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Nicotine replacement therapy versus control for smoking cessation (Review)

Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T

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[Intervention Review]

Nicotine replacement therapy versus control for smoking cessation

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ABSTRACT

Background

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

Objectives

To determine the effectiveness and safety of nicotine replacement therapy (NRT), including gum, transdermal patch, intranasal spray and inhaled and oral preparations, for achieving long-term smoking cessation, compared to placebo or 'no NRT' interventions.

Search methods

We searched the Cochrane Tobacco Addiction Group trials register for papers mentioning 'NRT' or any type of nicotine replacement therapy in the title, abstract or keywords. Date of most recent search is July 2017.

Selection criteria

Randomized trials in people motivated to quit which compared NRT to placebo or to no treatment. We excluded trials that did not report cessation rates, and those with follow-up of less than six months, except for those in pregnancy (where less than six months, these were excluded from the main analysis). We recorded adverse events from included and excluded studies that compared NRT with placebo. Studies comparing different types, durations, and doses of NRT, and studies comparing NRT to other pharmacotherapies, are covered in separate reviews.

Data collection and analysis

Screening, data extraction and 'Risk of bias' assessment followed standard Cochrane methods. 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 136 studies; 133 with 64,640 participants contributed to the primary comparison between any type of NRT and a placebo or non-NRT control group. The majority of studies were conducted in adults and had similar numbers of men and women. People enrolled in the studies typically smoked at least 15 cigarettes a day at the start of the studies. We judged the evidence to be of high quality; we judged most studies to be at high or unclear risk of bias but restricting the analysis to only those studies at low risk of bias did not significantly alter the result. The RR of abstinence for any form of NRT relative to control was 1.55 (95% confidence interval (CI) 1.49 to 1.61). The pooled RRs for each type were 1.49 (95% CI 1.40 to 1.60, 56 trials, 22,581 participants) for nicotine gum; 1.64 (95% CI 1.53 to 1.75, 51 trials, 25,754 participants) for nicotine patch; 1.52 (95% CI 1.32 to 1.74, 8 trials, 4439 participants) for oral tablets/lozenges; 1.90 (95% CI 1.36 to 2.67, 4 trials, 976 participants) for nicotine inhalator; and 2.02 (95% CI 1.49 to 2.73, 4 trials, 887 participants) for nicotine nasal spray. The effects were largely independent of the definition of abstinence, the intensity of additional support provided or the setting in which the NRT was offered. A subset of six trials conducted in pregnant women found a statistically significant benefit of NRT on abstinence close to the time of delivery (RR 1.32, 95% CI 1.04 to 1.69; 2129 participants); in the four trials that followed up participants post-partum the result was no longer statistically significant (RR 1.29, 95% CI 0.90 to 1.86; 1675 participants). Adverse events from using NRT were related to the type of product, and include skin irritation from patches and irritation to the inside of the mouth from gum and tablets. Attempts to quantitatively synthesize the incidence of various adverse effects were hindered by extensive variation in reporting the nature, timing and duration of symptoms. The odds ratio (OR) of chest pains or palpitations for any form of NRT relative to control was 1.88 (95% CI 1.37 to 2.57, 15 included and excluded trials, 11,074 participants). However, chest pains and palpitations were rare in both groups and serious adverse events were extremely rare.

Authors' conclusions

There is high-quality evidence that all of the licensed forms of NRT (gum, transdermal patch, nasal spray, inhalator and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50% to 60%, regardless of setting, and further research is very unlikely to change our confidence in the estimate of the effect. The relative 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. NRT often causes minor irritation of the site through which it is administered, and in rare cases can cause non-ischaemic chest pain and palpitations.

PLAIN LANGUAGE SUMMARY

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

Background

We reviewed the evidence about whether NRT helps people who want to quit smoking to stop smoking at six months or longer. NRT aims to reduce withdrawal symptoms associated with stopping smoking by replacing the nicotine from cigarettes. NRT is available as skin patches that deliver nicotine slowly, and chewing gum, nasal and oral sprays, inhalators, and lozenges/tablets, all of which deliver nicotine to the brain more quickly than skin patches, but less rapidly than from smoking cigarettes.

Study characteristics

This review includes 136 trials of NRT, with 64,640 people in the main analysis. All studies were conducted in people who wanted to quit smoking. Most studies were conducted in adults and had similar numbers of men and women. Six studies were conducted in pregnant women. People enrolled in the studies typically smoked at least 15 cigarettes a day at the start of the studies. The evidence is current to July 2017. Trials lasted for at least six months, except for two in pregnant women which ended at the time of delivery.

Key results

We found evidence that all forms of NRT made it more likely that a person's attempt to quit smoking would succeed. The chances of stopping smoking were increased by 50% to 60%. NRT works with or without additional counselling, and does not need to be prescribed by a doctor. Side 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. In pregnant women, evidence suggests that NRT can increase the chance of quitting at the time of delivery.

Quality of evidence

The overall quality of the evidence is high, meaning that further research is very unlikely to change our conclusions.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Nicotine replacement therapy versus control for smoking cessation

Patient or population: people who smoke cigarettes
Settings: clinical and non-clinical, including over the counter
Intervention: nicotine replacement therapy of any form

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Nicotine replacement therapy of any form				
Smoking cessation at 6+ months follow-up Follow-up: 6 to 24 months	**Study population**		**RR 1.55** (1.49 to 1.61)	64,640 (133 studies)	⊕⊕⊕⊕ **high**[1,2]	
	105 per 1000	**162 per 1000** (156 to 168)				
	Limited behavioural support					
	40 per 1000	**62 per 1000** (60 to 64)				
	Intensive behavioural support					
	150 per 1000	**232 per 1000** (224 to 242)				

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Most studies are judged to be at unclear or high risk of bias, but restricting to only studies at low risk of bias did not significantly alter the effect.

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

BACKGROUND

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

Nicotine patches differ from the other products in that they deliver the nicotine dose slowly and passively. They do not replace any of the behavioural activities of smoking. In contrast the other types of NRT are faster-acting, but require more effort on the part of the user. Transdermal patches are available in several different doses, and deliver between 5 mg and 52.5 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers (Fiore 1992). Some brands of patch are designed to be worn for 24 hours whilst others are to be worn for 16 hours each day. Nicotine gum is available in both 2 mg and 4 mg strengths, and nicotine lozenges are available in 1 mg, 1.5 mg, 2 mg and 4 mg strengths. Nicotine nasal sprays are available in either 0.5 mg or 1 mg per spray strengths, and nicotine inhalators are available in both 10 mg and 15 mg strengths. The amount of nicotine absorbed by the user is less than the original dose. None of the available products deliver such high doses of nicotine as quickly as cigarettes. An average cigarette delivers between 1 and 3 mg of nicotine and a person who smokes 20 cigarettes per day 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.

This review was first published over 20 years ago, in 1996, and has been regularly updated since. In previous versions, this review addressed not only the effect of NRT in comparison to placebo for helping people stop smoking, but also looked at comparisons between different forms and doses of NRT, and between NRT and different pharmacotherapies. 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 2008; Italy ISS 2004; Le Foll 2005; NICE 2008; NZ MoH 2014; Woolacott 2002; Zwar 2011). We have therefore split the previous version of the review; this review now only looks at NRT versus placebo or no pharmacotherapy, with the intention that, given the stability of this comparison, this review will no longer require regular updates. Studies which compare doses, delivery, forms, and schedules of NRT will now be covered in a companion review, which will continue to be regularly updated, and is in development at the time of writing. Comparisons between NRT and other frontline pharmacotherapies are covered in separate Cochrane Reviews (Cahill 2016; Hughes 2014). Studies of NRT in pregnancy are included in this review but also in a separate Cochrane Review (Coleman 2015), which will continue to be updated.

OBJECTIVES

To determine the effectiveness and safety of nicotine replacement therapy (NRT), including gum, transdermal patch, intranasal spray and inhaled and oral preparations, for achieving long-term smoking cessation, compared to placebo or 'no NRT' interventions.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. We also include trials where allocation to treatment was by a quasi-randomized method, but use appropriate sensitivity analysis to determine whether their inclusion alters the results.

Types of participants

We include men or women who smoked and were motivated to quit, irrespective of the setting from which they were recruited or their initial level of nicotine dependence, or both. 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. We have not included trials that randomized physicians or other therapists to receive an educational intervention, which included encouraging their patients to use NRT, but have reviewed them separately (Carson 2012).

Types of interventions

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

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, we categorized the level of additional support as high. The high-intensity category included trials where there were a large number of visits to the clinic or trial centre, but these were often brief, spread over an extended period during treatment and follow-up, and did not include a specific counselling component. To provide a more fine-grained analysis and to distinguish between high-intensity group-based support and other trials within the high-intensity category, we have therefore specified where the support included multi-session group-based counselling with frequent sessions around the quit date.

Previously, this review had also included studies where all arms received NRT (e.g. testing different doses, types) and studies comparing NRT with bupropion. These comparisons are now covered elsewhere; comparisons between different NRT treatments are covered in a companion review, currently under development, and comparisons between NRT and bupropion are found in Hughes 2014.

Types of outcome measures

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

For the 2012 update and for this current update we collected data on adverse events in both the included and excluded studies, where they were reported. We have not attempted to pool these findings, apart from one meta-analysis of reports of palpitations, tachycardia or chest pains.

We have not included trials that evaluated the effect of NRT for individuals who were attempting to reduce the number of cigarettes smoked rather than to quit in this review. They are covered by a separate review on harm reduction approaches (Lindson-Hawley 2016).

Search methods for identification of studies

We searched the specialized register of the Cochrane Tobacco Addiction Group on 6 July 2017 for any reports of trials making reference to the use of nicotine replacement therapy of any type, by searching for 'NRT', or 'nicotine' near to terms for nicotine replacement products in the title, abstract or keywords. The most recent issues of the databases included in the register as searched for the current update of this review were:

- Cochrane Central Register of Controlled trials (CENTRAL), issue 11, 2016;
- MEDLINE (via OVID) to update 20170526;
- Embase (via OVID) to week 201724;
- PsycINFO (via OVID) to update 20170529.

The search strategy for the Register is given in Appendix 1. For details of the searches used to create the specialized register see the Tobacco Addiction Group Module in the Cochrane Library. The trials register also includes trials identified by handsearching of abstract books from meetings of the Society for Research on Nicotine and 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 have not repeated the exercise for subsequent updates.

Data collection and analysis

Selection of studies

In previous versions of this review, one review author screened records retrieved by searches, to exclude papers that were not reports of potentially relevant studies. For the last two updates, two review authors independently screened references. Reports that linked to potentially relevant studies but did not report the outcomes of interest are listed along with the main study report in the 'References to Studies' section. The primary reference to the study is indicated, and for most studies the first author and year used as the study identifier corresponds to the primary reference. Where we extracted data for a study from more than one report we have noted this in the Characteristics of included studies table.

Data extraction and management

Two review authors independently extracted data from the published reports and abstracts. We resolved disagreements by discussion or by referral to a third party. We made no attempt to blind these review authors either to the results of the primary studies

or to which treatment participants received. We examined reports published only in non-English language journals with the assistance of translators.

Assessment of risk of bias in included studies

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

Measures of treatment effect

We extracted smoking cessation rates in the intervention and control groups from the reports at six or 12 months. Since not all studies reported cessation rates at exactly these intervals, we allowed a window period of six weeks at each follow-up point. For trials which also reported follow-up for more than a year we used 12-month outcomes in most cases. (We note length of follow-up for each study in the Characteristics of included studies table). For trials of NRT in pregnant women, we extracted smoking cessation outcomes at the closest follow-up to end of pregnancy, and also at longest follow-up post-partum if reported. We only included studies in pregnant women in the main analysis if they reported results at six months or longer. Following the Cochrane Tobacco Addiction Group's recommended method of data analysis, we use the risk ratio (RR) for summarizing individual trial outcomes and for estimates of pooled effect. Whilst there are circumstances in which odds ratios may be preferable, there is a danger that they will be interpreted as if they are risk ratios, making the treatment effect seem larger (Deeks 2005).

