 2.86]
Campbell 1996	24/115	17/119		0.8 %	1.46 [0.83, 2.57]
CEASE 1999	406/2861	71/714		5.3 %	1.43 [1.12, 1.81]
Cinciripini 1996	12/32	7/32		0.3 %	1.71 [0.78, 3.79]
Daughton 1991	28/106	4/52		0.3 %	3.43 [1.27, 9.28]
Daughton 1998	25/184	16/185		0.8 %	1.57 [0.87, 2.84]
Davidson 1998	33/401	16/401		0.8 %	2.06 [1.15, 3.69]
Ehrsam 1991	7/56	2/56		0.1 %	3.50 [0.76, 16.12]
Fiore 1994A	15/44	9/44		0.4 %	1.67 [0.82, 3.40]
Fiore 1994B	10/57	4/55		0.2 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		0.4 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		0.6 %	2.42 [1.33, 4.39]

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Favours control Favours treatment

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Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hays 1999	62/636	14/322		0.9 %	2.24 [1.28, 3.94]
Hughes 1999	171/779	34/260		2.4 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		0.4 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		0.3 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		0.8 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		2.5 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		0.5 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		1.7 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		1.0 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		0.6 %	0.95 [0.47, 1.94]
Lewis 1998	6/62	7/123		0.2 %	1.70 [0.60, 4.84]
Moolchan 2005	9/34	2/40		0.1 %	5.29 [1.23, 22.85]
Oncken 2007	19/57	28/95		1.0 %	1.13 [0.70, 1.83]
Otero 2006	193/597	122/602		5.7 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.2 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.1 %	3.20 [0.96, 10.71]
Prapavessis 2007	13/59	7/62		0.3 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		0.7 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		0.5 %	2.65 [1.35, 5.19]
Sonderskov 1997	20/251	14/267		0.6 %	1.52 [0.78, 2.94]
Stapleton 1995	77/800	19/400		1.2 %	2.03 [1.24, 3.30]
TNSG 1991	111/537	31/271		1.9 %	1.81 [1.25, 2.62]
Tonnesen 1991	24/145	6/144		0.3 %	3.97 [1.67, 9.43]
Tonnesen 2000	9/104	2/109		0.1 %	4.72 [1.04, 21.32]
Westman 1993	16/78	2/80		0.1 %	8.21 [1.95, 34.51]
Wisborg 2000	19/124	18/126		0.8 %	1.07 [0.59, 1.94]
Wong 1999	14/51	4/49		0.2 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**10963**	**7274**	◆	**37.1 %**	**1.66 [1.53, 1.81]**
Total events: 1734 (NRT), 718 (Control)					
Heterogeneity: Chi^2 = 50.05, df = 40 (P = 0.13); I^2 =20%					
Test for overall effect: Z = 11.98 (P < 0.00001)					
3 Inhaler/ Inhalator					
Hjalmarson 1997	35/123	22/124		1.0 %	1.60 [1.00, 2.57]

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Favours control Favours treatment

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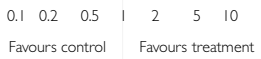
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Leischow 1996	12/110	6/110		0.3 %	2.00 [0.78, 5.14]
Schneider 1996	15/112	9/111		0.4 %	1.65 [0.75, 3.62]
Tonnesen 1993	22/145	7/141		0.3 %	3.06 [1.35, 6.93]
Subtotal (95% CI)	**490**	**486**		**2.1 %**	**1.90 [1.36, 2.67]**
Total events: 84 (NRT), 44 (Control)					
Heterogeneity: Chi^2 = 1.93, df = 3 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 3.73 (P = 0.00019)					
4 Tablets/ Lozenges					
Dautzenberg 2001	25/211	18/222		0.8 %	1.46 [0.82, 2.60]
Glover 2002	22/120	12/121		0.6 %	1.85 [0.96, 3.56]
Shiffman 2002 (2mg)	82/459	44/458		2.1 %	1.86 [1.32, 2.62]
Shiffman 2002 (4mg)	67/450	28/451		1.3 %	2.40 [1.57, 3.65]
Tonnesen 2006	26/185	5/185		0.2 %	5.20 [2.04, 13.25]
Wallstrom 2000	28/123	19/124		0.9 %	1.49 [0.88, 2.52]
Subtotal (95% CI)	**1548**	**1561**		**5.9 %**	**2.00 [1.63, 2.45]**
Total events: 250 (NRT), 126 (Control)					
Heterogeneity: Chi^2 = 7.32, df = 5 (P = 0.20); I^2 =32%					
Test for overall effect: Z = 6.73 (P < 0.00001)					
5 Intranasal Spray					
Blondal 1997	20/79	13/78		0.6 %	1.52 [0.81, 2.84]
Hjalmarson 1994	34/125	18/123		0.9 %	1.86 [1.11, 3.11]
Schneider 1995	23/128	10/127		0.5 %	2.28 [1.13, 4.60]
Sutherland 1992	30/116	11/111		0.5 %	2.61 [1.38, 4.95]
Subtotal (95% CI)	**448**	**439**		**2.5 %**	**2.02 [1.49, 2.73]**
Total events: 107 (NRT), 52 (Control)					
Heterogeneity: Chi^2 = 1.63, df = 3 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 4.53 (P < 0.00001)					
6 Patch and inhaler					
Hand 2002	20/136	15/109		0.8 %	1.07 [0.57, 1.99]
Subtotal (95% CI)	**136**	**109**		**0.8 %**	**1.07 [0.57, 1.99]**
Total events: 20 (NRT), 15 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
7 Choice of NRT product					
Kralikova 2002	39/209	9/105		0.6 %	2.18 [1.10, 4.32]
Molyneux 2003	10/91	4/91		0.2 %	2.50 [0.81, 7.68]
Subtotal (95% CI)	**300**	**196**		**0.8 %**	**2.26 [1.26, 4.05]**
Total events: 49 (NRT), 13 (Control)					



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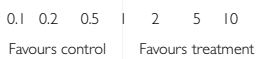
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.73 (P = 0.0064)					
Total (95% CI)	**22732**	**20308**		**100.0 %**	**1.58 [1.50, 1.66]**
Total events: 3840 (NRT), 2122 (Control)					
Heterogeneity: Chi^2 = 145.06, df = 110 (P = 0.01); I^2 =24%					
Test for overall effect: Z = 17.85 (P < 0.00001)					



Analysis 2.1. Comparison 2 Subgroup: Definition of abstinence, Outcome 1 Nicotine gum. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 2 Subgroup: Definition of abstinence

Outcome: 1 Nicotine gum. Smoking cessation

Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Sustained 12m					
Blondal 1989	30/92	22/90		2.1 %	1.33 [0.84, 2.13]
Br Thor Society 1983	39/410	111/1208		5.2 %	1.04 [0.73, 1.46]
Campbell 1987	13/424	9/412		0.8 %	1.40 [0.61, 3.25]
Campbell 1991	21/107	21/105		2.0 %	0.98 [0.57, 1.69]
Clavel 1985	24/205	6/222		0.5 %	4.33 [1.81, 10.38]
Clavel-Chapelon 1992	47/481	42/515		3.7 %	1.20 [0.81, 1.78]
Cooper 2005	17/146	15/147		1.4 %	1.14 [0.59, 2.20]
Fagerstrom 1984	28/96	5/49		0.6 %	2.86 [1.18, 6.94]
Garvey 2000	75/405	17/203		2.1 %	2.21 [1.34, 3.64]
Gilbert 1989	11/112	9/111		0.8 %	1.21 [0.52, 2.81]
Hall 1996	24/98	28/103		2.5 %	0.90 [0.56, 1.44]
Harackiewicz 1988	12/99	7/52		0.8 %	0.90 [0.38, 2.15]
Herrera 1995	30/76	13/78		1.2 %	2.37 [1.34, 4.18]

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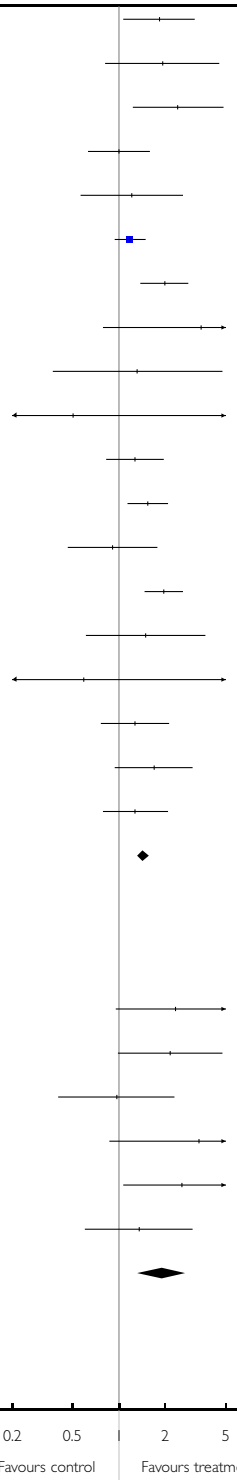
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hjalmarson 1984	31/106	16/100		1.5 %	1.83 [1.07, 3.13]
Hughes 1989	23/210	6/105		0.7 %	1.92 [0.81, 4.56]
Jarvis 1982	22/58	9/58		0.8 %	2.44 [1.23, 4.85]
Jensen 1991	49/211	19/82		2.5 %	1.00 [0.63, 1.59]
Killen 1984	16/44	6/20		0.8 %	1.21 [0.56, 2.63]
Killen 1990	129/600	112/617		10.2 %	1.18 [0.94, 1.49]
Llivina 1988	61/113	28/103		2.7 %	1.99 [1.39, 2.84]
Moolchan 2005	8/46	2/40		0.2 %	3.48 [0.78, 15.44]
Niaura 1994	5/84	4/89		0.4 %	1.32 [0.37, 4.77]
Niaura 1999	1/31	2/31		0.2 %	0.50 [0.05, 5.23]
Ockene 1991	40/402	33/420		3.0 %	1.27 [0.82, 1.97]
Pirie 1992	75/206	50/211		4.6 %	1.54 [1.14, 2.08]
Richmond 1993	17/200	14/150		1.5 %	0.91 [0.46, 1.79]
Russell 1983	81/729	78/1377		5.0 %	1.96 [1.46, 2.64]
Schneider 1985A	9/30	6/30		0.6 %	1.50 [0.61, 3.69]
Schneider 1985B	1/13	3/23		0.2 %	0.59 [0.07, 5.11]
Segnan 1991	22/294	37/629		2.2 %	1.27 [0.76, 2.12]
Tonnesen 1988	23/60	12/53		1.2 %	1.69 [0.94, 3.06]
Zelman 1992	23/58	18/58		1.7 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**6246**	**7491**		**63.6 %**	**1.43 [1.31, 1.56]**
Total events: 1007 (Nicotine gum), 760 (Control)					
Heterogeneity: Chi^2 = 47.87, df = 31 (P = 0.03); I^2 =35%					
Test for overall effect: Z = 7.93 (P < 0.00001)					
2 Sustained 6m					
Garcia 1989	21/68	5/38		0.6 %	2.35 [0.96, 5.72]
Gross 1995	37/131	6/46		0.8 %	2.17 [0.98, 4.79]
Hughes 1990	15/59	5/19		0.7 %	0.97 [0.40, 2.31]
Malcolm 1980	6/73	3/121		0.2 %	3.32 [0.86, 12.85]
Nakamura 1990	13/30	5/30		0.5 %	2.60 [1.06, 6.39]
Page 1986	9/93	13/182		0.8 %	1.35 [0.60, 3.05]
Subtotal (95% CI)	**454**	**436**		**3.6 %**	**1.90 [1.32, 2.73]**
Total events: 101 (Nicotine gum), 37 (Control)					
Heterogeneity: Chi^2 = 4.42, df = 5 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 3.47 (P = 0.00052)					