Dealing with missing data

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

Assessment of heterogeneity

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

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

In comparing NRT to placebo or control, we performed subgroup analysis for each form of NRT. We did additional subgroup analyses within type of NRT (gum, patch, etc.) to investigate whether the relative treatment effect differed according to the way in which smoking cessation was defined, the intensity of behavioural support, and the recruitment/treatment setting.

Summary of findings table

Following standard Cochrane methodology, we created a 'Summary of findings' table. Also following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

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

RESULTS

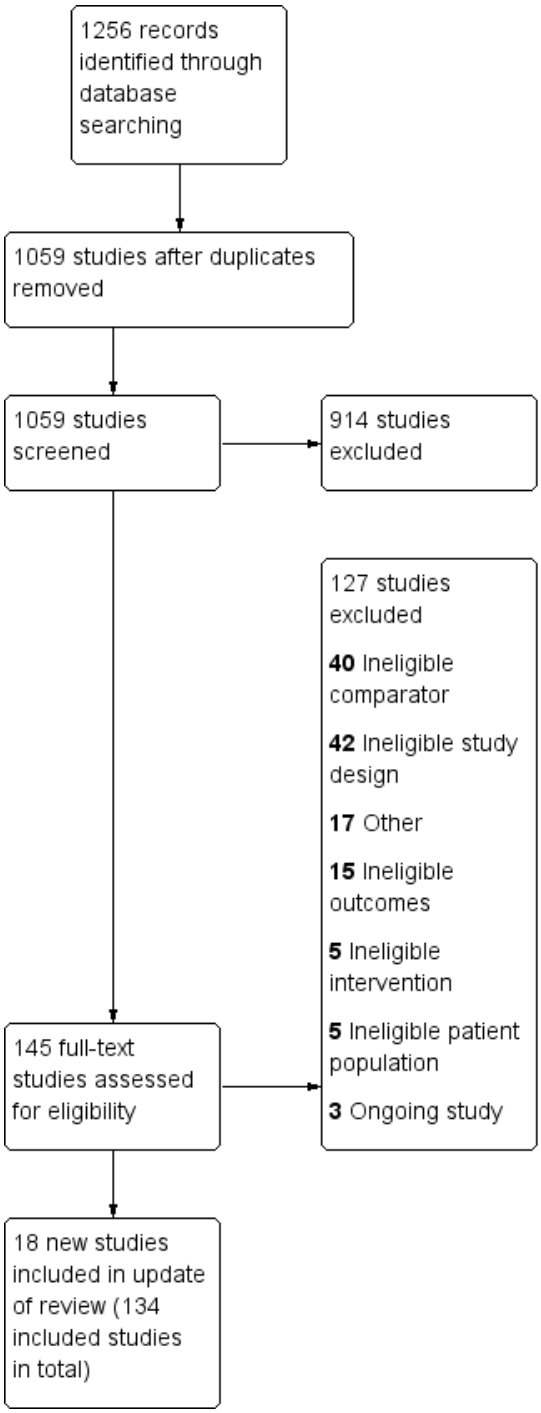
Description of studies

Included studies

The review includes 136 studies, 18 of which are new in this update (Anthenelli 2016; Berlin 2014; Cummins 2016; Cunningham 2016; El-Mohandes 2013; Fraser 2014; Gallagher 2007; Graham 2017; Hasan 2014; Heydari 2012; Heydari 2013; Johns 2017; Lerman 2015; NCT00534404; Scherphof 2014; Stein 2013; Tuisku 2016; Ward 2013). Two studies which gave different doses of NRT based on level of dependency are treated as four separate trials for the purpose of this review (Shiffman 2002 (2 mg); Shiffman 2002 (4 mg); Shiffman 2009 (2 mg); Shiffman 2009 (4 mg)). For this update, we also added longer follow-up data for one previously included study (Coleman 2012). The most recent search screened 1059 studies. Along with the 18 new included studies, there were three ongoing studies, and 124 studies

excluded at full-text screening. The most common reasons for exclusion were ineligible study design and using an irrelevant comparison (NRT vs NRT rather than control). See Figure 1 for study flow information relating to the most recent search presented in a PRISMA diagram. Trials were conducted in North America (62 studies), Europe (56 studies), Australasia (two studies), Japan (two studies), South America (two studies), Iran (two studies), in multiple regions (two studies), and in India, Syria, Taiwan, and Thailand (one study each). The median sample size was 257 but ranged from fewer than 50 to over 8000 participants. We treated each of the intervention groups in the two studies by Shiffman in 2002 and 2009 separately in the meta-analysis (Shiffman 2002 (2 mg); Shiffman 2002 (4 mg); Shiffman 2009 (2 mg); Shiffman 2009 (4 mg)), and listed Brantmark 1973b, CEASE 1999, Bolliger 2000b, Wennike 2003b, Bullen 2010, Schnoll 2010 in the Characteristics of included studies tables, despite being excluded studies, because they provided data on adverse events.

Figure 1. Study flow diagram for most recent update



Participants

Participants were typically adult cigarette smokers with an average age of 40 to 50. Two trials recruited adolescents (Moolchan 2005; Scherphof 2014). Most trials had approximately similar numbers of men and women. Six trials recruited only pregnant women (Berlin 2014; Coleman 2012; El-Mohandes 2013; Oncken 2008; Pollak 2007; Wisborg 2000); a further four recruited only women (Cooper 2005; Oncken 2007; Pirie 1992; Prapavessis 2007). Two trials recruited African-American smokers (Ahluwalia 1998; Ahluwalia 2006).

Trials typically recruited people who smoked at least 15 cigarettes a day. Although some trials included lighter smokers as well, the average number smoked was over 20 a day in most studies. Ahluwalia 2006 recruited only people who smoked 10 or fewer cigarettes a day and two trials recruited only people smoking 30 or more a day (Hughes 1990; Hughes 2003). One trial recruited people with a history of alcohol dependence (Hughes 2003), one recruited methadone-maintained smokers (Stein 2013), and one recruited people with a history of drug abuse including opiates or narcotics (Heydari 2013). Joseph 1996 recruited people with a history of cardiac disease, Hasan 2014 recruited people admitted to hospital with a cardiac or pulmonary illness, Gallagher 2007 recruited people diagnosed with psychotic-spectrum or affective disorders resulting in long-term mental illness and experiencing significant symptoms and functional impairment, and Gourlay 1995 recruited relapsed smokers.

Type and dose of nicotine replacement therapy

One hundred and thirty-three studies contribute 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 56 trials of nicotine gum, 51 of transdermal nicotine patch, eight of an oral nicotine tablet or lozenge, seven offering a choice of products, four of intranasal nicotine spray, four of nicotine inhalator, two providing patch and gum (Hasan 2014; Stein 2013), one of oral spray (Tønnesen 2012), one providing patch and inhalator (Hand 2002), one providing patch and lozenge (Piper 2009), and one providing patch, gum and lozenge (Heydari 2013).

Three studies did not contribute to the primary analysis; two were conducted in pregnant women and did not follow up participants at six months or longer (Berlin 2014; El-Mohandes 2013), and one was conducted in recently relapsed smokers and is hence reported narratively in the text (Gourlay 1995).

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 4 mg dose (Blondal 1989; Puska 1979). In three trials the physician offered nicotine gum but participants did not necessarily accept or use it (Ockene 1991; Page 1986; Russell 1983). In one trial participants self-selected 2 mg or 4 mg doses; we treat the two groups as separate trials in the meta-analysis (Shiffman 2009 (2 mg); Shiffman 2009 (4 mg)). The treatment period was typically two to three months, but ranged from three 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-two studies used a 24-hour formulation and nine a 16-hour product; the rest did not specify. One study offered, among other dosage options, a 52.5 mg/24-hour patch (Wittchen 2011). If studies tested more than one dose we combined all active arms in the comparison to placebo. For one study we included an arm with a lower maximum dose of 14 mg but excluded a 7 mg-dose arm (TNSG 1991). The minimum duration of therapy ranged from three weeks (Glavas 2003a, half the participants of Glavas 2003b), to three months.

There are eight studies of nicotine sublingual tablets or lozenges. Three used 2 mg sublingual tablets (Glover 2002; Tønnesen 2006; Wallstrom 2000). One used a 1 mg nicotine lozenge (Dautzenberg 2001). One used 2 mg or 4 mg lozenges according to dependence level based on manufacturers' instructions (Piper 2009), and one used 2 mg or 4 mg based on participants' time to first cigarette of the day (TTFC); smokers whose TTFC was more than 30 minutes were randomized to 2 mg lozenges or placebo (Shiffman 2002 (2 mg)), whilst smokers with a TTFC less than 30 minutes had higher-dose 4 mg lozenges or placebo (Shiffman 2002 (4 mg)). The two groups are treated in the meta-analysis as separate trials. One trial did not report the lozenge dose (Fraser 2014).

There are four trials of intranasal nicotine spray (Blondal 1997; Hjalmarson 1994; Schneider 1995; Sutherland 1992), one trial of oral nicotine spray (Tønnesen 2012), and four trials of nicotine inhalator (Hjalmarson 1997; Leischow 1996a; Schneider 1996; Tønnesen 1993).

As described above, seven studies tested combinations of patch and a short-acting form of NRT (Hand 2002; Hasan 2014; Heydari 2013; Kornitzer 1995; Moolchan 2005; Stein 2013; Tønnesen 2000). Six studies offered participants a choice of products (Graham 2017; Johns 2017; Kralikova 2009; Molyneux 2003; Ortega 2011; Pollak 2007).

Treatment setting (studies in main comparison)

Twenty-one trials in the main comparison recruited participants from primary care practices. A further two gum trials were undertaken in workplace clinics (Fagerström 1984; Roto 1987), and

one in a university clinic (Harackiewicz 1988). One trial recruited through community physicians (Niaura 1994). Since participants in these trials were recruited in a similar way to primary care, we have aggregated them in the subgroup analysis by setting. We also included one patch trial conducted in Veterans Affairs Medical Centers and recruiting people with cardiac diseases in the primary care category (Joseph 1996). We kept four trials recruiting pregnant women in antenatal clinics in a separate category (Coleman 2012; Oncken 2008; Piper 2009; Wisborg 2000). Six of the gum trials, two of the nasal spray trials, an inhalator trial, an oral spray trial, and a patch trial were carried out in specialized smoking cessation clinics to which participants had usually been referred. Thirteen trials (five patch, three gum, three giving a combination of products and two giving a choice of products) were undertaken with hospital in- or outpatients, some of whom were recruited because they had a co-existing smoking-related illness. Three patch trials (Davidson 1998; Hays 1999; Sønderskov 1997) and one gum trial (split into Shiffman 2009 (2 mg) and Shiffman 2009 (4 mg)) were undertaken in settings intended to resemble 'over-the-counter' (OTC) use of NRT. Two trials were undertaken in drug abuse treatment centres (Heydari 2013; Stein 2013), one in schools (Scherphof 2014), and one in a psychiatric treatment setting. The remaining trials were undertaken in participants from the community, most of whom had volunteered in response to media advertisements, but who were treated in clinical settings.

Excluded studies

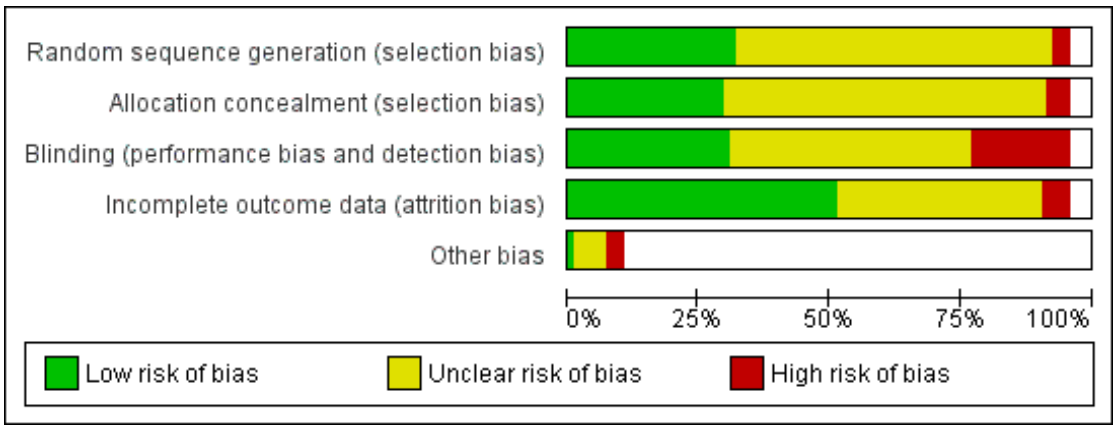
Thirty-four previously included studies were removed from this update, as they did not contain a NRT-versus-control comparison. As described in the Methods, studies which contribute to comparisons between multiple forms of NRT are now found in a separate Cochrane Review, in development at the time of publication. Previously-included studies that compare NRT with bupropion can be found in Hughes 2014. Other studies that were potentially relevant but excluded are listed with reasons in the Characteristics of excluded studies table. Some studies contribute to the adverse events meta-analysis but not to the main analysis (e.g. due to short follow-up or short duration of time where comparison was NRT versus control); these are listed in the Characteristics of included studies but we do not count them as included studies. Some studies were excluded due to short follow-up. Some of these had as their primary outcome withdrawal symptoms rather than cessation. We exclude studies that provided NRT or placebo to people trying to cut down their smoking but not to make an immediate quit attempt, and we consider them in detail in a separate review of interventions for reduction (Lindson-Hawley 2016). We excluded two trials in which NRT was provided to encourage a quit attempt but participants did not need to be planning to quit: Velicer 2006 proactively recruited people by telephone, with those in one intervention group being mailed a six-week course of nicotine patches if they were judged to be in the preparation stage or in contemplation and had more pros than cons for quitting; Carpenter 2011 encouraged all participants to make a practice quit attempt, and gave the intervention group trial samples of nicotine lozenges. We excluded one trial in which callers to the NHS Quitline were randomized to be offered free NRT or not to receive the offer; the control group had access to and used free NRT and other stop-smoking medication at high levels (Ferguson 2012).

Risk of bias in included studies

Six trials are included based only on data available from abstracts, conference presentations, or trial registries (Dautzenberg 2001; Johns 2017; Kralikova 2009; Mori 1992; Nakamura 1990; NCT00534404), so had limited methodological details.

Overall, we judged 12 studies to be at low risk of bias (low risk of bias across all domains), 36 at high risk of bias (high risk of bias in at least one domain), and the rest at unclear risk of bias. The main findings were not sensitive to the exclusion from the meta-analysis of trials at unclear risk, or of trials at unclear and at high risk of bias. A summary illustration of the risk of bias profile across trials is shown in Figure 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Thirty-nine studies (29%) reported allocation procedures in sufficient detail to be rated as being at low risk for their attempts to control selection bias, by using a system of treatment allocation which could not be known or predicted until a participant is enrolled and assigned to a study condition. Twenty-four of these low-risk trials (62%) also reported adequate sequence generation procedures. Most studies either did not report how randomization was performed and allocation concealed, or reported them in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made (rated as being at unclear risk). A small number of nicotine gum trials randomized to treatment according to day or week of clinic attendance (Page 1986; Richmond 1993; Russell 1983), or to birth date (Fagerström 1984), and were consequently rated as being at high risk of bias. In one study (Gallagher 2007), study staff oversaw allocation and hence we rated this at high risk of bias. One study randomized by physician and there was no information about avoidance of selection bias in enrolment of smokers (Nebot 1992), so we also rated this as being at high risk.

We judged 44 of the included studies to be at low risk of performance and detection bias (33%). We judged 23 (17%) to be at high risk of bias in this domain, most commonly because they were not blinded (although we judged some studies which were not double-blind to be at low risk in this domain due to other study factors). Forty-three trials did not have a matched placebo control (24 gum trials, nine patch trials, six choice of product trials, three combination trials, and one lozenge trial). A further two had both a placebo and a non-placebo control which we combined for the meta-analysis control group (Buchkremer 1988; Russell 1983). Approximately one-third of the trials reported some measure of blinding, but we did not assess whether the integrity of the procedure was tested, in line with the CONSORT guidelines (CONSORT 2001). Where they are done, assessments of blinding integrity should always be carried out before the clinical outcome has been determined, and the findings reported (Altman 2004). Mooney 2004 notes that few published trials report this information. While those that do provide some evidence that participants are likely to assess their treatment assignment correctly, it is insufficient to assess whether this is associated with differences in treatment effects. Further, there may be an apparent breaking of the blinding in trials where the treatment effect is marked, for either an intended outcome or an adverse event, but participants who successfully decipher assignment may disguise their unblinding actions (Altman 2004). It is also possible that those who believe that they are receiving a placebo may be more likely to stop trying to quit.

Definitions of abstinence varied considerably. Eighty-nine trials (66%) 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-nine (29%) reported only point prevalence abstinence at the longest follow-up. In six studies it was unclear exactly how abstinence was defined. In four trials, participants who smoked two or three cigarettes a week were still classified as abstinent (Abelin 1989; Ehrsam 1991; Glavas 2003a; Glavas 2003b). Sensitivity analyses excluding these four trials made no difference to the overall findings. Most studies reported follow-up at least 12 months from start of treatment. Fifteen gum trials, 19 patch trials, four combination 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. Six trials in pregnant women reported abstinence close to the time of delivery. Four of these also reported outcomes post-partum (Coleman 2012; Oncken 2008;

Pollak 2007; Wisborg 2000), at between six weeks and two years after delivery. In Analysis 1.1 we used the results at longest follow-up (as long as these were at six months or longer), but in a separate analysis we pooled peripartum and post-partum results separately (Analysis 5.1).

One hundred and seventeen (87%) of the trials used biochemical validation of self-reported smoking cessation at longest follow-up. The most common form of validation was measurement of carbon monoxide (CO) in expired air. The 'cut-off' level of CO used to define abstinence varied from less than 4 to 11 parts per million. Some of the 21 trials that did not validate all self-report at longest follow-up did use biochemical confirmation at earlier points, or validated some self-reports. The main findings were not sensitive to the exclusion of 17 studies contributing to that analysis that did not attempt to validate all reported abstinence (Ahluwalia 1998; Buchkremer 1988; Clavel-Chapelon 1992; Daughton 1991; Fraser 2014; Graham 2017; Huber 1988; NCT00534404; Otero 2006; Page 1986; Puska 1979; Roto 1987; Sønderskov 1997; Tuisku 2016; Villa 1999; Wisborg 2000; Wittchen 2011).

Effects of interventions

See: **Summary of findings for the main comparison** Nicotine replacement therapy

Any type of NRT versus placebo or no NRT control, six months or longer follow-up

Analysis 1.1 included 131 trials (133 comparisons), with over 64,000 participants (Summary of findings for the main comparison). A small number of trials contributed to more than one subgroup and two trials were treated as two separate studies in the analyses. Each of the six forms of nicotine replacement therapy (NRT) significantly increased the rate of cessation compared to placebo or no NRT, as did a choice of product. The pooled risk ratio (RR) for abstinence for any form of NRT relative to control was 1.55 (95% confidence interval (CI) 1.49 to 1.61; 64,640 participants). The I^2 statistic was 39%, indicating that little of the variability was attributable to between-trial differences. The risk ratio and 95% CI for each type are tabulated below.

Type of NRT	RR	95% CI	I^2	N of studies	N of participants Intervention/Control
Gum	1.49	1.40 to 1.60	40%	56*	10,596 / 11,985
Patch	1.64	1.53 to 1.75	24%	51	13,773 / 11,981
Inhalator	1.90	1.36 to 2.67	0%	4	490 / 486
Intranasal spray	2.02	1.49 to 2.73	0%	4	448 / 439
Tablets/lozenges	1.52	1.32 to 1.74	71%	8*	2326 / 2113
Oral spray	2.48	1.24 to 4.94	N/A	1	318 / 161
Choice of product	1.37	1.25 to 1.52	42%	7	4179 / 4109
Patch and inhalator	1.07	0.57 to 1.99	NA	1	136 / 109
Patch and lozenge	1.83	1.01 to 3.31	N/A	1	267 / 41
Patch and gum	1.15	0.64 to 2.06	50%	2	173 / 86
Patch, gum and lozenge	15.00	2.00 to 112.54	N/A	1	212 / 212

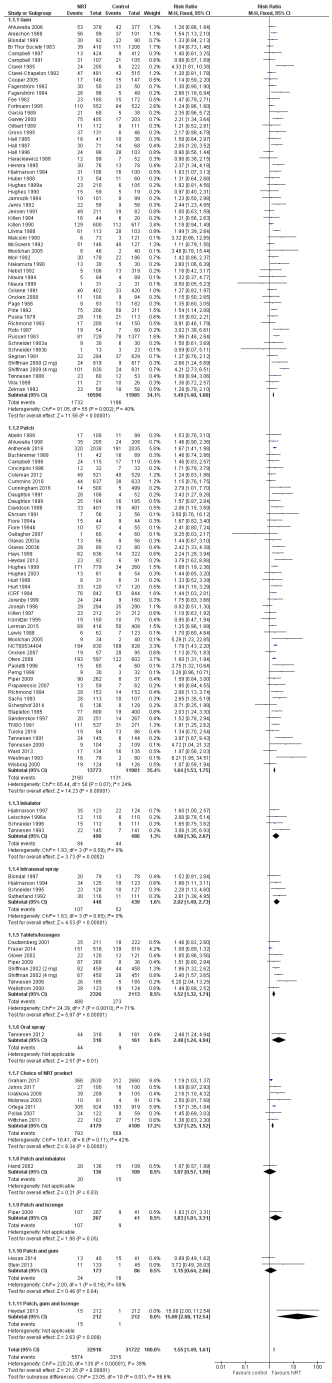
* includes 1 study treated as 2 for analysis; N/A: not applicable

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. One subgroup based on product type had a confidence interval which did not overlap with the pooled estimate; this group consisted of only one study in which only one participant in the control group had successfully quit smoking (Heydari 2013). In the tablets/lozenges subgroup, the I^2 statistic was 71%, indicating substantial statistical heterogeneity. In all trials in this subgroup, more participants quit in the intervention arm than in control, but in one study new for this update the point estimate was considerably lower (RR 1.08) (Fraser 2014); this study drove the observed statistical heterogeneity.

Twelve studies had lower quit rates in the treatment than in the control group at the end of follow-up (all of which had confidence intervals which crossed the line of no effect), and in a further 73% of trials the 95% confidence interval for the RR included 1 (i.e. the trials did not detect a significant treatment effect). Many of these trials had small numbers of smokers, and hence insufficient power to detect a modest treatment effect with reasonable certainty. One large trial of nicotine patches for people with cardiovascular disease had lower quit rates in the intervention than in the control group (Joseph 1996); at six months the quit rates were 14% for active patch and 11% for placebo, but after 48 weeks there had been greater relapse in the active group and rates were 10% and 12% respectively.