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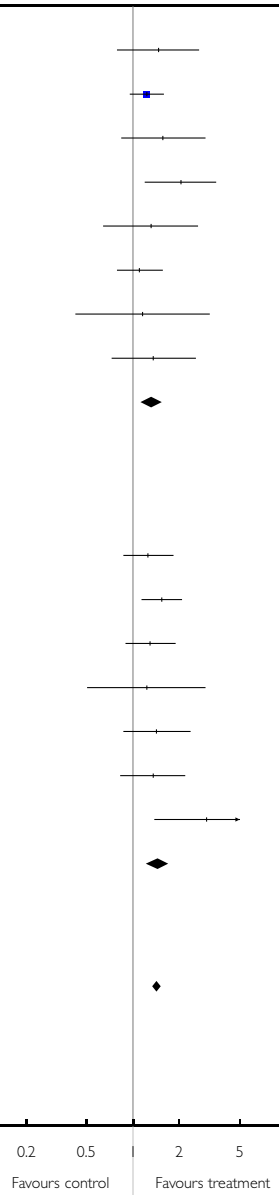
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 PP/uncertain 12m					
Fee 1982	23/180	15/172		1.4 %	1.47 [0.79, 2.71]
Fortmann 1995	110/552	84/522		8.0 %	1.24 [0.96, 1.60]
Hall 1985	18/41	10/36		1.0 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		1.3 %	2.05 [1.20, 3.52]
Huber 1988	13/54	11/60		1.0 %	1.31 [0.64, 2.68]
McGovern 1992	51/146	40/127		4.0 %	1.11 [0.79, 1.56]
Nebot 1992	5/106	13/319		0.6 %	1.16 [0.42, 3.17]
Villa 1999	11/21	10/26		0.8 %	1.36 [0.72, 2.57]
Subtotal (95% CI)	**1171**	**1330**		**18.0 %**	**1.31 [1.12, 1.55]**
Total events: 261 (Nicotine gum), 197 (Control)					
Heterogeneity: Chi^2 = 4.30, df = 7 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 3.27 (P = 0.0011)					
4 PP/uncertain 6m					
Ahluwalia 2006	53/378	42/377		3.9 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		3.4 %	1.54 [1.13, 2.10]
Fagerstrom 1982	30/50	23/50		2.1 %	1.30 [0.90, 1.90]
Jamrozik 1984	10/101	8/99		0.7 %	1.23 [0.50, 2.98]
Mori 1992	30/178	22/186		2.0 %	1.42 [0.86, 2.37]
Puska 1979	29/116	21/113		2.0 %	1.35 [0.82, 2.21]
Roto 1987	19/54	7/60		0.6 %	3.02 [1.38, 6.61]
Subtotal (95% CI)	**976**	**986**		**14.7 %**	**1.44 [1.21, 1.71]**
Total events: 227 (Nicotine gum), 160 (Control)					
Heterogeneity: Chi^2 = 4.55, df = 6 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 4.12 (P = 0.000039)					
Total (95% CI)	**8847**	**10243**		**100.0 %**	**1.43 [1.33, 1.53]**
Total events: 1596 (Nicotine gum), 1154 (Control)					
Heterogeneity: Chi^2 = 64.01, df = 52 (P = 0.12); I^2 =19%					
Test for overall effect: Z = 10.01 (P < 0.00001)					



Analysis 2.2. Comparison 2 Subgroup: Definition of abstinence, Outcome 2 Nicotine patch: Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 2 Subgroup: Definition of abstinence

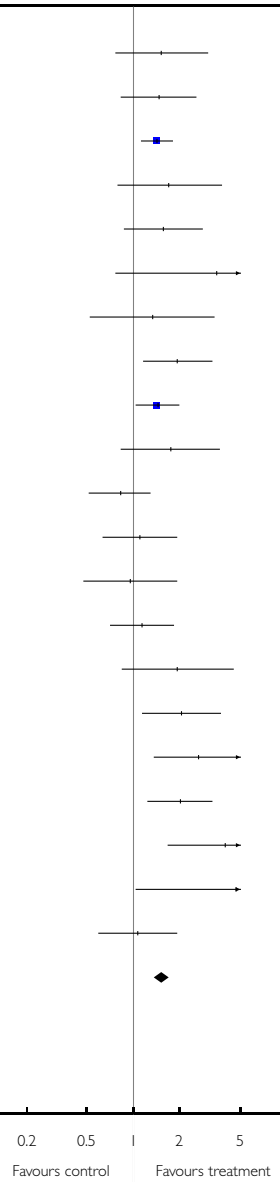
Outcome: 2 Nicotine patch: Smoking cessation

Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Sustained 12m					
Abelin 1989	17/100	11/99		1.4 %	1.53 [0.76, 3.10]
Campbell 1996	24/115	17/119		2.1 %	1.46 [0.83, 2.57]
CEASE 1999	406/2861	71/714		14.4 %	1.43 [1.12, 1.81]
Cinciripini 1996	12/32	7/32		0.9 %	1.71 [0.78, 3.79]
Daughton 1998	25/184	16/185		2.0 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.3 %	3.50 [0.76, 16.12]
Hurt 1990	8/31	6/31		0.8 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		2.2 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		6.7 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		1.4 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		4.5 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		2.7 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		1.7 %	0.95 [0.47, 1.94]
Oncken 2007	19/57	28/95		2.7 %	1.13 [0.70, 1.83]
Prapavessis 2007	13/59	7/62		0.9 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.8 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		1.3 %	2.65 [1.35, 5.19]
Stapleton 1995	77/800	19/400		3.2 %	2.03 [1.24, 3.30]
Tonnesen 1991	24/145	6/144		0.8 %	3.97 [1.67, 9.43]
Tonnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Wisborg 2000	19/124	18/126		2.3 %	1.07 [0.59, 1.94]
Subtotal (95% CI)	**6796**	**4132**		**54.0 %**	**1.51 [1.35, 1.70]**

Total events: 921 (Nicotine gum), 379 (Control)

Heterogeneity: Chi^2 = 27.43, df = 20 (P = 0.12); I^2 =27%

Test for overall effect: Z = 6.95 (P < 0.00001)



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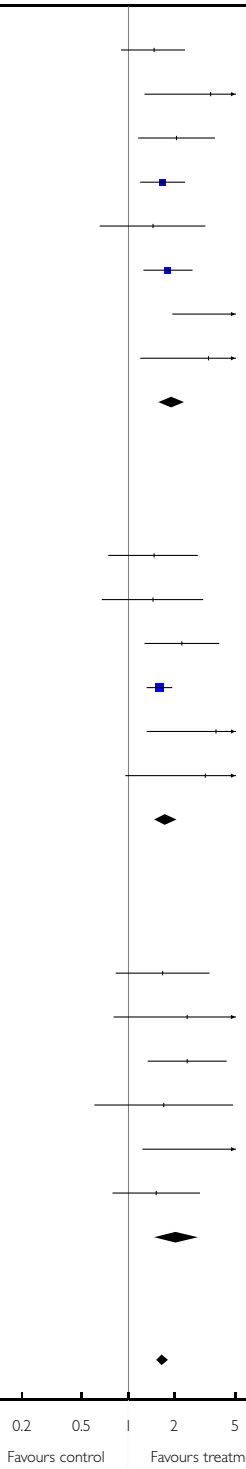
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Sustained 6m					
Ahluwalia 1998	35/205	24/205		3.0 %	1.46 [0.90, 2.36]
Daughton 1991	28/106	4/52		0.7 %	3.43 [1.27, 9.28]
Davidson 1998	33/401	16/401		2.0 %	2.06 [1.15, 3.69]
Hughes 1999	171/779	34/260		6.5 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.1 %	1.44 [0.65, 3.20]
TNSG 1991	111/537	31/271		5.2 %	1.81 [1.25, 2.62]
Westman 1993	16/78	2/80		0.3 %	8.21 [1.95, 34.51]
Wong 1999	14/51	4/49		0.5 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**2218**	**1372**		**19.3 %**	**1.90 [1.57, 2.30]**
Total events: 421 (Nicotine gum), 123 (Control)					
Heterogeneity: Chi^2 = 8.77, df = 7 (P = 0.27); I^2 =20%					
Test for overall effect: Z = 6.60 (P < 0.00001)					
3 PP/uncertain 12m					
Buchkremer 1988	11/42	16/89		1.3 %	1.46 [0.74, 2.86]
Glavas 2003a	13/56	9/56		1.1 %	1.44 [0.67, 3.10]
Hays 1999	62/636	14/322		2.4 %	2.24 [1.28, 3.94]
Otero 2006	193/597	122/602		15.4 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.5 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.4 %	3.20 [0.96, 10.71]
Subtotal (95% CI)	**1421**	**1161**		**21.1 %**	**1.73 [1.46, 2.05]**
Total events: 303 (Nicotine gum), 168 (Control)					
Heterogeneity: Chi^2 = 5.04, df = 5 (P = 0.41); I^2 =1%					
Test for overall effect: Z = 6.29 (P < 0.00001)					
4 PP/uncertain 6m					
Fiore 1994A	15/44	9/44		1.1 %	1.67 [0.82, 3.40]
Fiore 1994B	10/57	4/55		0.5 %	2.41 [0.80, 7.24]
Glavas 2003b	29/80	12/80		1.5 %	2.42 [1.33, 4.39]
Lewis 1998	6/62	7/123		0.6 %	1.70 [0.60, 4.84]
Moolchan 2005	9/34	2/40		0.2 %	5.29 [1.23, 22.85]
Sonderskov 1997	20/251	14/267		1.7 %	1.52 [0.78, 2.94]
Subtotal (95% CI)	**528**	**609**		**5.7 %**	**2.04 [1.47, 2.83]**
Total events: 89 (Nicotine gum), 48 (Control)					
Heterogeneity: Chi^2 = 3.22, df = 5 (P = 0.67); I^2 =0.0%					
Test for overall effect: Z = 4.29 (P = 0.000018)					
Total (95% CI)	**10963**	**7274**		**100.0 %**	**1.66 [1.53, 1.81]**