Figure 3

Figure 3. Forest plot of comparison: 1 Any type of NRT versus placebo/no NRT control, outcome: 1.1 Smoking cessation at 6+ months follow up.



Sensitivity to definition of abstinence

For nicotine gum and patch we assessed whether trials that reported sustained abstinence at 12 months had different treatment effects from those that only reported a point prevalence outcome, or had shorter follow-up (Analysis 2.1; Analysis 2.2). Subgroup categories were sustained abstinence at 12 months or more, sustained abstinence at six months, point prevalence or unclear definition at 12 months, and point prevalence/unclear at six months. For nicotine gum 32/55 studies (56 comparisons) (58%) reported sustained 12-month abstinence and the estimate was similar to that for all 55 studies: sustained 12-month RR 1.43, 95% CI 1.31 to 1.56 (13,737 participants), compared with RR 1.49, 95% CI 1.40 to 1.60. The highest estimate was for the subgroup of eight studies reporting sustained abstinence at six months, where confidence intervals did not overlap: RR 2.77, 95% CI 2.14 to 3.59; 4187 participants. This seems to be attributable to one study (Shiffman 2009 (2 mg); Shiffman 2009 (4 mg)), and is unlikely to be of methodological or clinical significance. For nicotine patch, 21/49 studies (43%) reported sustained 12-month abstinence, and the RR was also similar to that for all 49 studies: sustained 12-month RR 1.52, 95% CI 1.34 to 1.74 (7622 participants), compared with RR 1.64, 95% CI 1.53 to 1.75 (25,754 participants) overall). For patch studies there was no evidence that the RRs differed significantly between subgroups.

Sensitivity to intensity of behavioural support

All trials provided the same behavioural support in terms of advice, counselling, and number of follow-up visits to the active pharmacotherapy and control groups, but different trials provided different amounts of support. We conducted subgroup analyses by intensity of support for gum and patch trials separately (Analysis 3.1; Analysis 3.2). There was no evidence of a significantly different effect between groups. For nicotine gum the RR was similar across all three subgroups. The control group quit rates varied as expected, averaging 3.5% with low-intensity support, 9% with high-intensity individual support and 11.7% with group-based support. Nicotine patch trials showed the same pattern; the RRs were similar for each subgroup and the average control group quit rates were 9.0% with low-intensity support, 9.5% with high-intensity individual support and 17.0% with group-based support.

Sensitivity to treatment settings

We conducted further subgroup analyses for each type of setting in which smokers were recruited or treated (with type of NRT as a subgroup beneath setting). The pooled RR for trials in community volunteers where care was provided in a medical setting was 1.62 (95% CI 1.53 to 1.72, 65 trials, 24,597 participants; Analysis 4.1) and was similar to that of trials conducted in smoking clinics (RR 1.70, 95% CI 1.48 to 1.96, 12 trials, 3300 participants; Analysis 4.2), trials conducted in primary care settings (RR 1.50, 95% CI 1.33 to 1.69, 24 trials, 11,974 participants; Analysis 4.3), trials conducted in hospitals (RR 1.39, 95% CI 1.24 to 1.55, 13 trials, 7037 participants; Analysis 4.4), and trials conducted in settings similar to 'over the counter' (OTC) (RR 1.40, 95% CI 1.26 to 1.55, 9 trials, 13,163 participants; Analysis 4.5). Pooled results from four trials in antenatal clinics were lower than in other settings (RR 1.22, 95% CI 0.92 to 1.62, 1675 participants; Analysis 4.6); this was the only setting in which results did not show a statistically significant effect of the intervention. In a meta-regression we checked whether there was any evidence of interaction between the treatment setting and type of NRT used. The effect of nicotine gum was highest in the OTC setting and this seems to be attributable to the same study that contributed heterogeneity in the abstinence subgroup analysis above (Shiffman 2009 (2 mg); Shiffman 2009 (4 mg)).

Control group quit rates varied by setting; the lowest rates were found in OTC (8.4%) and primary care (6.9%) studies, and the highest rate in smoking clinics (14.3%). Falling within this range, control group rates were 9.3% in antenatal clinics, 12.5% in community volunteers where treatment was provided in a medical setting, and 12.3% in hospitals.

Sensitivity to risk of bias and study methods

Excluding those studies at high risk of bias did not significantly alter the point estimate for the main comparison: RR 1.61, 95% CI 1.52 to 1.69, *analysis not shown*. Similarly, restricting the main analysis to only those 12 studies at low risk of bias across all domains led to results consistent with the main analysis: RR 1.53, 95% CI 1.37 to 1.71, *analysis not shown*. Removing those studies without biochemical validation did not substantially influence the effect estimate: RR 1.62, 95% CI 1.55 to 1.70, *analysis not shown*, nor did restricting the analysis to only placebo-controlled studies: RR 1.61, 95% CI 1.53 to 1.70, *analysis not shown*.

Pregnant women

Six trials evaluated the effectiveness of NRT use in pregnant women. Cessation outcomes at longest follow-up (where this was six months or longer) are used in Analysis 1.1. In a separate analysis (Analysis 5.1) we pooled peripartum and post-partum effects separately. For abstinence close to the time of delivery NRT showed a statistically significant benefit (RR 1.32, 95% CI 1.04 to 1.69, 2129 participants; I^2 = 23%). Pooling the post-partum outcomes from four trials did not demonstrate a significant difference between NRT and control groups (RR 1.29, 95% CI 0.90 to 1.86,

1675 participants; I^2 = 0%), although confidence intervals were wide.

Relapsed smokers

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

Adverse events

We have made no systematic attempt in this review to synthesize quantitatively the incidence of the various adverse events reported with the different NRT preparations. This was because of the extensive variation in reporting of the nature, timing and duration of symptoms. In the included studies, attrition rates in NRT groups were generally similar to or lower than in control groups. Appendix 3 summarises the main adverse events reported in the included and excluded studies, where the data were available.

The most common adverse events usually reported with nicotine gum include hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems (Fiore 1992; Palmer 1992). The only adverse event that appears to interfere with use of the patch is skin sensitivity and local skin 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 adverse events reported with the nicotine inhalator and nasal and oral sprays are related to local irritation at the site of administration (mouth and nose respectively). For example, symptoms such as throat irritation, coughing, and oral burning were reported significantly more frequently with participants allocated to the nicotine inhalator 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 adverse events. In the study of oral spray, hiccoughs and throat irritation were the most commonly reported adverse events (Tønnesen 2012). Nicotine sublingual tablets have been reported to cause hiccoughs, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers (Wallstrom 1999). Adolescents report similar adverse events to adults (Bailey 2012).

A review of adverse events based on 35 trials with over 9000 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). A meta-analysis of adverse events associated with NRT included 92 RCTs and 28 observational studies, and addressed a possible excess of chest pains and heart palpitations among users of NRT compared with placebo groups (Mills 2010). The authors report an OR of 2.06 (95% CI 1.51 to 2.82) across 12 studies. We replicated this data collection exercise and analysis where data were available (included and excluded) in this review, and detected a similar but slightly lower estimate, OR 1.88 (95% CI 1.37 to 2.57; 15 studies; 11,074 participants; OR rather than RR calculated for comparison; Analysis 6.1). Chest pains and heart palpitations were an extremely rare event, occurring at a rate of 2.5% in the NRT groups compared with 1.4% in the control groups in the 15 trials in which they were reported at all. A recent network meta-analysis of cardiovascular events associated with smoking cessation pharmacotherapies (Mills 2014), including 21 RCTs comparing NRT with placebo, found statistically significant evidence that the rate of cardiovascular events with NRT was higher (RR 2.29 95% CI 1.39 to 3.82). However, when only serious adverse cardiac events (myocardial infarction, stroke and cardiovascular death) were considered, the finding was not statistically significant (RR 1.95 95% CI 0.26 to 4.30). A sensitivity analysis demonstrated that lower-level events, predominantly tachycardia and arrhythmia, accounted for the observed increased risk of cardiovascular events. Chest pains and palpitations are the only clinically significant adverse events to emerge from the trials, and no evidence of significant harm has been identified.

When first licensed there was concern about the safety of NRT in smokers with cardiac disease (TNWG 1994). A trial of nicotine patch 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 (Joseph 1996). Events related to cardiovascular disease, such as an increase in angina severity, occurred in approximately 16% of participants, but did not differ according to whether or not they were receiving NRT. A review of safety in people 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 we excluded from the present review (Tzivoni 1998; Working Group 1994), and a case-control study in a population-based sample. An analysis of 187 smokers admitted to hospital with acute coronary syndromes who received nicotine patches showed no evidence of difference in short- or long-term mortality compared to a propensity-matched sample of smokers in the same database who did not receive NRT (Meine 2005). A subgroup analysis within a network meta-analysis of cardiovascular events (Mills 2014), found no increased risk of cardiovascular events with NRT amongst individuals with predisposing conditions that placed them at an increased risk of having an event (RR 1.24, 95% CI 0.77 to 2.02). Another recent network meta-analysis in people with cardiovascular disease found a slightly higher number of cardiovascular events with NRT but was not able to draw quantitative conclusions due to the low number of trials reporting adverse events and the variation in adverse event definitions used (Suissa 2017).

The six trials assessing NRT use in pregnant women did not detect significant increases in serious adverse events amongst the treatment groups (Berlin 2014; Coleman 2012; El-Mohandes 2013; Oncken 2008; Pollak 2007; Wisborg 2000). Recruitment for Pollak 2007 was suspended early when interim analysis found a higher rate of adverse birth outcomes in the NRT arm (primarily preterm birth); however, when adjusted for previous birth outcomes the adverse event rate between the two groups was not significantly different in final analysis. The effects of NRT use on neonatal health are discussed further in a separate Cochrane Review, which found no statistically significant differences in rates of any serious adverse events between treatment and control groups (Coleman 2015). Subsequent analysis of two-year follow-up data from the study by Coleman 2012 has shown that two-year-olds born to women who used NRT were more likely to have survived without any developmental impairment compared to two-year-olds born to women who used placebo (OR 1.40, 95% CI 1.05 to 1.86).

DISCUSSION

This review provides high-quality evidence from trials including over 64,000 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 but 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 (Etter 2006).

The absolute effects of NRT use will depend on the baseline quit rate, which varies in different clinical settings. Studies of people attempting to quit on their own suggest that success rates after six to 12 months are 3% to 5% (Hughes 2004). Use of NRT might be expected to increase the rate by 2% to 3%, giving a number needed to treat for an additional beneficial outcome (NNTB) of 56. If, however, the quit rate without pharmacotherapy was estimated to be 15%, either because the population had other predictors of successful quitting or received intensive behavioural support, then another 8% might be expected to quit, giving an NNTB of 11.

Intensity of additional support and treatment setting

We did not detect important differences in relative effect within patch or gum studies by our classification of level of support. A letter prior to the previous update of this review identified inconsistencies in the classification of low- and high-intensity support in this review (Walsh 2007). In response, we changed the classification of a small number of trials. This did not alter the conclusion that intensity of support does not appear to be an important moderator of NRT effect.

We also did not detect differences in relative effect according to the setting of recruitment and treatment. This subgroup analysis had considerable overlap with the support subgroup since, for example, people recruited in primary care settings typically had lower-intensity support.

There has been continuing debate about the amount of evidence for the 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; Sønderskov 1997), that review includes one study excluded here due to short follow-up (Shiffman 2002a). It also pools four trials comparing NRT provided OTC to NRT provided under prescription. We exclude one trial that compared both gum and patch in these settings, but was not randomized (Shiffman 2002b), and another that has not been published and for which we have been unable to obtain reliable data for inclusion (Korberly 1999). The abstract reported that there were no significant differences in quit rates between users of nicotine patch who purchased it through a non-healthcare facility, and those receiving it on prescription. It has also been suggested that the 'real world' effectiveness of NRT declines or disappears once it becomes available to purchase without requiring contact with a health professional who can offer behavioural support and guidance on appropriate use (Kotz 2014; Pierce 2002). A comparison of two cross-sectional surveys in California found that quit rates for self-selected NRT users were higher than rates for non-users prior to OTC availability, but after the switch to OTC this difference disappeared (Pierce 2002). In addition, a prospective cohort study found that the odds of cessation in people who had used OTC NRT were lower than in people who had not used any cessation pharmacotherapy or accessed a national stop-smoking service (OR 0.69, 95% CI 0.49 to 0.94) (Kotz 2014). However, these observational studies are at risk of residual confounding from unmeasured confounders, such as psychological factors, as participants self-selected their treatment. These studies are also at risk of bias, as unaided quit attempts are less likely to be recalled than those involving NRT.

A report of a prospective cohort study questioned the effectiveness of NRT outside of the clinical trial setting after finding no dif-

ference in relapse rates between smokers trying to quit who used NRT and those who did not use NRT (Alpert 2012). However, the design of this study has been criticized for not addressing initial quit rates in the two groups (Stapleton 2012). Furthermore, two multi-country prospective cohort studies observed that NRT users had higher quit rates than non-users (Kasza 2012; West 2007), although in the former study this effect was limited to NRT patches, with no effect detected for oral nicotine products. Again, these are observational studies and are at risk of confounding and bias.

Trials in special populations

We now include six trials of NRT in pregnant women in the review (Berlin 2014; Coleman 2012; El-Mohandes 2013; Oncken 2007; Pollak 2007; Wisborg 2000) with Coleman 2012 contributing over 1000 of around 2100 participants. For these trials we evaluated cessation at the closest follow-up to end of pregnancy as well as at the longest follow-up. At the end of pregnancy we found a statistically significant benefit of NRT, which is consistent with results from a separate Cochrane Review of smoking cessation pharmacotherapies in pregnancy (Coleman 2015), although further research is needed to confirm this. We found no significant benefit of treatment at longest follow-up/post-partum follow-up. None of the studies found evidence of a significant increase in serious adverse events in the NRT arms.

Trials generally restricted recruitment to adults over the age of 18; in a small number of trials the age range was not specified. Two relatively small studies in adolescents did not detect an effect of NRT on quitting at six months or longer (Moolchan 2005; Scherphof 2014). A separate Cochrane Review of tobacco cessation interventions for young people did not detect an effect of NRT, although confidence intervals were wide and did not preclude the possibility of a clinically important effect (Fanshawe 2017). This is likely to remain an active area of research.

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

Re-treating relapsed smokers

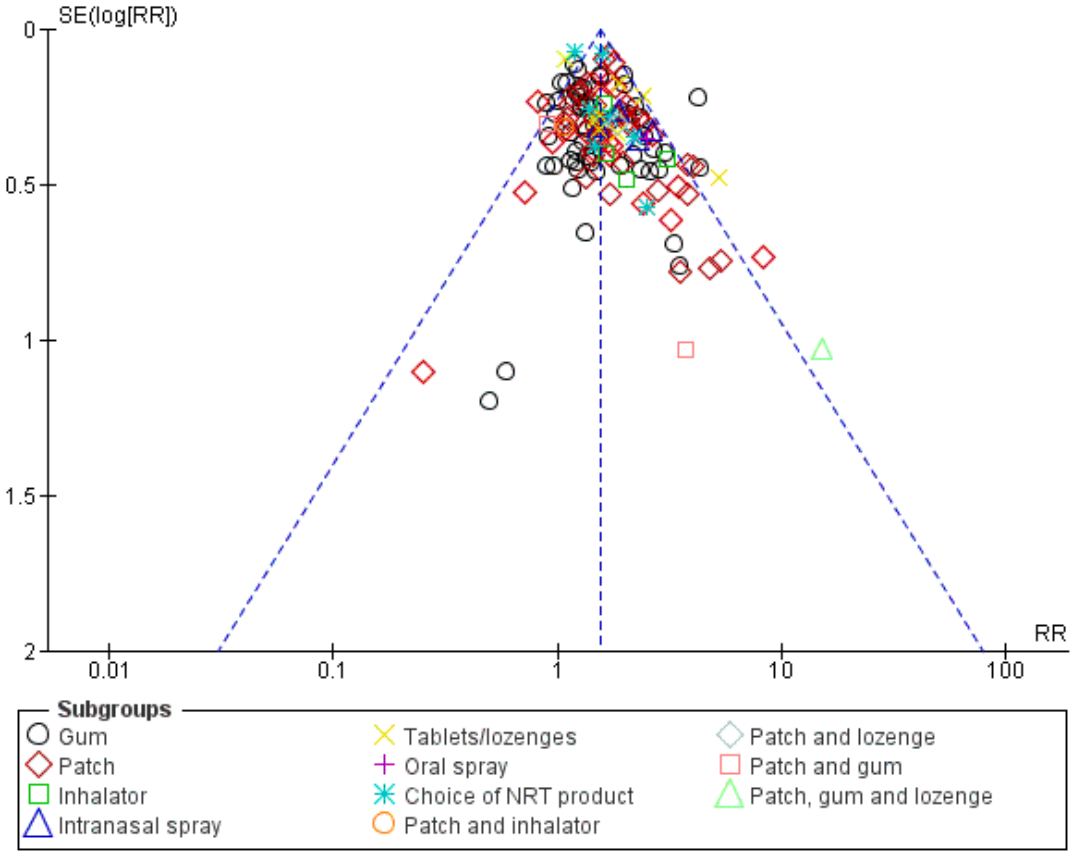
Whilst end-of-treatment success rates may be quite high, many people relapse after the end of therapy. There is suggestive evidence that repeated use of NRT in people who have relapsed after an initial course may produce further quitters, although the absolute effect is small (Gourlay 1995). A subgroup analysis in another trial 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 (Jorenby 1999, reported in Durcan 2002). 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.

Limitations of the evidence base

Two possible limitations to this evidence base need to be borne in mind: risk of bias in individual studies and publication bias. For the former, although we judged most of our included studies to be at unclear or high risk of bias in at least one domain, restricting the analysis to only those studies at low risk of bias overall did not significantly alter the pooled effect. For the latter, we tried to partly address any shortcomings from having limited our analysis to reported data by approaching investigators, where necessary, to obtain additional unpublished data or to clarify areas of uncertainty. Although we took steps 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, although we have searched clinical trials registries. 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 funnel plot (Figure 4) shows some evidence of asymmetry for trials in the main comparison; however, given the

large number of trials in the review, the funnel plot does not suggest that results would be altered significantly were smaller studies with lower RRs included. A meta-analysis has also demonstrated that nicotine gum and patch studies that received pharmaceutical industry funding have on average slightly higher effect sizes than other studies after controlling for some trial characteristics (Etter 2007). The practical effect of these considerations is that the magnitude of the effectiveness of NRT may be smaller than our estimates suggest.

Figure 4. Funnel plot of comparison: 1 Any type of NRT versus placebo/no NRT control, outcome: 1.1 Smoking cessation at 6+ months follow up.



A possible further limitation relates to length of follow-up. This review excludes studies with less than a six-month follow-up from the start of treatment; the outcome used reflects the effect of NRT after the end of active treatment. A comparison of abstinence rates during treatment and abstinence at one year suggests that the relative effect of NRT declines once active therapy stops (Fagerström 2003), i.e. 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. However, a meta-analysis comparing one-year and long-term outcomes in 12 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).

Stability of the evidence base

This review was first published in 1996. Despite the number of included studies more than doubling over this time, the effect estimate has remained remarkably stable, and our intention is that this publication is the final time the Cochrane Tobacco Addiction Group will review the evidence comparing NRT to placebo or to no pharmacotherapy. This is not to say that all questions about NRT have been answered; evidence is still needed comparing different forms, doses, and durations of NRT, comparing NRT to other pharmacotherapies, and testing NRT in special populations where we may reasonably hypothesize that its effectiveness differs from that in the general population (e.g. pregnant women, adolescents). Further studies are also needed of electronic cigarettes containing nicotine, which some consider a form of NRT (but which we have never included in this review). However, we will cover these in separate reviews which we will continue to update regularly (Cahill 2016; Coleman 2015; Fanshawe 2017; Hartmann-Boyce 2016; Hughes 2014). In summary, based on 20 years of research and 136 randomized controlled trials in over 64,000 participants, we believe the question of whether NRT helps people to quit smoking to be definitively answered. We consider that further research is highly unlikely to change our confidence in the effect of NRT, and funders and researchers should give careful thought before pursuing further studies comparing established forms of NRT with control.

AUTHORS' CONCLUSIONS

Implications for practice

1. All of the commercially available forms of nicotine replacement therapy (NRT), i.e. gum, transdermal patch, nasal spray, inhalator, oral spray, lozenge and sublingual tablet, are effective as part of a strategy to promote smoking cessation. They increase the rate of long-term quitting by approximately 50% to 60%, regardless of setting. These conclusions apply to smokers who are motivated to quit. There is little evidence about the role of NRT for individuals smoking fewer than 10 to 15 cigarettes a day.

2. The form of delivery of NRT is unrelated to effectiveness, so other considerations such as preferences, availability, or cost might determine the form of NRT chosen.

3. The effectiveness of NRT, in terms of the risk ratio, appears to be largely independent of the intensity of additional support provided. Intensive behavioural support is not essential for NRT to be effective. However, it should be noted that the absolute increase in success rates attributable to the use of NRT will be larger when the baseline chance of success is already raised by the provision of intensive behavioural support.

4. NRT causes non-ischaemic chest pain and palpitations in a minority of users but there is no evidence of an excess of serious cardiac problems, even in people with established cardiac disease.

5. NRT commonly leads to minor adverse reactions which reflect irritation of the site of use of the form of NRT. These reactions are usually not severe enough to prompt discontinuation of treatment

Implications for research

There is high-quality evidence that nicotine replacement therapy increases quit rates at six months or longer in adults motivated to quit. We consider that further research is highly unlikely to change our confidence in the effect of NRT in this population.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abelin 1989

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

Risk of bias

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

Ahluwalia 1998

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

Risk of bias

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

Ahluwalia 2006

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

Ahluwalia 2006 (*Continued*)

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

Risk of bias

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

Anthenelli 2016

Methods	Countries: Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Denmark, Finland, Germany, Mexico, New Zealand, Russian Federation, Slovakiam South Africa, Spain, USA Recruitment: community (media advertisements, posters, fliers)
Participants	8144 smokers (≥ 10 cpd), treatment-seeking, exhaled CO > 10 ppm at screening. Participants in the psychiatric disorder cohort had to have a current or lifetime stable psychiatric diagnosis 44% men, mean age 46, mean CPD 20.7, mean FTND 5.8
Interventions	1. Varenicline, 1 mg x 2/day (1 week titrated, then 11 weeks full dose) 2. Bupropion SR, 150 mg x 2/day (titrated for 3 days, then full dose for 11 weeks) 3. Nicotine patch, 21 mg x 7 weeks, 14 mg x 2 weeks, 7 mg x 2 weeks (11 weeks, 24 v 16 h not specified)