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Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 1734 (Nicotine gum), 718 (Control)					
Heterogeneity: Chi² = 50.05, df = 40 (P = 0.13); I² =20%					
Test for overall effect: Z = 11.98 (P < 0.00001)					

Analysis 3.1. Comparison 3 Subgroup: Level of behavioural support, Outcome 1 Nicotine gum. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 3 Subgroup: Level of behavioural support

Outcome: 1 Nicotine gum. Smoking cessation

Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low intensity support					
Br Thor Society 1983	39/410	111/1208		5.3 %	1.04 [0.73, 1.46]
Campbell 1987	13/424	9/412		0.9 %	1.40 [0.61, 3.25]
Fagerstrom 1984	28/96	5/49		0.6 %	2.86 [1.18, 6.94]
Fortmann 1995	110/552	84/522		8.2 %	1.24 [0.96, 1.60]
Gilbert 1989	11/112	9/111		0.9 %	1.21 [0.52, 2.81]
Harackiewicz 1988	12/99	7/52		0.9 %	0.90 [0.38, 2.15]
Hughes 1989	23/210	6/105		0.8 %	1.92 [0.81, 4.56]
Hughes 1990	15/59	5/19		0.7 %	0.97 [0.40, 2.31]
Jamrozik 1984	10/101	8/99		0.8 %	1.23 [0.50, 2.98]
Mori 1992	30/178	22/186		2.0 %	1.42 [0.86, 2.37]
Nebot 1992	5/106	13/319		0.6 %	1.16 [0.42, 3.17]
Page 1986	9/93	13/182		0.8 %	1.35 [0.60, 3.05]
Roto 1987	19/54	7/60		0.6 %	3.02 [1.38, 6.61]
Russell 1983	81/729	78/1377		5.1 %	1.96 [1.46, 2.64]
Schneider 1985B	1/13	3/23		0.2 %	0.59 [0.07, 5.11]

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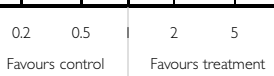
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**3236**	**4724**		**28.5 %**	**1.42 [1.24, 1.63]**
Total events: 406 (Nicotine gum), 380 (Control)					
Heterogeneity: Chi² = 18.04, df = 14 (P = 0.20); I² =22%					
Test for overall effect: Z = 5.02 (P < 0.00001)					
2 High intensity individual support					
Ahluwalia 2006	53/378	42/377		4.0 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		3.5 %	1.54 [1.13, 2.10]
Campbell 1991	21/107	21/105		2.0 %	0.98 [0.57, 1.69]
Clavel-Chapelon 1992	47/481	42/515		3.8 %	1.20 [0.81, 1.78]
Cooper 2005	17/146	15/147		1.4 %	1.14 [0.59, 2.20]
Fagerstrom 1982	30/50	23/50		2.2 %	1.30 [0.90, 1.90]
Garvey 2000	75/405	17/203		2.1 %	2.21 [1.34, 3.64]
Gross 1995	37/131	6/46		0.8 %	2.17 [0.98, 4.79]
Jensen 1991	49/211	19/82		2.6 %	1.00 [0.63, 1.59]
Killen 1990	129/600	112/617		10.5 %	1.18 [0.94, 1.49]
Malcolm 1980	6/73	3/121		0.2 %	3.32 [0.86, 12.85]
Moolchan 2005	8/46	2/40		0.2 %	3.48 [0.78, 15.44]
Nakamura 1990	13/30	5/30		0.5 %	2.60 [1.06, 6.39]
Niaura 1994	5/84	4/89		0.4 %	1.32 [0.37, 4.77]
Richmond 1993	17/200	14/150		1.5 %	0.91 [0.46, 1.79]
Schneider 1985A	9/30	6/30		0.6 %	1.50 [0.61, 3.69]
Segnan 1991	22/294	37/629		2.2 %	1.27 [0.76, 2.12]
Subtotal (95% CI)	**3365**	**3332**		**38.6 %**	**1.33 [1.18, 1.49]**
Total events: 594 (Nicotine gum), 405 (Control)					
Heterogeneity: Chi² = 17.32, df = 16 (P = 0.37); I² =8%					
Test for overall effect: Z = 4.81 (P < 0.00001)					
3 High intensity group-based support					
Blondal 1989	30/92	22/90		2.1 %	1.33 [0.84, 2.13]
Clavel 1985	24/205	6/222		0.5 %	4.33 [1.81, 10.38]
Fee 1982	23/180	15/172		1.5 %	1.47 [0.79, 2.71]
Garcia 1989	21/68	5/38		0.6 %	2.35 [0.96, 5.72]
Hall 1985	18/41	10/36		1.0 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		1.4 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		2.6 %	0.90 [0.56, 1.44]



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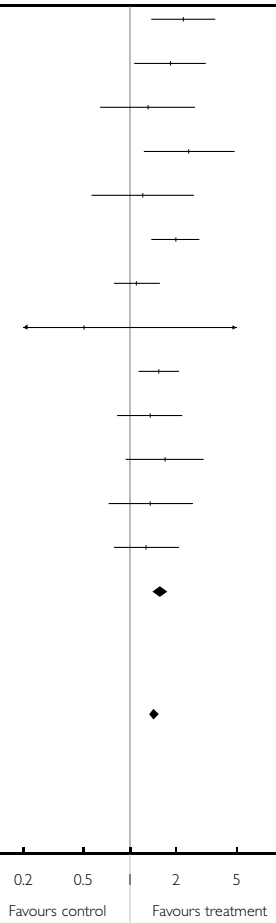
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Herrera 1995	37/76	17/78		1.6 %	2.23 [1.38, 3.61]
Hjalmarson 1984	31/106	16/100		1.6 %	1.83 [1.07, 3.13]
Huber 1988	13/54	11/60		1.0 %	1.31 [0.64, 2.68]
Jarvis 1982	22/58	9/58		0.9 %	2.44 [1.23, 4.85]
Killen 1984	16/44	6/20		0.8 %	1.21 [0.56, 2.63]
Llivina 1988	61/113	28/103		2.8 %	1.99 [1.39, 2.84]
McGovern 1992	51/146	40/127		4.1 %	1.11 [0.79, 1.56]
Niaura 1999	1/31	2/31		0.2 %	0.50 [0.05, 5.23]
Pirie 1992	75/206	50/211		4.7 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		2.0 %	1.35 [0.82, 2.21]
Tonnesen 1988	23/60	12/53		1.2 %	1.69 [0.94, 3.06]
Villa 1999	11/21	10/26		0.8 %	1.36 [0.72, 2.57]
Zelman 1992	23/58	18/58		1.7 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**1844**	**1767**		**33.0 %**	**1.57 [1.40, 1.76]**
Total events: 563 (Nicotine gum), 340 (Control)					
Heterogeneity: Chi^2 = 25.32, df = 19 (P = 0.15); I^2 =25%					
Test for overall effect: Z = 7.64 (P < 0.00001)					
Total (95% CI)	**8445**	**9823**		**100.0 %**	**1.43 [1.34, 1.54]**
Total events: 1563 (Nicotine gum), 1125 (Control)					
Heterogeneity: Chi^2 = 64.10, df = 51 (P = 0.10); I^2 =20%					
Test for overall effect: Z = 10.04 (P < 0.00001)					



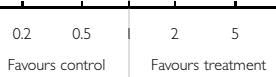
Analysis 3.2. Comparison 3 Subgroup: Level of behavioural support, Outcome 2 Nicotine patch. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 3 Subgroup: Level of behavioural support

Outcome: 2 Nicotine patch. Smoking cessation

Study or subgroup	Nicotine patch n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low intensity support					
Abelin 1989	17/100	11/99		1.4 %	1.53 [0.76, 3.10]
Daughton 1991	28/106	4/52		0.7 %	3.43 [1.27, 9.28]
Daughton 1998	25/184	16/185		2.0 %	1.57 [0.87, 2.84]
Davidson 1998	33/401	16/401		2.0 %	2.06 [1.15, 3.69]
Glavas 2003a	13/56	9/56		1.1 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		1.5 %	2.42 [1.33, 4.39]
Hays 1999	62/636	14/322		2.4 %	2.24 [1.28, 3.94]
Killen 1997	23/212	21/212		2.7 %	1.10 [0.63, 1.92]
Lewis 1998	6/62	7/123		0.6 %	1.70 [0.60, 4.84]
Otero 2006	57/189	39/194		4.9 %	1.50 [1.05, 2.14]
Paoletti 1996	15/60	4/60		0.5 %	3.75 [1.32, 10.64]
Sonderskov 1997	20/251	14/267		1.7 %	1.52 [0.78, 2.94]
Subtotal (95% CI)	**2337**	**2051**		**21.5 %**	**1.78 [1.49, 2.12]**
Total events: 328 (Nicotine patch), 167 (Control)					
Heterogeneity: Chi^2 = 10.16, df = 11 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 6.35 (P < 0.00001)					
2 High intensity support					
Ahluwalia 1998	35/205	24/205		3.0 %	1.46 [0.90, 2.36]
Campbell 1996	24/115	17/119		2.1 %	1.46 [0.83, 2.57]
CEASE 1999	406/2861	71/714		14.4 %	1.43 [1.12, 1.81]
Ehrsam 1991	7/56	2/56		0.3 %	3.50 [0.76, 16.12]
Fiore 1994B	10/57	4/55		0.5 %	2.41 [0.80, 7.24]
Hurt 1990	8/31	6/31		0.8 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		2.2 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		6.7 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		1.4 %	1.75 [0.83, 3.66]



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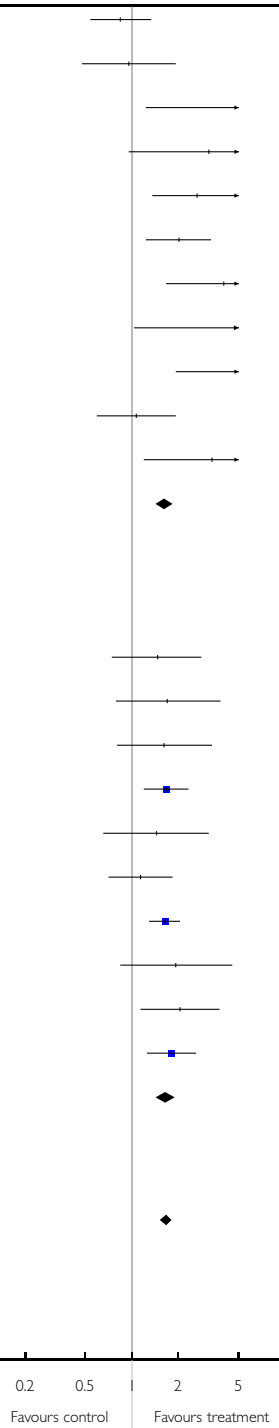
Study or subgroup	Nicotine patch n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Joseph 1996	29/294	34/290		4.3 %	0.84 [0.53, 1.34]
Kornitzer 1995	19/150	10/75		1.7 %	0.95 [0.47, 1.94]
Moolchan 2005	9/34	2/40		0.2 %	5.29 [1.23, 22.85]
Perng 1998	9/30	3/32		0.4 %	3.20 [0.96, 10.71]
Sachs 1993	28/113	10/107		1.3 %	2.65 [1.35, 5.19]
Stapleton 1995	77/800	19/400		3.2 %	2.03 [1.24, 3.30]
Tonnesen 1991	24/145	6/144		0.8 %	3.97 [1.67, 9.43]
Tonnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Westman 1993	16/78	2/80		0.3 %	8.21 [1.95, 34.51]
Wisborg 2000	19/124	18/126		2.3 %	1.07 [0.59, 1.94]
Wong 1999	14/51	4/49		0.5 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**6454**	**3756**		**46.5 %**	**1.62 [1.43, 1.84]**
Total events: 876 (Nicotine patch), 313 (Control)					
Heterogeneity: Chi^2 = 35.04, df = 19 (P = 0.01); I^2 =46%					
Test for overall effect: Z = 7.57 (P < 0.00001)					
3 High intensity group-based support					
Buchkremer 1988	11/42	16/89		1.3 %	1.46 [0.74, 2.86]
Cinciripini 1996	12/32	7/32		0.9 %	1.71 [0.78, 3.79]
Fiore 1994A	15/44	9/43		1.2 %	1.63 [0.80, 3.32]
Hughes 1999	171/779	34/260		6.5 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.1 %	1.44 [0.65, 3.20]
Oncken 2007	19/57	28/95		2.7 %	1.13 [0.70, 1.83]
Otero 2006	136/408	83/408		10.5 %	1.64 [1.29, 2.07]
Prapavessis 2007	13/59	7/62		0.9 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.8 %	2.06 [1.13, 3.74]
TNSG 1991	111/537	31/271		5.2 %	1.81 [1.25, 2.62]
Subtotal (95% CI)	**2172**	**1466**		**31.9 %**	**1.65 [1.43, 1.90]**
Total events: 530 (Nicotine patch), 237 (Control)					
Heterogeneity: Chi^2 = 3.55, df = 9 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 6.88 (P < 0.00001)					
Total (95% CI)	**10963**	**7273**		**100.0 %**	**1.67 [1.53, 1.81]**
Total events: 1734 (Nicotine patch), 717 (Control)					
Heterogeneity: Chi^2 = 49.41, df = 41 (P = 0.17); I^2 =17%					
Test for overall effect: Z = 12.00 (P < 0.00001)					



Analysis 3.3. Comparison 3 Subgroup: Level of behavioural support, Outcome 3 Long versus short support.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 3 Subgroup: Level of behavioural support

Outcome: 3 Long versus short support

Study or subgroup	NRT % longer support n/N	NRT % briefsupport n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nicotine gum					
Fagerstrom 1984	16/50	12/46		14.7 %	1.23 [0.65, 2.31]
Marshall 1985	17/100	14/100		16.5 %	1.21 [0.63, 2.33]
Subtotal (95% CI)	**150**	**146**		**31.2 %**	**1.22 [0.77, 1.92]**
Total events: 33 (NRT % longer support), 26 (NRT % briefsupport)					
Heterogeneity: Chi^2 = 0.00, df = 1 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 0.86 (P = 0.39)					
2 Nicotine patch					
Jorenby 1995	96/335	44/169		68.8 %	1.10 [0.81, 1.49]
Subtotal (95% CI)	**335**	**169**		**68.8 %**	**1.10 [0.81, 1.49]**
Total events: 96 (NRT % longer support), 44 (NRT % briefsupport)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.62 (P = 0.54)					
Total (95% CI)	**485**	**315**		**100.0 %**	**1.14 [0.88, 1.47]**
Total events: 129 (NRT % longer support), 70 (NRT % briefsupport)					
Heterogeneity: Chi^2 = 0.14, df = 2 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 1.00 (P = 0.32)					

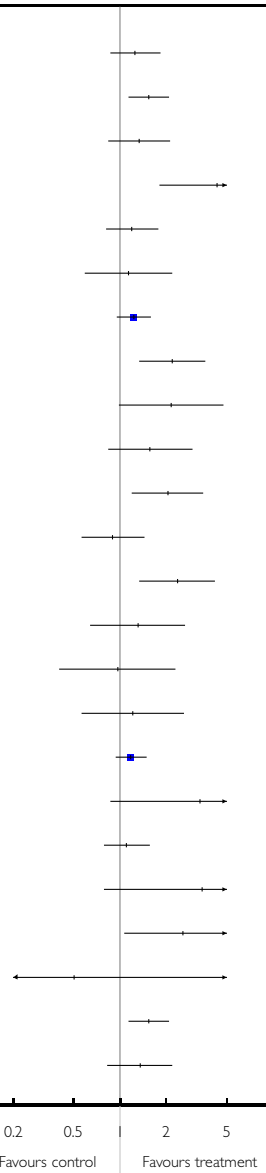
Analysis 4.1. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 1 Nicotine gum. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 1 Nicotine gum. Smoking cessation

Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Community volunteer					
Ahluwalia 2006	53/378	42/377		3.9 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		3.4 %	1.54 [1.13, 2.10]
Blondal 1989	30/92	22/90		2.1 %	1.33 [0.84, 2.13]
Clavel 1985	24/205	6/222		0.5 %	4.33 [1.81, 10.38]
Clavel-Chapelon 1992	47/481	42/515		3.7 %	1.20 [0.81, 1.78]
Cooper 2005	17/146	15/147		1.4 %	1.14 [0.59, 2.20]
Fortmann 1995	110/552	84/522		8.0 %	1.24 [0.96, 1.60]
Garvey 2000	75/405	17/203		2.1 %	2.21 [1.34, 3.64]
Gross 1995	37/131	6/46		0.8 %	2.17 [0.98, 4.79]
Hall 1985	18/41	10/36		1.0 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		1.3 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		2.5 %	0.90 [0.56, 1.44]
Herrera 1995	30/76	13/78		1.2 %	2.37 [1.34, 4.18]
Huber 1988	13/54	11/60		1.0 %	1.31 [0.64, 2.68]
Hughes 1990	15/59	5/19		0.7 %	0.97 [0.40, 2.31]
Killen 1984	16/44	6/20		0.8 %	1.21 [0.56, 2.63]
Killen 1990	129/600	112/617		10.2 %	1.18 [0.94, 1.49]
Malcolm 1980	6/73	3/121		0.2 %	3.32 [0.86, 12.85]
McGovern 1992	51/146	40/127		4.0 %	1.11 [0.79, 1.56]
Moolchan 2005	8/46	2/40		0.2 %	3.48 [0.78, 15.44]
Nakamura 1990	13/30	5/30		0.5 %	2.60 [1.06, 6.39]
Niaura 1999	1/31	2/31		0.2 %	0.50 [0.05, 5.23]
Pirie 1992	75/206	50/211		4.6 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		2.0 %	1.35 [0.82, 2.21]



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Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Schneider 1985A	9/30	6/30		0.6 %	1.50 [0.61, 3.69]
Schneider 1985B	1/13	3/23		0.2 %	0.59 [0.07, 5.11]
Villa 1999	11/21	10/26		0.8 %	1.36 [0.72, 2.57]
Zelman 1992	23/58	18/58		1.7 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**4302**	**4034**		**59.3 %**	**1.40 [1.28, 1.53]**
Total events: 951 (Nicotine gum), 630 (Control)					
Heterogeneity: Chi^2 = 33.51, df = 27 (P = 0.18); I^2 =19%					
Test for overall effect: Z = 7.27 (P < 0.00001)					
2 Smoking Clinic					
Fagerstrom 1982	30/50	23/50		2.1 %	1.30 [0.90, 1.90]
Fee 1982	23/180	15/172		1.4 %	1.47 [0.79, 2.71]
Hjalmarson 1984	31/106	16/100		1.5 %	1.83 [1.07, 3.13]
Jarvis 1982	22/58	9/58		0.8 %	2.44 [1.23, 4.85]
Jensen 1991	49/211	19/82		2.5 %	1.00 [0.63, 1.59]
Llivina 1988	61/113	28/103		2.7 %	1.99 [1.39, 2.84]
Subtotal (95% CI)	**718**	**565**		**11.1 %**	**1.58 [1.30, 1.91]**
Total events: 216 (Nicotine gum), 110 (Control)					
Heterogeneity: Chi^2 = 8.15, df = 5 (P = 0.15); I^2 =39%					
Test for overall effect: Z = 4.66 (P < 0.00001)					
3 Primary Care					
Campbell 1987	13/424	9/412		0.8 %	1.40 [0.61, 3.25]
Fagerstrom 1984	28/96	5/49		0.6 %	2.86 [1.18, 6.94]
Garcia 1989	21/68	5/38		0.6 %	2.35 [0.96, 5.72]
Gilbert 1989	11/112	9/111		0.8 %	1.21 [0.52, 2.81]
Harackiewicz 1988	12/99	7/52		0.8 %	0.90 [0.38, 2.15]
Hughes 1989	23/210	6/105		0.7 %	1.92 [0.81, 4.56]
Jamrozik 1984	10/101	8/99		0.7 %	1.23 [0.50, 2.98]
Nebot 1992	5/106	13/319		0.6 %	1.16 [0.42, 3.17]
Niaura 1994	5/84	4/89		0.4 %	1.32 [0.37, 4.77]
Ockene 1991	40/402	33/420		3.0 %	1.27 [0.82, 1.97]
Page 1986	9/93	13/182		0.8 %	1.35 [0.60, 3.05]
Richmond 1993	17/200	14/150		1.5 %	0.91 [0.46, 1.79]
Roto 1987	19/54	7/60		0.6 %	3.02 [1.38, 6.61]
Russell 1983	81/729	78/1377		5.0 %	1.96 [1.46, 2.64]