	4. Triple-dummy placebo for each arm of the trial (12 weeks) Level of support: high (counselling (up to 10 mins) at all contacts: up to 15 face-to-face visits and 11 telephone visits)
Outcomes	6 months continuous abstinence weeks 9 to 24 Validation: CO < 10 ppm
Notes	New for 2017 update. For this review, arm 3 v 4 only Trial funded by Pfizer and GlaxoSmithKline Some data extraction and risk of bias taken from Cahill 2016. N quit extrapolated from percentages given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomisation schedule ... using a block size of 8 (1:1:1:1 ratio) for each of the 20 diagnosis by region combinations"
Allocation concealment (selection bias)	Low risk	Quote: "Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Study product kit codes did not allow deciphering of randomised treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignment" "The triple dummy design feature required participants to take study medication as masked tablets dispensed in separate varenicline and bupropion pill bottles each with matching placebo along with with either applying active or placebo patches on a daily basis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses fully accounted for; ITT analysis conducted throughout. 790/1025 NRT and 765/1036 placebo completed study

Areechon 1988

Methods	Country: Thailand Recruitment: community volunteers
Participants	200 smokers (≥ 15 cpd) 6% female, average age 39, average cpd 24 Participants were motivated to quit
Interventions	1. Gum (2 mg) x 8 boxes 2. Placebo gum x 8 boxes Level of support: high (weekly visits with physician, unspecified frequency and duration)
Outcomes	PP abstinence at 6 months Validation: CO
Notes	Support level reclassified as high, 2008 Study funded by Merrel Dow (Bangkok, Thailand), with products supplied by A.B. Leo, Helsinborg, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Insufficient information
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind. "Neither the investigators nor the subjects knew which subjects received the active gum and which received the placebo"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Significant differences between NRT (20 dropouts) and placebo (37 dropouts; P < 0.01) at 6 months
Other bias	High risk	10/93 quitters did not provide CO validation, but distribution not reported. All are included in MA

Berlin 2014

Methods	Country: France Recruitment: multicentre, advertisements and letters from participating healthcare settings
Participants	403 pregnant smokers (≥ 5 cpd) at 9 to 20 weeks amenorrhoea, motivated to quit 100% female, average age 29, average cpd 11, median FTND 4.5, median gestational

Berlin 2014 (*Continued*)

	age 17 weeks
Interventions	1. Nicotine patch, 16 h, from TQD to delivery. Daily dose 10 to 30 mg/day based on salivary cotinine, adjusted at 6 and 12 weeks post-randomization 2. Placebo on same schedule Level of support: high (1 h behavioural counselling at baseline, at least 10 mins counselling at following 6 visits)
Outcomes	Continuous abstinence at 20 weeks post-TQD Validation: CO ≤ 8 ppm
Notes	New for 2017 update 2-month cessation data post-delivery also collected but not reported. Data at 20 weeks post-TQD included in Analysis 5.1.1. Not included in main analysis because follow-up was less than 6 months Funding: Ministry of Health, France and Assistance publique-Hôpitaux de Paris

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A computer generated randomisation list (allocation ratio 1:1) in blocks of four was prepared and kept double blinded. "
Allocation concealment (selection bias)	Low risk	Quote: "…the randomisation number was attributed automatically at the completion of the randomisation visit. A statistician…who was fully independent of the trial, prepared the random, computer generated allocation sequence. The randomisation code was kept in a sealed envelope in a safe. A copy of the randomisation code was kept separately in case of a serious adverse event necessitating exposure of a participant's group assignment. Investigators, members of the coordination centre, hospital pharmacists, and the study statistician were kept blinded until the code was opened before witnesses on 19 February 2013."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All study staff (investigators, pharmacists, members of the coordination centre and of the drug safety monitoring board, laboratory staff, statistician) were double blinded to treatment allocation." "The placebo patches were manufactured

Berlin 2014 (*Continued*)

		by the same company, with specific quality control guidelines to ensure double blinding." "Determinations of saliva cotinine levels were carried out blinded. The investigators were not aware of the results" "Data were analysed blinded to treatment"
Incomplete outcome data (attrition bias) All outcomes	High risk	92/203 and 113/199 withdrew, 107/203 and 123/199 not followed up at every visit (needed for strictest measure) (> 50% attrition overall)

Blondal 1989

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Assignment was by group (6 to active gum, 6 to placebo); whether randomized or not is unclear
Allocation concealment (selection bias)	Unclear risk	Probably. "Each subgroup knew they would either get nicotine gum or a placebo"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind

Blondal 1989 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	7/59 claiming abstinence at 12 months were not CO-confirmed (4 missing and 3 > 10 ppm), and counted as continuing smokers
Other bias	Low risk	44/92 in NRT group were highly nicotine-dependent, compared with 28/90 in placebo group (P = 0.03)

Blondal 1997

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization code", with spray dispensed by University pharmacy
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Subject and therapist were blind to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant lost to follow-up, assumed to be a smoker. Dropout rates not reported

Bolliger 2000b

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

Br Thor Society 1983

Methods	Country: UK (95 centres) Recruitment: hospital chest clinics (80%) and inpatient wards
Participants	1618 clinic patients age 18 to 65 with a smoking-related illness (pulmonary or vascular) 39% female, average age 49, average cpd 24
Interventions	1. Brief advice from physician 2. Brief advice + booklet 3. Brief advice + booklet + placebo chewing gum 4. Brief advice + booklet + nicotine chewing gum (2 mg for up to 3 months, up to 6 months on request) Level of support: low (1 month and 3 month follow-up visits)
Outcomes	Sustained validated abstinence at 6 months and 12 months Validation: Venous carboxyhaemoglobin
Notes	Includes both placebo and no-placebo groups. 4 vs 1 + 2 + 3 used in main comparison. 4 vs 3 has lower OR (0.8) but does not alter MA notably Study was funded by Health Education Council and Lundbeck Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Each physician had a balanced block of 12 treatments. Assignment was by numbered envelope
Allocation concealment (selection bias)	Low risk	Physician opened envelope at first treatment session
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Placebo and nicotine gums were indistinguishable in appearance and taste, and neither the physician nor the patient knew which gum had been issued"

Br Thor Society 1983 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Lower losses from gum groups (10 and 10) than from Advice groups (24 and 24), but 18 VA and VAB participants were prescribed Nicorette in error; removing these made differences non-significant

Brantmark 1973b

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

Buchkremer 1988

Methods	Country: Germany Recruitment: community volunteers
Participants	131 smokers 50% female, average age 35, average cpd 29 Participants were motivated to give up
Interventions	1. Nicotine patch (24 h/day, 8 weeks, 15 cm 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 12 months Validation: none
Notes	Placebo and no-placebo groups. 1 vs 2 + 3 used in main comparison Study was funded by Deutsche Forschungsgemeinschaft

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "smokers were randomly assigned ... Randomization included matching by age, sex and initial cigarette consumption"
Allocation concealment (selection bias)	Unclear risk	Not stated

Buchkremer 1988 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Described as double-blind; "checked by questioning both the training personnel and the probands of nicotine- and placebo-groups". No significant differences in right and wrong guesses
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates not reported

Bullen 2010

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

Campbell 1987

Methods	Country: UK Recruitment: primary care (45 GPs in 11 centres)
Participants	836 primary care patients agreeing to try to stop smoking after brief advice from their doctor 61% female, average age 39
Interventions	1. Nicotine gum (2 mg) x 6 boxes 2. Placebo gum x 6 boxes Level of support: low (no further face-to-face contact, ⅔ received a letter after 1 month)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	Study funded by Chest, Heart and Stroke Association; discounted Nicorette gum supplied by Lunbeck, free chewing gum by Wrigleys

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "in a double-blind random fashion". Control participants were recruited sequentially after the gum cohort had been

Campbell 1987 (*Continued*)

		assembled
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	37% losses at 12 months
Other bias	Unclear risk	Placebo gum was actually Wrigleys gum, repackaged and labelled

Campbell 1991

Methods	Country: UK Recruitment: hospital inpatients
Participants	212 patients with smoking-related diseases 44% female, 53% aged 50+, 61% smoked > 15 cpd
Interventions	1. Nicotine gum 2 to 4 mg (3 months) 2. Placebo gum Level of support: high (support at 2, 3, 5 weeks, 3 months, 6 months)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	Study was supported by Pharmacia LEO

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "those who had agreed were given packages of identical appearance randomly containing either nicotine (2 mg) or placebo gum"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Non-attenders were classified as failures"; rate of dropouts not reported

Campbell 1996

Methods	Country: UK Recruitment: hospital inpatients and outpatients
Participants	234 adult smokers (> 1 cpd in previous week) (172 outpatients, 62 inpatients) Stratified on FTND. Participants were motivated to quit 54% female, average age 49
Interventions	1. Nicotine patch (21 mg, 24 h, 12 weeks with dose tapering) 2. Placebo patch Level of support: high (counselling at 2, 4, 8,12 weeks)
Outcomes	Continuous abstinence at 12 months Validation: CO
Notes	Originally included as Burton 1992 which was an abstract of the same trial Study was funded and supplied by Ciba-Geigy Ltd

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants stratified by inpatient/outpatient status, and outpatients also by FTND score. Participants "were randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Abstract describes the trial as "double-blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	57 NRT and 56 placebo participants did not complete the 12-week course. By 52 weeks, 28 participants had dropped out of the NRT group, and 40 from the placebo group

CEASE 1999

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

Cinciripini 1996

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Sixty-four participants ... were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported, but failures and missing were counted as non-abstinent

Clavel 1985

Methods	Country: France Recruitment: community volunteers
Participants	427 smokers (≥ 5 cpd) 51% female, average age 34, average cpd 22 for intermediate group (Clavel 1984). Participants were motivated to quit
Interventions	1. Nicotine gum (2 mg) x 1 box 2. Control group (time lock-controlled cigarette case) (Acupuncture arm not included in this review) Level of support: High (3 x 1 h group therapy sessions in first month)

Clavel 1985 (*Continued*)

Outcomes	Sustained abstinence at 13 months Validation: "Smoking cessation adjusted using exhaled CO figures from published trials"
Notes	Classification of support corrected to high in 2008 update Study was supported by the Haut Comité d'Aide à la Lutte Contre le Cancer, and Laboratoire Léo, Sweden

Risk of bias

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

Clavel-Chapelon 1992

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

Clavel-Chapelon 1992 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomly allocated"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Treatments were administrated blindly"
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants abstinent at 1 month were followed up. 2 participants were lost between months 9 and 12, and 32 between year 1 and year 4. Losses "were considered successes until the date of the last follow-up and afterwards were not considered anymore"

Coleman 2012

Methods	Country: UK Recruitment: pregnant women attending hospital clinics
Participants	1050 pregnant women at 12 to 24 weeks gestation smoking ≥ 5 cpd Average age 26, average cpd at time of recruitment 14, average cpd before pregnancy 20
Interventions	1. Nicotine patch 15 mg/16 h for 8 weeks (participants given 4 week supply at outset, if not smoking at 4 weeks given another 4-week supply) 2. 'Visually identical' placebo on same schedule Level of support: high. Behavioural cessation support ≤ 1 h at enrolment + 3 phone calls (on quit date, 3 days after quit date, 4 weeks after quit date). If collecting another 4-week supply of NRT/placebo, participants given another face-to-face session
Outcomes	Continuous abstinence from quit date to delivery and prolonged abstinence at 2 years from delivery. Lapses of up to 5 cigarettes (on 5 occasions) permitted Validation: at delivery: salivary cotinine < 10 ng/ml, CO ≥ 8 ppm, primary outcomes required saliva cotinine validation, with or without CO. At 2 years, no validation
Notes	Funded by NIHR Health Assessment Technology Programme Similar rates of adverse pregnancy and birth outcomes in both groups; at 2 years, infants born to women who used NRT during pregnancy were more likely to have unimpaired development Low compliance in both arms (7.2% active treatment and 2.8% placebo group reported using patch for more than 1 month) Longer-term follow-up data (2 year post-delivery) added for 2017 update