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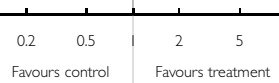
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Segnan 1991	22/294	37/629		2.2 %	1.27 [0.76, 2.12]
Tonnesen 1988	23/60	12/53		1.2 %	1.69 [0.94, 3.06]
Subtotal (95% CI)	**3132**	**4145**		**20.4 %**	**1.58 [1.35, 1.85]**
Total events: 339 (Nicotine gum), 260 (Control)					
Heterogeneity: Chi^2 = 14.54, df = 15 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 5.67 (P < 0.00001)					
4 Hospitals					
Br Thor Society 1983	39/410	111/1208		5.2 %	1.04 [0.73, 1.46]
Campbell 1991	21/107	21/105		2.0 %	0.98 [0.57, 1.69]
Mori 1992	30/178	22/186		2.0 %	1.42 [0.86, 2.37]
Subtotal (95% CI)	**695**	**1499**		**9.1 %**	**1.11 [0.86, 1.43]**
Total events: 90 (Nicotine gum), 154 (Control)					
Heterogeneity: Chi^2 = 1.27, df = 2 (P = 0.53); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.43)					
Total (95% CI)	**8847**	**10243**		**100.0 %**	**1.43 [1.33, 1.53]**
Total events: 1596 (Nicotine gum), 1154 (Control)					
Heterogeneity: Chi^2 = 64.01, df = 52 (P = 0.12); I^2 =19%					
Test for overall effect: Z = 10.01 (P < 0.00001)					



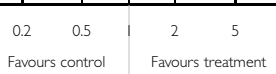
Analysis 4.2. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 2 Nicotine patch. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 2 Nicotine patch. Smoking cessation

Study or subgroup	Nicotine patch n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Community volunteer (treatment provided in medical setting)					
Buchkremer 1988	11/42	16/89		1.3 %	1.46 [0.74, 2.86]
CEASE 1999	406/2861	71/714		14.4 %	1.43 [1.12, 1.81]
Cinciripini 1996	12/32	7/32		0.9 %	1.71 [0.78, 3.79]
Daughton 1991	28/106	4/52		0.7 %	3.43 [1.27, 9.28]
Fiore 1994A	15/44	9/44		1.1 %	1.67 [0.82, 3.40]
Fiore 1994B	10/57	4/55		0.5 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		1.1 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		1.5 %	2.42 [1.33, 4.39]
Hughes 1999	171/779	34/260		6.5 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.1 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		0.8 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		2.2 %	1.94 [1.15, 3.29]
Jorenby 1999	24/244	9/160		1.4 %	1.75 [0.83, 3.66]
Killen 1997	23/212	21/212		2.7 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		1.7 %	0.95 [0.47, 1.94]
Moolchan 2005	9/34	2/40		0.2 %	5.29 [1.23, 22.85]
Oncken 2007	19/57	28/95		2.7 %	1.13 [0.70, 1.83]
Otero 2006	193/597	122/602		15.4 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.5 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.4 %	3.20 [0.96, 10.71]
Prapavessis 2007	13/59	7/62		0.9 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.8 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		1.3 %	2.65 [1.35, 5.19]
TNSG 1991	111/537	31/271		5.2 %	1.81 [1.25, 2.62]



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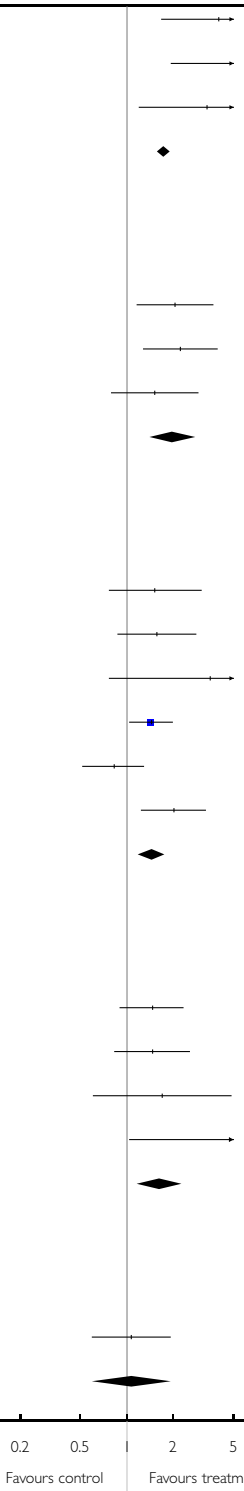
Study or subgroup	Nicotine patch n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tonnesen 1991	24/145	6/144		0.8 %	3.97 [1.67, 9.43]
Westman 1993	16/78	2/80		0.3 %	8.21 [1.95, 34.51]
Wong 1999	14/51	4/49		0.5 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**6789**	**3728**		**67.6 %**	**1.72 [1.56, 1.90]**
Total events: 1295 (Nicotine patch), 470 (Control)					
Heterogeneity: Chi^2 = 32.85, df = 26 (P = 0.17); I^2 =21%					
Test for overall effect: Z = 10.66 (P < 0.00001)					
2 Community volunteer (treatment provided in 'Over the Counter' setting)					
Davidson 1998	33/401	16/401		2.0 %	2.06 [1.15, 3.69]
Hays 1999	62/636	14/322		2.4 %	2.24 [1.28, 3.94]
Sonderskov 1997	20/251	14/267		1.7 %	1.52 [0.78, 2.94]
Subtotal (95% CI)	**1288**	**990**		**6.1 %**	**1.98 [1.40, 2.79]**
Total events: 115 (Nicotine patch), 44 (Control)					
Heterogeneity: Chi^2 = 0.82, df = 2 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.87 (P = 0.00011)					
3 Primary Care					
Abelin 1989	17/100	11/99		1.4 %	1.53 [0.76, 3.10]
Daughton 1998	25/184	16/185		2.0 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.3 %	3.50 [0.76, 16.12]
ICRF 1994	76/842	53/844		6.7 %	1.44 [1.03, 2.01]
Joseph 1996	29/294	35/290		4.5 %	0.82 [0.51, 1.30]
Stapleton 1995	77/800	19/400		3.2 %	2.03 [1.24, 3.30]
Subtotal (95% CI)	**2276**	**1874**		**18.1 %**	**1.44 [1.17, 1.77]**
Total events: 231 (Nicotine patch), 136 (Control)					
Heterogeneity: Chi^2 = 9.00, df = 5 (P = 0.11); I^2 =44%					
Test for overall effect: Z = 3.45 (P = 0.00056)					
4 Hospitals					
Ahluwalia 1998	35/205	24/205		3.0 %	1.46 [0.90, 2.36]
Campbell 1996	24/115	17/119		2.1 %	1.46 [0.83, 2.57]
Lewis 1998	6/62	7/123		0.6 %	1.70 [0.60, 4.84]
Tonnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Subtotal (95% CI)	**486**	**556**		**6.0 %**	**1.62 [1.16, 2.26]**
Total events: 74 (Nicotine patch), 50 (Control)					
Heterogeneity: Chi^2 = 2.24, df = 3 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0049)					
5 Antenatal clinic (pregnant women)					
Wisborg 2000	19/124	18/126		2.3 %	1.07 [0.59, 1.94]
Subtotal (95% CI)	**124**	**126**		**2.3 %**	**1.07 [0.59, 1.94]**



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Study or subgroup	Nicotine patch n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 19 (Nicotine patch), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					
Total (95% CI)	**10963**	**7274**	◆	**100.0 %**	**1.66 [1.53, 1.81]**
Total events: 1734 (Nicotine patch), 718 (Control)					
Heterogeneity: Chi^2 = 50.05, df = 40 (P = 0.13); I^2 =20%					
Test for overall effect: Z = 11.98 (P < 0.00001)					

0.2 0.5 1 2 5

Favours control Favours treatment

Analysis 4.3. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 3 Nicotine Inhaler/inhalator. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 3 Nicotine Inhaler/inhalator. Smoking cessation

Study or subgroup	Nicotine inhaler n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Community volunteer					
Leischow 1996	12/110	6/110		13.6 %	2.00 [0.78, 5.14]
Schneider 1996	15/112	9/111		20.5 %	1.65 [0.75, 3.62]
Subtotal (95% CI)	**222**	**221**		**34.1 %**	**1.79 [0.98, 3.27]**
Total events: 27 (Nicotine inhaler), 15 (Control)					
Heterogeneity: Chi^2 = 0.09, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.058)					
2 Smoking Clinic					
Hjalmarson 1997	35/123	22/124		49.7 %	1.60 [1.00, 2.57]
Tonnesen 1993	22/145	7/141		16.1 %	3.06 [1.35, 6.93]
Subtotal (95% CI)	**268**	**265**		**65.9 %**	**1.96 [1.30, 2.95]**
Total events: 57 (Nicotine inhaler), 29 (Control)					
Heterogeneity: Chi^2 = 1.83, df = 1 (P = 0.18); I^2 =45%					
Test for overall effect: Z = 3.23 (P = 0.0012)					
Total (95% CI)	**490**	**486**		**100.0 %**	**1.90 [1.36, 2.67]**
Total events: 84 (Nicotine inhaler), 44 (Control)					
Heterogeneity: Chi^2 = 1.93, df = 3 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 3.73 (P = 0.00019)					

0.2 0.5 1 2 5

Favours control Favours treatment

Analysis 4.4. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 4 Nicotine tablet/lozenge. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 4 Nicotine tablet/lozenge. Smoking cessation

Study or subgroup	Nicotine n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Community volunteer					
Dautzenberg 2001	25/211	18/222		14.0 %	1.46 [0.82, 2.60]
Glover 2002	22/120	12/121		9.5 %	1.85 [0.96, 3.56]
Shiffman 2002 (2mg)	82/459	44/458		35.1 %	1.86 [1.32, 2.62]
Shiffman 2002 (4mg)	67/450	28/451		22.3 %	2.40 [1.57, 3.65]
Tonnesen 2006	26/185	5/185		4.0 %	5.20 [2.04, 13.25]
Wallstrom 2000	28/123	19/124		15.1 %	1.49 [0.88, 2.52]
Total (95% CI)	**1548**	**1561**		**100.0 %**	**2.00 [1.63, 2.45]**

Total events: 250 (Nicotine), 126 (Control)

Heterogeneity: $Chi^2 = 7.32$, df = 5 (P = 0.20); $I^2 = 32\%$

Test for overall effect: Z = 6.73 (P < 0.00001)

Analysis 4.5. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 5 Nicotine Intranasal spray. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 5 Nicotine Intranasal spray. Smoking cessation

Study or subgroup	Nicotine spray n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Community volunteer					
Blondal 1997	20/79	13/78		24.9 %	1.52 [0.81, 2.84]
Schneider 1995	23/128	10/127		19.1 %	2.28 [1.13, 4.60]
Subtotal (95% CI)	**207**	**205**		**44.0 %**	**1.85 [1.16, 2.95]**
Total events: 43 (Nicotine spray), 23 (Control)					
Heterogeneity: Chi^2 = 0.73, df = 1 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 2.59 (P = 0.0096)					
2 Smoking Clinic					
Hjalmarson 1994	34/125	18/123		34.6 %	1.86 [1.11, 3.11]
Sutherland 1992	30/116	11/111		21.4 %	2.61 [1.38, 4.95]
Subtotal (95% CI)	**241**	**234**		**56.0 %**	**2.15 [1.44, 3.20]**
Total events: 64 (Nicotine spray), 29 (Control)					
Heterogeneity: Chi^2 = 0.66, df = 1 (P = 0.42); I^2 =0.0%					
Test for overall effect: Z = 3.74 (P = 0.00018)					
Total (95% CI)	**448**	**439**		**100.0 %**	**2.02 [1.49, 2.73]**
Total events: 107 (Nicotine spray), 52 (Control)					
Heterogeneity: Chi^2 = 1.63, df = 3 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 4.53 (P < 0.00001)					