Coleman 2012 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated sequence, in random permuted blocks of randomly varying size and with stratification by recruiting site"
Allocation concealment (selection bias)	Low risk	Quote: "eligibility criteria were entered into a secure online database before randomization"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "identically packaged study patches were dispensed, and all participants and study personnel were unaware of the study assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	981/1050 participants provided data at delivery; participants missing data counted as smokers

Cooper 2005

Methods	Country: USA Recruitment: community volunteers
Participants	439 female smokers (≥ 10 cpd) Average age 38, average cpd 23
Interventions	1. Nicotine gum (2 mg), 10 to 12 pieces/day recommended, for 9 weeks, weaning last 3 weeks 2. Placebo gum Level of support: high. 13 x 1-h weekly cognitive behavioural group sessions. Reduction prior to TQD week 5 (3rd arm tested phenylpropanolamine gum, not included in review)
Outcomes	PP abstinence at 12 months Validation: CO < 10 ppm Weight change in quitters was also a primary outcome in the trial
Notes	First included as Cooper 2003. Published report from 2007 Sources of support not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Cooper 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible participants ... were randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported, all analyses conducted as ITT. Dropouts (if any) counted as treatment failures in our analysis

Cummins 2016

Methods	Country: USA Recruitment: inpatients at participating hospitals (multicentre)
Participants	1270 hospitalied smokers (excl. obstetrics, surgery and behavioural health patients), smoked in last 30 days and at least 6 cpd on days smoked 57% male, average age 50, average cpd 15
Interventions	1. NRT patches for 8 weeks, doses based on cpd. If 6 cpd to 10 cpd: 14 mg for 6 weeks, 7 mg for 2 weeks. If > 10 cpd: 21 mg for 4 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks. (NS if 16-h or 24-h patches) 2. No NRT Level of support: varied. All were provided quitline number. Hospital systems, individual hospitals, and even individual units had their own approach to usual care for smokers, with differences in providing counselling or prescribing quitting aids during hospitalisation. There was no attempt to constrain these activities. Some participants in the NRT and the no-NRT groups also received counselling due to factorial design (2 x 2 factorial design: NRT/counselling/NRT and counselling/usual care). Counselling was by the Quitline service. Authors tested for an interaction between NRT and counselling and this was not significant, therefore results collapsed for this review
Outcomes	7-day PP at 6 months validation: saliva cotinine < 10 ng/ml
Notes	New for 2017 update Funding: National Cancer Institute (CA159533) N quit extrapolated from percentages given. Not included in support subgroups as support varied by study centre

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Cummins 2016 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "randomly assigned by computer to one of four groups"
Allocation concealment (selection bias)	Low risk	Recruiters "entered study-related information into a secure website that randomised the subject."
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo. Participants therefore aware if on NRT or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	NRT 205/637, no-NRT 208/633 dropout < 50%. (return of saliva kits at 6 months for validation 57%, still > 50%)

Cunningham 2016

Methods	Country: Canada Recruitment: by random digit dialling
Participants	1000 smokers (≥ 10 cpd) 51% female, average age 49, average cpd 18, mean FTND 5
Interventions	1. Nicotine patches. 5 weeks total, tapered: 3 weeks 21 mg, 1 week 14 mg, 1 week 7 mg (unclear if 16 or 24 h) 2. No intervention Level of support: low; no support provided (patches mailed to intervention participants)
Outcomes	30-day PP at 6 months Validation: Saliva cotinine < 15 µg/L
Notes	New for 2017 update Total n followed up from author correspondence Funding: Canadian Institutes of Health Research, Centre for Addiction and Mental Health, Canada Foundation for Innovation, Ontario Ministry of Research and Innovation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants randomized "using a random number generator contained in the computer assisted telephone interview program" This was "conducted in blocks of 10 with a 1:1 allocation to the experimental group within each block and no stratifica-

Cunningham 2016 (*Continued*)

		tion“
Allocation concealment (selection bias)	Low risk	As above
Blinding (performance bias and detection bias) All outcomes	High risk	The participants knew which group they were in, although the interviewers were masked to the experimental group at each follow-up point ”(ensured through use of the computer-assisted telephone interview program)” No placebo control
Incomplete outcome data (attrition bias) All outcomes	Low risk	389/500 and 415/499 followed up at 6 months

Daughton 1991

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “All 158 study-eligible volunteers were randomly assigned”
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as “double-blind”; “All of the patches were physically identical in appearance”

Daughton 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts (if any) not reported; included as treatment failures in our analysis; results presented on an ITT basis

Daughton 1998

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a random code was generated" for equal numbers of active and placebo within blocks of 10
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Participants were assigned randomly, in a double-blind fashion"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses low at 3 months (1.1%), 6 months (1.6%) and 12 months (2.2%). Those lost to follow-up were included as failures

Dautzenberg 2001

Methods	Country: France Recruitment: community volunteers
Participants	433 smokers (excludes 25 from ITT population) 52% female, average age 39, average cpd 21
Interventions	1. Nicotine lozenge (1 mg, 8 to 24/day, 6 weeks + 6 weeks weaning for quitters) 2. Placebo lozenge Level of support: not stated
Outcomes	PP abstinence at 26 weeks Validation: CO < 10 ppm
Notes	Based on published abstract Study was funded by Novartis Consumer Health

Risk of bias

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

Davidson 1998

Methods	Country: USA (4 centres) Recruitment: community volunteers in shopping malls (OTC setting)
Participants	802 smokers (> 20 cpd) who scored 5+ on a questionnaire assessing motivation 54% female, average age 39, average cpd 29
Interventions	1. Nicotine patch (22 mg, 24 h, for up to 6 weeks) 2. Placebo patch Level of support: low (self-help book provided. Participants visited mall weekly to obtain patches. CO levels were monitored)

Davidson 1998 (*Continued*)

Outcomes	Sustained abstinence at 24 weeks (from week 2) Validation: Expired CO ≤ 8 ppm at each weekly visit, but 24 week quit based on self-report	
Notes	541/802 did not complete the 6 weekly visits Study was funded by Elan Pharmaceutical Corporation	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated randomization schedule"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses were included as failures. 67.5% withdrew before study completion; placebo losses higher than active, but differences not statistically significant

Ehrsam 1991

Methods	Country: Switzerland Recruitment: University (primary care)	
Participants	112 smokers at 2 universities Average age 26, average cpd 23	
Interventions	1. Nicotine patch (21 or 14 mg/24 h, 9 weeks, tapered) 2. Placebo patch Level of support: high (no counselling)	
Outcomes	Sustained abstinence at 12 months (0 to 3 cigarettes per week) Validation: urinary cotinine	
Notes	Study funding not reported	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ehrsam 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Method not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "doppelblinden" but no further information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts included as failures. 36% dropped out of active group, and 55% out of placebo group
Other bias	Unclear risk	Abstinence defined as 0 to 3 cigarettes a week, with CO < 12 ppm. Relapse defined as ≥ 1 cpd, or ≥ 14 cigarettes over 2 weeks

El-Mohandes 2013

Methods	Country: USA Recruitment: healthcare (3 prenatal care sites)
Participants	52 pregnant (< 30 weeks gestation) smokers motivated to quit, self-identified as ethnic minority 100% female, average age 28, average cpd 6, mean gestational age at baseline 9 weeks
Interventions	1. Nicotine patch, 10 weeks. Dose based on baseline salivary cotinine: if baseline salivary cotinine level ≥ 100 ng/ml then 21 mg patches for 2 weeks, 14 mg patches for 4 weeks and 7 mg patches for 4 weeks. If baseline salivary cotinine level 20 to 99 ng/ml then 14 mg patches for 6 weeks and 7 mg patches for 4 weeks 2. No pharmacotherapy Level of support: high (6 individual in person counselling visits)
Outcomes	Abstinence since last visit (approximately 3 weeks) at 20 weeks Validation: CO ≤ 8 ppm
Notes	New for 2017 update Does not contribute to primary analyses as follow-up < 6 months. 20-week abstinence (pre-delivery) included in Analysis 5.1.1 Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

El-Mohandes 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "Using a 1:1 ratio, women were randomized to either the NRT patch and continued CBT (Group 1) or CBT only (Group 2)… The web-based database management system was programmed to randomize after entering the necessary data to verify eligibility and administration of the baseline survey."
Allocation concealment (selection bias)	Low risk	Quote: "The web-based database management system was programmed to randomize after entering the necessary data to verify eligibility and administration of the baseline survey."
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Telephone interviewers were blinded to group assignment." "The intervention specialists were blinded to group assignment." No placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	At the strictest quit timepoint (salivary continine levels at final visit), 34/52 participants lacked data (> 50%). If already delivered before 20 week follow-up, did not have a visit 6 and smoking status not known

Fagerström 1982

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

Fagerström 1982 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned.. . in blocks of ten"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All patients were told that the chewing gum they received contained nicotine"; participants did not know that they were involved in a study "the experimenter's guess of nicotine or placebo gum was in the direction of better than chance, but not significantly so"
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 early dropouts (3 active, 1 placebo) excluded from analysis; all other dropouts counted as smokers in final analysis

Fagerström 1984

Methods	Country: Sweden Recruitment: general practices and industrial clinics (primary care)
Participants	145 smokers motivated to quit 56% female, average age 40 years, average 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 mg or 4 mg) 4. Long follow-up plus nicotine gum Level of support: low
Outcomes	Sustained abstinence at 12 months (and at 1, 6 months) Validation: 15% deception rate detected by expired CO > 4 ppm in a random subset of claimed non-smokers at 6 months. Self-reported 12 month rates used in MA
Notes	3 and 4 vs 1 and 2 in Comparison 1 Study funding not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: "Patients were randomly assigned" by birthdate; participants born 1st to 20th received active gum, 21st to 31st no gum. Those born on even dates got long follow-

Fagerström 1984 (*Continued*)

		up, odd dates short follow-up
Allocation concealment (selection bias)	High risk	Not used
Blinding (performance bias and detection bias) All outcomes	High risk	Not used
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants abstinent at 1 follow-up were seen again for the next one. All losses counted as failures
Other bias	High risk	Physicians selected for the study were personal acquaintances of the author, and all except 1 were non-smokers

Fee 1982

Methods	Country: UK Recruitment: smoking cessation clinic
Participants	352 smokers, no other demographic data
Interventions	1. Gum (2 mg) given for 5 weeks 2. Placebo gum given for 5 weeks Level of support: high (10 group therapy sessions)
Outcomes	PP abstinence at 12 months Validation: Blood carboxyhaemoglobin
Notes	Study was supported by LEO Laboratories, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Allocation was carried out by external staff, using a random selection procedure unknown to the authors"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information

Fee 1982 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Significantly higher losses from placebo (47.7%) than from active group (36.7%). Losses taken as failures

Fiore 1994a

Methods	Country: USA Recruitment: community volunteers
Participants	88 smokers (> 15 cpd), motivated to quit.
Interventions	1. Nicotine patch (22 mg/24 h, 8 weeks, no weaning) 2. Placebo patch Level of support: high (intensive group counselling)
Outcomes	PP abstinence at 6 months (7-day PP) Validation: CO
Notes	Reported in same paper as Fiore 1994b Studies supported by Elan Pharmaceutical Research Corporation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a pregenerated computer sequence" and stratified by FTQ score
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Ten placebo and 1 active participant failed to complete the NRT course. 25 participants lost to follow-up at 6 months were included as failures

Fiore 1994b

Methods	Country: USA Recruitment: community volunteers
Participants	112 smokers (> 15 cpd)

Fiore 1994b (*Continued*)

Interventions	1. Nicotine patch (22 mg/24 h, 6 weeks including weaning) 2. Placebo patch Level of support: high (8 weekly 10 min to 20 min individual counselling)
Outcomes	PP abstinence at 6 months (7 days PP) Validation: CO
Notes	Reported in same paper as Fiore 1994a. Studies supported by Elan Pharmaceutical Research Corporation