Analysis 4.6. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 6 Combination of NRT. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

Outcome: 6 Combination of NRT. Smoking cessation

Study or subgroup	Combination NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Hospitals					
Hand 2002	20/136	15/109		100.0 %	1.07 [0.57, 1.99]
Total (95% CI)	**136**	**109**		**100.0 %**	**1.07 [0.57, 1.99]**

Total events: 20 (Combination NRT), 15 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.21 (P = 0.83)

Analysis 4.7. Comparison 4 Subgroup: Recruitment /treatment setting, Outcome 7 Choice of NRT. Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 4 Subgroup: Recruitment /treatment setting

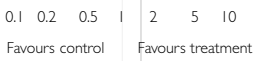
Outcome: 7 Choice of NRT. Smoking cessation

Study or subgroup	NRT choice n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Hospitals					
Molyneux 2003	10/91	4/91		100.0 %	2.50 [0.81, 7.68]
Total (95% CI)	**91**	**91**		**100.0 %**	**2.50 [0.81, 7.68]**

Total events: 10 (NRT choice), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 1.60 (P = 0.11)



Analysis 5.1. Comparison 5 Nicotine gum: 4mg versus 2mg dose, Outcome 1 Smoking Cessation.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking Cessation

Study or subgroup	4 mg dose n/N	2 mg dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High dependency smokers					
Garvey 2000	24/116	18/115		22.2 %	1.32 [0.76, 2.30]
Herrera 1995	30/87	13/81		16.5 %	2.15 [1.21, 3.82]
Kornitzer 1987	24/73	16/86		18.0 %	1.77 [1.02, 3.06]
Tonnesen 1988	12/27	4/33		4.4 %	3.67 [1.33, 10.08]
Subtotal (95% CI)	**303**	**315**		**61.2 %**	**1.85 [1.36, 2.50]**
Total events: 90 (4 mg dose), 51 (2 mg dose)					
Heterogeneity: Chi^2 = 3.46, df = 3 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 3.94 (P = 0.000081)					
2 Low Dependency Smokers					
Garvey 2000	16/87	17/87		20.9 %	0.94 [0.51, 1.74]
Hughes 1990	5/19	8/20		9.6 %	0.66 [0.26, 1.66]
Kornitzer 1987	5/17	5/8		8.4 %	0.47 [0.19, 1.17]
Subtotal (95% CI)	**123**	**115**		**38.8 %**	**0.77 [0.49, 1.21]**
Total events: 26 (4 mg dose), 30 (2 mg dose)					
Heterogeneity: Chi^2 = 1.64, df = 2 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 1.14 (P = 0.25)					
Total (95% CI)	**426**	**430**		**100.0 %**	**1.43 [1.12, 1.83]**
Total events: 116 (4 mg dose), 81 (2 mg dose)					
Heterogeneity: Chi^2 = 16.10, df = 6 (P = 0.01); I^2 =63%					
Test for overall effect: Z = 2.82 (P = 0.0048)					

Analysis 6.1. Comparison 6 Nicotine gum: Fixed versus ad lib dose schedule, Outcome 1 Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking cessation

Study or subgroup	Fixed dosing n/N	Ad lib dosing n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Goldstein 1989	13/47	12/42		18.2 %	0.97 [0.50, 1.88]
Killen 1990	72/299	57/301		81.8 %	1.27 [0.93, 1.73]
Total (95% CI)	**346**	**343**		**100.0 %**	**1.22 [0.92, 1.61]**

Total events: 85 (Fixed dosing), 69 (Ad lib dosing)

Heterogeneity: Chi^2 = 0.53, df = 1 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 1.37 (P = 0.17)

Analysis 7.1. Comparison 7 Nicotine patch: High versus standard dose patches, Outcome 1 Smoking cessation at maximum follow up.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 7 Nicotine patch: High versus standard dose patches

Outcome: 1 Smoking cessation at maximum follow up

Study or subgroup	High dose n/N	Standard dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 44mg vs 22mg (Intensive counselling)					
Dale 1995	12/18	6/17		1.7 %	1.89 [0.92, 3.89]
Hughes 1999	67/259	52/260		14.7 %	1.29 [0.94, 1.78]
Jorenby 1995	68/252	72/252		20.4 %	0.94 [0.71, 1.25]
Kalman 2006	6/65	11/65		3.1 %	0.55 [0.21, 1.39]
Subtotal (95% CI)	**594**	**594**		**40.0 %**	**1.08 [0.89, 1.32]**
Total events: 153 (High dose), 141 (Standard dose)					
Heterogeneity: Chi^2 = 6.45, df = 3 (P = 0.09); I^2 =54%					
Test for overall effect: Z = 0.79 (P = 0.43)					
2 25mg vs 15mg patches					
CEASE 1999	224/1430	182/1431		51.5 %	1.23 [1.03, 1.48]

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Study or subgroup	High dose n/N	Standard dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Killen 1999	20/206	20/202		5.7 %	0.98 [0.54, 1.77]
Paoletti 1996	8/87	10/90		2.8 %	0.83 [0.34, 2.00]
Subtotal (95% CI)	**1723**	**1723**		**60.0 %**	**1.19 [1.00, 1.41]**
Total events: 252 (High dose), 212 (Standard dose)					
Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² =0.0%					
Test for overall effect: Z = 2.00 (P = 0.046)					
Total (95% CI)	**2317**	**2317**		**100.0 %**	**1.15 [1.01, 1.30]**
Total events: 405 (High dose), 353 (Standard dose)					
Heterogeneity: Chi² = 8.04, df = 6 (P = 0.24); I² =25%					
Test for overall effect: Z = 2.08 (P = 0.038)					

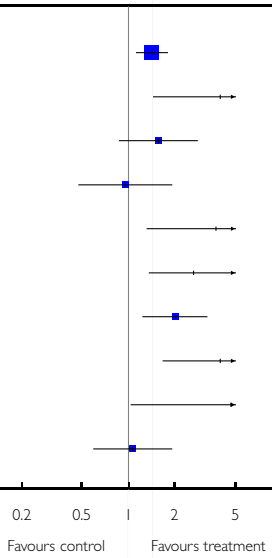
Analysis 8.1. Comparison 8 Nicotine patch: 16hr or 24hr use, subgroups & direct comparison, Outcome 1 Smoking Cessation.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking Cessation

Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 16 hour patch, active versus placebo					
CEASE 1999	406/2861	71/714		53.5 %	1.43 [1.12, 1.81]
Daughton 1991	17/55	4/52		1.9 %	4.02 [1.45, 11.16]
Daughton 1998	25/184	16/185		7.5 %	1.57 [0.87, 2.84]
Kornitzer 1995	19/150	10/75		6.3 %	0.95 [0.47, 1.94]
Paoletti 1996	15/60	4/60		1.9 %	3.75 [1.32, 10.64]
Sachs 1993	28/113	10/107		4.8 %	2.65 [1.35, 5.19]
Stapleton 1995	77/800	19/400		11.9 %	2.03 [1.24, 3.30]
Tonnesen 1991	24/145	6/144		2.8 %	3.97 [1.67, 9.43]
Tonnesen 2000	9/104	2/109		0.9 %	4.72 [1.04, 21.32]
Wisborg 2000	19/124	18/126		8.4 %	1.07 [0.59, 1.94]



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Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**4596**	**1972**		**100.0 %**	**1.71 [1.44, 2.01]**
Total events: 639 (), 160 ()					
Heterogeneity: Chi² = 19.59, df = 9 (P = 0.02); I² =54%					
Test for overall effect: Z = 6.31 (P < 0.00001)					
2 24 hour patch, active versus placebo					
Abelin 1989	17/100	11/99		2.4 %	1.53 [0.76, 3.10]
Ahluwalia 1998	35/205	24/205		5.2 %	1.46 [0.90, 2.36]
Buchkremer 1988	11/42	16/89		2.2 %	1.46 [0.74, 2.86]
Campbell 1996	24/115	17/119		3.6 %	1.46 [0.83, 2.57]
Cinciripini 1996	12/32	7/32		1.5 %	1.71 [0.78, 3.79]
Daughton 1991	11/51	4/52		0.9 %	2.80 [0.95, 8.23]
Davidson 1998	33/401	16/401		3.5 %	2.06 [1.15, 3.69]
Ehrsam 1991	7/56	2/56		0.4 %	3.50 [0.76, 16.12]
Fiore 1994A	15/44	9/43		2.0 %	1.63 [0.80, 3.32]
Fiore 1994B	10/57	4/55		0.9 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		2.0 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		2.6 %	2.42 [1.33, 4.39]
Hays 1999	62/636	14/322		4.1 %	2.24 [1.28, 3.94]
Hughes 1999	171/779	34/260		11.1 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.9 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		1.3 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		3.7 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		11.5 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		2.4 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		7.7 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		4.6 %	1.10 [0.63, 1.92]
Lewis 1998	6/62	7/123		1.0 %	1.70 [0.60, 4.84]
Moolchan 2005	9/34	2/40		0.4 %	5.29 [1.23, 22.85]
Oncken 2007	19/57	28/95		4.6 %	1.13 [0.70, 1.83]
Perng 1998	9/30	3/32		0.6 %	3.20 [0.96, 10.71]
Prapavessis 2007	13/59	7/62		1.5 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		3.1 %	2.06 [1.13, 3.74]
Sonderskov 1997	20/251	14/267		3.0 %	1.52 [0.78, 2.94]

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Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
TNSG 1991	111/537	31/271		9.0 %	1.81 [1.25, 2.62]
Westman 1993	16/78	2/80		0.4 %	8.21 [1.95, 34.51]
Wong 1999	14/51	4/49		0.9 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**5770**	**4751**		**100.0 %**	**1.67 [1.50, 1.86]**
Total events: 902 (), 440 ()					
Heterogeneity: Chi^2 = 32.19, df = 30 (P = 0.36); I^2 =7%					
Test for overall effect: Z = 9.23 (P < 0.00001)					
3 24 hour versus 16 hour nicotine patch					
Daughton 1991	11/51	17/55		100.0 %	0.70 [0.36, 1.34]
Subtotal (95% CI)	**51**	**55**		**100.0 %**	**0.70 [0.36, 1.34]**
Total events: 11 (), 17 ()					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.08 (P = 0.28)					

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Favours control Favours treatment

Analysis 9.1. Comparison 9 Nicotine patch: Duration of therapy, subgroups & direct comparison, Outcome 1 Smoking Cessation.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking Cessation

Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Patch provided for 8 weeks or less					
Buchkremer 1988	11/42	16/89		4.2 %	1.46 [0.74, 2.86]
Daughton 1991	28/106	4/52		2.2 %	3.43 [1.27, 9.28]
Davidson 1998	33/401	16/401		6.5 %	2.06 [1.15, 3.69]
Fiore 1994A	15/44	9/43		3.7 %	1.63 [0.80, 3.32]
Fiore 1994B	10/57	4/55		1.7 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		3.7 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		4.9 %	2.42 [1.33, 4.39]

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Favours control Favours treatment

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Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hays 1999	62/636	14/322		7.6 %	2.24 [1.28, 3.94]
Hurt 1994	33/120	17/120		6.9 %	1.94 [1.15, 3.29]
Jorenby 1999	24/244	9/160		4.4 %	1.75 [0.83, 3.66]
Lewis 1998	6/62	7/123		1.9 %	1.70 [0.60, 4.84]
Moolchan 2005	9/34	2/40		0.7 %	5.29 [1.23, 22.85]
Otero 2006	193/597	122/602		49.6 %	1.60 [1.31, 1.94]
Perng 1998	9/30	3/32		1.2 %	3.20 [0.96, 10.71]
Westman 1993	16/78	2/80		0.8 %	8.21 [1.95, 34.51]
Subtotal (95% CI)	**2587**	**2255**		**100.0 %**	**1.89 [1.64, 2.18]**
Total events: 491 (), 246 ()					
Heterogeneity: Chi^2 = 13.50, df = 14 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 8.85 (P < 0.00001)					
2 Patch provided for more than 8 weeks					
Abelin 1989	17/100	11/99		2.5 %	1.53 [0.76, 3.10]
Ahluwalia 1998	35/205	24/205		5.5 %	1.46 [0.90, 2.36]
Campbell 1996	24/115	17/119		3.8 %	1.46 [0.83, 2.57]
Cinciripini 1996	12/32	7/32		1.6 %	1.71 [0.78, 3.79]
Daughton 1998	25/184	16/185		3.6 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.5 %	3.50 [0.76, 16.12]
Fiore 1994A	15/44	9/43		2.1 %	1.63 [0.80, 3.32]
Hughes 1999	171/779	34/260		11.6 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.9 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		1.4 %	1.33 [0.52, 3.39]
ICRF 1994	76/842	53/844		12.0 %	1.44 [1.03, 2.01]
Joseph 1996	29/294	35/290		8.0 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		4.8 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		3.0 %	0.95 [0.47, 1.94]
Oncken 2007	19/57	28/95		4.8 %	1.13 [0.70, 1.83]
Paoletti 1996	15/60	4/60		0.9 %	3.75 [1.32, 10.64]
Prapavessis 2007	13/59	7/62		1.6 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		3.2 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		2.3 %	2.65 [1.35, 5.19]
Sonderskov 1997	20/251	14/267		3.1 %	1.52 [0.78, 2.94]

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Favours control Favours treatment

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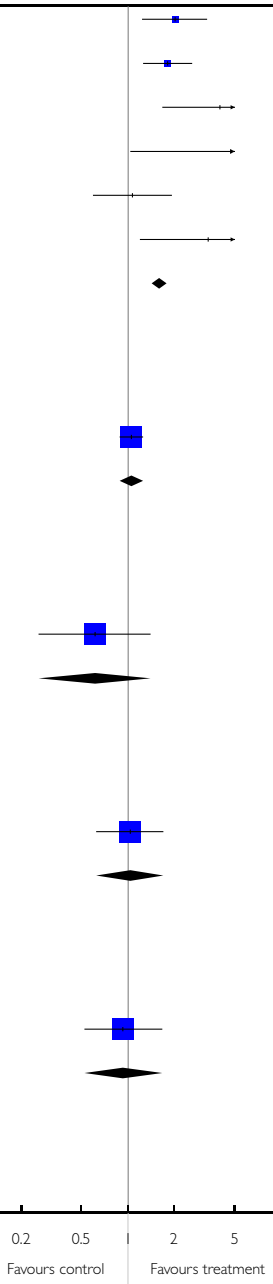
Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stapleton 1995	77/800	19/400		5.8 %	2.03 [1.24, 3.30]
TNSG 1991	111/537	31/271		9.4 %	1.81 [1.25, 2.62]
Tonnesen 1991	24/145	6/144		1.4 %	3.97 [1.67, 9.43]
Tonnesen 2000	9/104	2/109		0.4 %	4.72 [1.04, 21.32]
Wisborg 2000	19/124	18/126		4.1 %	1.07 [0.59, 1.94]
Wong 1999	14/51	4/49		0.9 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**5559**	**4347**		**100.0 %**	**1.60 [1.43, 1.79]**
Total events: 852 (), 410 ()					
Heterogeneity: Chi^2 = 32.66, df = 25 (P = 0.14); I^2 =23%					
Test for overall effect: Z = 8.11 (P < 0.00001)					
3 28 weeks versus 12 weeks					
CEASE 1999	208/1430	198/1431		100.0 %	1.05 [0.88, 1.26]
Subtotal (95% CI)	**1430**	**1431**		**100.0 %**	**1.05 [0.88, 1.26]**
Total events: 208 (), 198 ()					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.54 (P = 0.59)					
4 12 weeks versus 3 weeks					
Bolin 1999	7/48	12/50		100.0 %	0.61 [0.26, 1.41]
Subtotal (95% CI)	**48**	**50**		**100.0 %**	**0.61 [0.26, 1.41]**
Total events: 7 (), 12 ()					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.16 (P = 0.25)					
5 12 weeks versus 6 weeks					
Hilleman 1994	21/69	21/71		100.0 %	1.03 [0.62, 1.71]
Subtotal (95% CI)	**69**	**71**		**100.0 %**	**1.03 [0.62, 1.71]**
Total events: 21 (), 21 ()					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.91)					
6 6 weeks versus 3 weeks					
Glavas 2003b	14/40	15/40		100.0 %	0.93 [0.52, 1.67]
Subtotal (95% CI)	**40**	**40**		**100.0 %**	**0.93 [0.52, 1.67]**
Total events: 14 (), 15 ()					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.23 (P = 0.82)					



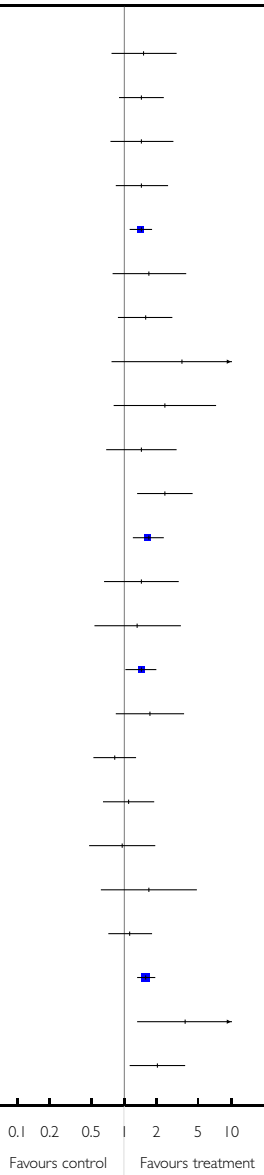
Analysis 10.1. Comparison 10 Nicotine patch: Effect of weaning/tapering dose at end of treatment, Outcome 1 Smoking Cessation.

Review: Nicotine replacement therapy for smoking cessation

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

Outcome: 1 Smoking Cessation

Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nicotine patch versus placebo. With Weaning					
Abelin 1989	17/100	11/99		1.4 %	1.53 [0.76, 3.10]
Ahluwalia 1998	35/205	24/205		3.0 %	1.46 [0.90, 2.36]
Buchkremer 1988	11/42	16/89		1.3 %	1.46 [0.74, 2.86]
Campbell 1996	24/115	17/119		2.1 %	1.46 [0.83, 2.57]
CEASE 1999	406/2861	71/714		14.2 %	1.43 [1.12, 1.81]
Cinciripini 1996	12/32	7/32		0.9 %	1.71 [0.78, 3.79]
Daughton 1998	25/184	16/185		2.0 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.3 %	3.50 [0.76, 16.12]
Fiore 1994B	10/57	4/55		0.5 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		1.1 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		1.5 %	2.42 [1.33, 4.39]
Hughes 1999	171/779	34/260		6.4 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		1.1 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		0.8 %	1.33 [0.52, 3.39]
ICRF 1994	76/842	53/844		6.6 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		1.4 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		4.4 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		2.6 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		1.7 %	0.95 [0.47, 1.94]
Lewis 1998	6/62	7/123		0.6 %	1.70 [0.60, 4.84]
Oncken 2007	19/57	28/95		2.6 %	1.13 [0.70, 1.83]
Otero 2006	193/597	122/602		15.2 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.5 %	3.75 [1.32, 10.64]
Richmond 1994	29/153	14/152		1.8 %	2.06 [1.13, 3.74]



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Study or subgroup	n/N	n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Sachs 1993	28/113	10/107		1.3 %	2.65 [1.35, 5.19]
Sonderskov 1997	20/251	14/267		1.7 %	1.52 [0.78, 2.94]
TNSG 1991	111/537	31/271		5.2 %	1.81 [1.25, 2.62]
Tonnesen 1991	24/145	6/144		0.8 %	3.97 [1.67, 9.43]
Westman 1993	16/78	2/80		0.2 %	8.21 [1.95, 34.51]
Wisborg 2000	19/124	18/126		2.2 %	1.07 [0.59, 1.94]
Wong 1999	14/51	4/49		0.5 %	3.36 [1.19, 9.51]
Subtotal (95% CI)	**8629**	**5692**		**85.8 %**	**1.58 [1.44, 1.72]**
Total events: 1446 (), 625 ()					
Heterogeneity: Chi^2 = 37.70, df = 30 (P = 0.16); I^2 =20%					
Test for overall effect: Z = 9.95 (P < 0.00001)					
2 Nicotine patch versus placebo. No weaning					
Daughton 1991	28/106	4/52		0.7 %	3.43 [1.27, 9.28]
Davidson 1998	33/401	16/401		2.0 %	2.06 [1.15, 3.69]
Fiore 1994A	15/44	9/43		1.1 %	1.63 [0.80, 3.32]
Hurt 1994	33/120	17/120		2.1 %	1.94 [1.15, 3.29]
Moolchan 2005	9/34	2/40		0.2 %	5.29 [1.23, 22.85]
Perng 1998	9/30	3/32		0.4 %	3.20 [0.96, 10.71]
Prapavessis 2007	13/59	7/62		0.9 %	1.95 [0.84, 4.55]
Tonnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Subtotal (95% CI)	**898**	**859**		**7.6 %**	**2.31 [1.74, 3.06]**
Total events: 149 (), 60 ()					
Heterogeneity: Chi^2 = 4.63, df = 7 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 5.81 (P < 0.00001)					
3 Nicotine patch. Abrupt withdrawal versus weaning					
Hilleman 1994	21/69	21/71		2.6 %	1.03 [0.62, 1.71]
Stapleton 1995	34/68	29/56		4.0 %	0.97 [0.68, 1.37]
Subtotal (95% CI)	**137**	**127**		**6.6 %**	**0.99 [0.74, 1.32]**
Total events: 55 (), 50 ()					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.06 (P = 0.95)					
Total (95% CI)	**9664**	**6678**		**100.0 %**	**1.59 [1.47, 1.73]**
Total events: 1650 (), 735 ()					
Heterogeneity: Chi^2 = 58.49, df = 40 (P = 0.03); I^2 =32%					
Test for overall effect: Z = 11.12 (P < 0.00001)					

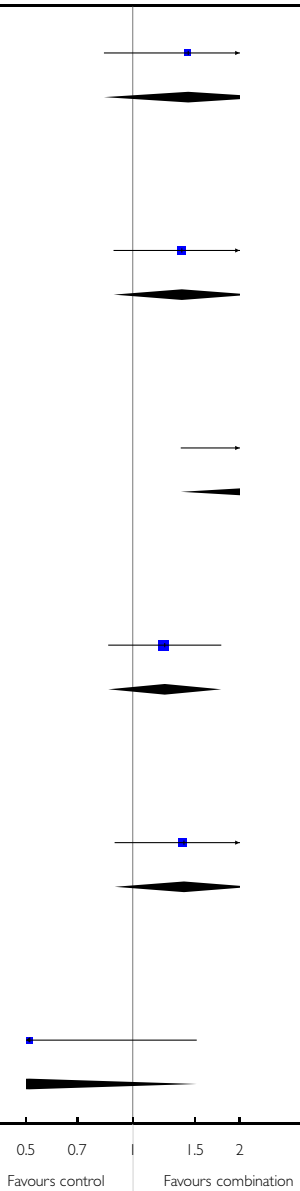
Analysis 11.1. Comparison 11 Combinations of different types of NRT, Outcome 1 Long-term smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 11 Combinations of different types of NRT

Outcome: 1 Long-term smoking cessation

Study or subgroup	Combination NRT n/N	Single/no NRT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Patch plus gum versus patch alone					
Kornitzer 1995	27/149	19/150		12.0 %	1.43 [0.83, 2.46]
Subtotal (95% CI)	**149**	**150**		**12.0 %**	**1.43 [0.83, 2.46]**
Total events: 27 (Combination NRT), 19 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
2 Patch plus gum versus gum alone					
Puska 1995	36/150	26/150		16.4 %	1.38 [0.88, 2.17]
Subtotal (95% CI)	**150**	**150**		**16.4 %**	**1.38 [0.88, 2.17]**
Total events: 36 (Combination NRT), 26 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.41 (P = 0.16)					
3 Nasal spray plus patch versus patch alone					
Blondal 1999	32/118	13/119		8.2 %	2.48 [1.37, 4.49]
Subtotal (95% CI)	**118**	**119**		**8.2 %**	**2.48 [1.37, 4.49]**
Total events: 32 (Combination NRT), 13 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.01 (P = 0.0026)					
4 Nasal spray plus patch versus either patch or spray alone					
Croghan 2003	42/462	68/922		28.7 %	1.23 [0.85, 1.78]
Subtotal (95% CI)	**462**	**922**		**28.7 %**	**1.23 [0.85, 1.78]**
Total events: 42 (Combination NRT), 68 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.27)					
5 Patch plus inhaler versus inhaler alone					
Bohadana 2000	39/200	28/200		17.7 %	1.39 [0.89, 2.17]
Subtotal (95% CI)	**200**	**200**		**17.7 %**	**1.39 [0.89, 2.17]**
Total events: 39 (Combination NRT), 28 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.46 (P = 0.14)					
6 Patch plus inhaler versus either patch or inhaler alone					
Tonnesen 2000	4/115	15/222		6.5 %	0.51 [0.17, 1.52]
Subtotal (95% CI)	**115**	**222**		**6.5 %**	**0.51 [0.17, 1.52]**



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Study or subgroup	Combination NRT n/N	Single/no NRT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 4 (Combination NRT), 15 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.21 (P = 0.23)					
7 Patch plus inhaler versus nothing					
Hand 2002	20/136	15/109		10.5 %	1.07 [0.57, 1.99]
Subtotal (95% CI)	**136**	**109**		**10.5 %**	**1.07 [0.57, 1.99]**
Total events: 20 (Combination NRT), 15 (Single/no NRT)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
Total (95% CI)	**1330**	**1872**		**100.0 %**	**1.35 [1.11, 1.63]**
Total events: 200 (Combination NRT), 184 (Single/no NRT)					
Heterogeneity: Chi^2 = 7.98, df = 6 (P = 0.24); I^2 =25%					
Test for overall effect: Z = 3.08 (P = 0.0021)					

Analysis 12.1. Comparison 12 Purchased NRT without support versus physician support, Outcome 1 Smoking cessation using physician prescribed NRT versus NRT without support (all NRT purchased).

Review: Nicotine replacement therapy for smoking cessation

Comparison: 12 Purchased NRT without support versus physician support

Outcome: 1 Smoking cessation using physician prescribed NRT versus NRT without support (all NRT purchased)

Study or subgroup	NRT, brief support n/N	NRT, no support n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Nicotine patch					
Leischow 1999	3/151	0/149		20.1 %	6.91 [0.36, 132.59]
Subtotal (95% CI)	**151**	**149**		**20.1 %**	**6.91 [0.36, 132.59]**
Total events: 3 (NRT, brief support), 0 (NRT, no support)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.28 (P = 0.20)					
2 Nicotine inhaler					
Leischow 2004	8/260	2/260		79.9 %	4.00 [0.86, 18.66]
Subtotal (95% CI)	**260**	**260**		**79.9 %**	**4.00 [0.86, 18.66]**
Total events: 8 (NRT, brief support), 2 (NRT, no support)					
Heterogeneity: not applicable					

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Study or subgroup	NRT, brief support n/N	NRT, no support n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 1.76 (P = 0.078)					
Total (95% CI)	**411**	**409**		**100.0 %**	**4.58 [1.18, 17.88]**
Total events: 11 (NRT, brief support), 2 (NRT, no support)					
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.75); I^2 =0.0%					
Test for overall effect: Z = 2.19 (P = 0.028)					

Analysis 13.1. Comparison 13 Direct comparisons between NRT types, Outcome 1 Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 13 Direct comparisons between NRT types

Outcome: 1 Smoking cessation

Study or subgroup	NRT type 1 n/N	NRT type 2 n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Inhaler versus patch					
Tonnesen 2000	6/118	9/104		13.3 %	0.59 [0.22, 1.60]
Subtotal (95% CI)	**118**	**104**		**13.3 %**	**0.59 [0.22, 1.60]**
Total events: 6 (NRT type 1), 9 (NRT type 2)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Nasal spray versus patch					
Croghan 2003	32/463	36/459		50.4 %	0.88 [0.56, 1.39]
Lerman 2004	24/175	26/175		36.3 %	0.92 [0.55, 1.54]
Subtotal (95% CI)	**638**	**634**		**86.7 %**	**0.90 [0.64, 1.27]**
Total events: 56 (NRT type 1), 62 (NRT type 2)					
Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					
Total (95% CI)	**756**	**738**		**100.0 %**	**0.86 [0.62, 1.18]**
Total events: 62 (NRT type 1), 71 (NRT type 2)					
Heterogeneity: Chi^2 = 0.64, df = 2 (P = 0.73); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					

Analysis 14.1. Comparison 14 Precessation treatment with nicotine patch, Outcome 1 Smoking cessation.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 14 Precessation treatment with nicotine patch

Outcome: 1 Smoking cessation

Study or subgroup	Precessation NRT n/N	Post cessation NRT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Rose 1994	6/24	4/24		14.3 %	1.50 [0.48, 4.65]
Rose 1998	12/40	6/40		21.4 %	2.00 [0.83, 4.81]
Rose 2006	10/48	6/48		21.4 %	1.67 [0.66, 4.22]
Schuurmans 2004	22/100	12/100		42.9 %	1.83 [0.96, 3.50]
Total (95% CI)	**212**	**212**		**100.0 %**	**1.79 [1.17, 2.72]**

Total events: 50 (Precessation NRT), 28 (Post cessation NRT)

Heterogeneity: $Chi^2 = 0.18$, df = 3 (P = 0.98); $I^2 = 0.0\%$

Test for overall effect: Z = 2.70 (P = 0.0070)

Analysis 15.1. Comparison 15 Nicotine patch and bupropion; direct comparisons and combinations, Outcome 1 Smoking cessation at longest follow up.

Review: Nicotine replacement therapy for smoking cessation

Comparison: 15 Nicotine patch and bupropion; direct comparisons and combinations

Outcome: 1 Smoking cessation at longest follow up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Direct comparison of nicotine patch versus bupropion					
Jorenby 1999	24/244	45/244		100.0 %	0.53 [0.34, 0.85]
Subtotal (95% CI)	**244**	**244**		**100.0 %**	**0.53 [0.34, 0.85]**
Total events: 24 (Intervention), 45 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.66 (P = 0.0077)					
2 Effect of combined nicotine patch and bupropion vs placebo					
Jorenby 1999	55/245	9/160		100.0 %	3.99 [2.03, 7.85]
Subtotal (95% CI)	**245**	**160**		**100.0 %**	**3.99 [2.03, 7.85]**
Total events: 55 (Intervention), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.01 (P = 0.000060)					
3 Effect of adding bupropion to nicotine (patch + bupropion vs patch alone)					
Jorenby 1999	55/245	24/244		100.0 %	2.28 [1.46, 3.56]
Subtotal (95% CI)	**245**	**244**		**100.0 %**	**2.28 [1.46, 3.56]**
Total events: 55 (Intervention), 24 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.63 (P = 0.00028)					
4 Effect of adding nicotine to bupropion (patch or gum + bupropion vs bupropion alone)					
Jorenby 1999	55/245	45/244		51.6 %	1.22 [0.86, 1.73]
Piper 2007	47/228	42/224		48.4 %	1.10 [0.76, 1.60]
Subtotal (95% CI)	**473**	**468**		**100.0 %**	**1.16 [0.90, 1.50]**
Total events: 102 (Intervention), 87 (Control)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 1.14 (P = 0.26)					

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 lead 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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(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: 31 October 2007.

16 April 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 2, 1996

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

LS, TL & CB have extracted data for the most recent update. The review text was updated by LS with review and suggestions from all other authors. CB contributed in particular to the sections on precessation use of NRT.

DECLARATIONS OF INTEREST

Chris Bullen is undertaking a trial on precessation use of NRT. 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)

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