Risk of bias

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

Fortmann 1995

Methods	Country: USA Setting: community volunteers (telephone recruitment)
Participants	1044 smokers aged 18 to 65, able to quit for 24 h, and without serious illness. Motivated to maintain abstinence 42% female, average age 40, average cpd 20
Interventions	1. Nicotine gum (2 mg, 1/h, 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 USD 100 for quitting at 6 months Level of support: low
Outcomes	PP abstinence at 12 months Validation: CO < 9 ppm/salivary cotinine < 20 ng/ml

Fortmann 1995 (*Continued*)

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 and 3 vs 2 and 4. The RR is unaltered but CIs narrow Study was funded by the National Heart, Lung, and Blood Institute

Risk of bias

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

Fraser 2014

Methods	Country: USA Recruitment: community (individuals who spontaneously accessed smokefree.gov portal)
Participants	1034 smokers of ≥ 5 cpd, motivated to quit, no prior use of smokefree.gov website 68% female, average age 39, average cpd 19.3, mean FTND 5.3
Interventions	1. Nicotine mini-lozenge for 2 weeks (mailed). 162 lozenges received (dosage not given but based on time to first cigarette), instructed to use 6 to 10 lozenges per day 2. No pharmacotherapy or placebo Level of support: variable (factorial study resulting in 32 distinct experimental conditions, behavioural elements varied on quitline counselling, messaging, brochures)
Outcomes	7-day PP at 7 months (by e-mail) Validation: none
Notes	New for 2017 update Factorial trial, NRT versus no NRT compared in main analyses, other factors related to behavioural support (authors tested for interaction. No interaction found between NRT and behavioural components, results therefore collapsed for our analysis) N quit extrapolated from percentages given Funding: Matthews Media Group, National Cancer Institute

Fraser 2014 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Through automated system: "Randomization occurred immediately after the confirmation call, and participants completing this step were sent an automated email welcoming them to the study and outlining services they would receive (based on their randomization)."
Allocation concealment (selection bias)	Low risk	Automated, see above
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding of participants. "Follow-up interviewers were blind as to treatment assignment". No placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 7 months, 828/1034 participants were followed up (> 50%). Dropout for each group not given but states follow-up across 5 different treatment factors 76% to 81%. Difference between groups not statistically significant

Gallagher 2007

Methods	Country: USA Recruitment: 3 psychiatric case management sites in La Frontera, Arizona
Participants	180 smokers, aged 18+, English-speaking, smoked at least 10 cpd for at least 3 years, CO > 10 ppm. Diagnosed with DSM-IV Axis 1 psychotic-spectrum or affective disorders resulting in long-term mental illness and experiencing significant symptoms and functional impairment 52% male, average age 43, av FTQ 6.1, average cpd 24.8
Interventions	1. Contingency reinforcement (CR): Weekly visits weeks 1 to 4 (Phase 1), fortnightly weeks 6 to 12 (Phase II), monthly weeks 16 to 24 (Phase III). Payments USD 25 for baseline assessment and USD 5 per visit, plus USD 20 per abstinent visit in Phase I, USD 40 in Phase II, USD 60 in Phase III, and USD 80 if abstinent at 36-week follow-up. Max payable USD 580 for attendance + abstinence. At each visit weight, pulse rate, smoking status, intention to quit, withdrawal symptoms, CO, BP measured 2. CR + NRT: As CR Group, plus 16-week course of 21 mg NRT patches (16 h or 24 h not stated), plus supporting instructions 3. Control: Visits at baseline and weeks 20 and 36, plus encouraged to use the community smoker helpline, ALA and ACS self-help information Level of support: high (contingency reinforcement)

Gallagher 2007 (*Continued*)

Outcomes	PP abstinence at week 36 Verified by expired CO < 10 ppm and by salivary cotinine < 15 ng/mL
Notes	New for 2017 update. Analysis compares 2 vs 1; 3 not included as comparison with NRT confounded Not required to commit to cessation, but 98% expressed interest either in quitting or in reducing Additional information supplied by the author. N quit extrapolated from percentages given Study funded by Arizona Biomedical Research Commission. Risk of bias and some data extraction from Cahill 2015

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Unconcealed computer-generated random number lists (personal communication)
Allocation concealment (selection bias)	High risk	Study staff oversaw allocation
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	No significant differences between groups: Attrition for CR at weeks 20 and 36 was 37% and 43%; CR+NRT at weeks 20 and 36 was 35% and 36%

García 1989

Methods	Country: Spain Recruitment: primary care
Participants	106 adult smokers (excludes 81 not beginning treatment) 65% female, average age 36, average cpd 25
Interventions	1. Gum (2 mg) for 3 to 4 months 2. Placebo gum for 3 to 4 months Level of support: high (group therapy, 7 sessions over 3 months)
Outcomes	Sustained abstinence at 6 months Validation: CO ≤ 7 ppm
Notes	Sources of support not reported

García 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "La asignación a los grupos de estudio se realizaba aleatoriamente al acudir a la primera entrevista"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind ("doble ciego")
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts reported at 1, 3 and 6 months. Analyses appear to be ITT-based, counting dropouts as failures

Garvey 2000

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Garvey 2000 (*Continued*)

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

Gilbert 1989

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

Risk of bias

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

Gilbert 1989 (*Continued*)

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

Glavas 2003a

Methods	Country: Croatia Recruitment: hospital health professionals
Participants	112 healthcare professionals smoking at least 1 cpd. 26% had FTND score 6+ 66% female, average age 34, average cpd: 24
Interventions	1. Nicotine patch, 24 h, 25 mg/15 mg/8 mg starting dose depending on baseline cpd. 3 weeks 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 cigarettes/week) at 1 year (5-year abstinence also reported, not used in MA) Validation: CO < 11 ppm
Notes	Study was supported by Novartis

Risk of bias

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

Glavas 2003a (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 dropouts by year 1 and year 5, classified as failures

Glavas 2003b

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

Risk of bias

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

Glover 2002

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

Risk of bias

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

Gourlay 1995

Methods	Country: Australia Recruitment: community volunteers
Participants	629 smokers (> 15 cpd) who had relapsed after transdermal nicotine and behavioural counselling in an earlier phase of the study Minimal additional support
Interventions	1. Nicotine patch 30 cm² (21 mg/24 h) for 4 weeks, 20cm² (14 mg/24 h) for 4 weeks, 10 cm² (7 mg/24 h) for 4 weeks. 2. Placebo patch

Gourlay 1995 (*Continued*)

Outcomes	Sustained abstinence at 6 months Validation: expired CO < 10 ppm
Notes	Does not contribute to main comparison. Test of patches vs placebo in recently relapsed smokers. Results given in text. Study was funded by Ciba-Geigy Australia, the Anti-Cancer Council of Australia and the Victorian Health Promotion Foundation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomised"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants invited at week 11 to guess their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts at each stage reported in full. Losses to follow-up included as failures

Graham 2017

Methods	Country: USA Recruitment: smoking cessation website
Participants	5290 current smokers 61% female, average age 42, average cpd 17, mean FTND 5.3
Interventions	1. 4 weeks of NRT patch, gum or lozenge depending on participant preference, mailed to participants. Standard dosing protocol as per labelling instructions 2. No NRT Level of support: low (use of interactive website. Some participants also received web-based social network intervention. 2 x 2 factorial design. No evidence of interaction between NRT and web-based social network intervention, therefore results collapsed for our analysis)
Outcomes	30-day PP at 9 months Validation: none
Notes	New for 2017 update 9-month data obtained from authors Funding: National Cancer Institute

Graham 2017 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomisation is stratified by gender and baseline motivation to quit. Within-strata randomisation assignments are automated using a computer algorithm"
Allocation concealment (selection bias)	Low risk	Central computer-based allocation
Blinding (performance bias and detection bias) All outcomes	High risk	Participants were not blinded but if research staff contacted participants by phone, they were blinded to treatment condition. No placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 50% followed up at 9 months (1600/2630 Intervention, 1418/2660 control)

Gross 1995

Methods	Country: USA Recruitment: community volunteers
Participants	177 smokers 51% female, average age 42, average cpd 33, average FTND 7.8
Interventions	1. Nicotine gum (2 mg), tapered from week 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 weeks)
Outcomes	Continuous abstinence at 6 months (up to 3 cigarettes allowed) Validation: CO $\leq$ 10 ppm. Saliva thiocyanate in week 2
Notes	No placebo. Long-term abstinence rates not affected by amount of gum, so these groups collapsed for comparison with no-gum condition Study was funded by National Institute of Drug Abuse, and supported by Marion Merrell Dow

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated

Gross 1995 (*Continued*)

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

Hall 1985

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned within time constraints to one of the three treatment conditions"
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo; no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts reported

Hall 1987

Methods	Country: USA Recruitment: community volunteers
Participants	139 adult smokers 47% female, average age 39, average cpd 30
Interventions	2 x 2 factorial trial of gum and behavioural support 1. Nicotine gum (2 mg) up to 12 months 2. Placebo gum up to 12 months Both levels of behavioural support classified as high intensity and collapsed in analysis (both group-based, 14 x 75-min sessions, or 5 x 60-min sessions)
Outcomes	PP abstinence at 12 months Validation: CO < 8 ppm and serum thiocyanate < 95 mm/l
Notes	Study funded by National Institute of Drug Abuse and Department of Veterans Affairs

Risk of bias

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

Hall 1996

Methods	Country: USA Recruitment: community volunteers
Participants	207 smokers of which 6 excluded from analyses because of protocol breaches 52% female, average age 40, average cpd 24
Interventions	2 x 2 factorial trial of gum and psychological treatment 1. Nicotine gum (2 mg) for 8 weeks, 1 piece/h for 12 h/day recommended 2. Placebo gum, same schedule Both levels of behavioural support classified as high intensity and collapsed in analysis (both group-based, 10 sessions over 8 weeks, TQD session 3)

Hall 1996 (*Continued*)

Outcomes	Sustained abstinence at 12 months (abstinent at all assessments) Validation: CO ≤ 10 ppm at 8, 12, 26 weeks and urinary cotinine ≤ 60 ng/ml at 52 weeks
Notes	Psychological treatment arms collapsed, no evidence of a significant interaction Study was funded by National Institute of Drug Abuse and Department of Veterans Affairs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were stratified according to depression history and number of cigarettes smoked per day; they were then randomly assigned from within stratified blocks"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants excluded from analyses for protocol violations. No further information on dropouts

Hand 2002

Methods	Country: UK Recruitment: hospital in- or outpatients referred by hospital doctor
Participants	245 patients with smoking-related disease 46% male, typically aged 50+, smoking 15+ cpd; participants were motivated to try and quit
Interventions	1. Nicotine patch (initially 30 or 20 mg based on smoking rate) and inhaler for 3 weeks including patch tapering. Same counselling as control 2. Individual counselling, 4 sessions in 4 weeks. No placebo Level of support: high
Outcomes	Sustained abstinence at 12 months (abstinent at all assessments) Validation: CO < 10 ppm

Hand 2002 (*Continued*)

Notes	No placebo. Compliance with NRT was low, 28% did not use, 30% used full supply Used in main comparisons Study was funded from one author's endowment fund	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	High risk	Quote: "randomised, according to month of entry"; unequal months, with imbalance in favour of NRT group
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo, so not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rates not reported, but all included in analyses

Harackiewicz 1988

Methods	Country: USA Recruitment: primary care (University Health Centre)	
Participants	197 smokers (151 used in MA), motivated to quit 63% female, average age 36, average cpd 26	
Interventions	1. Nicotine gum (2 mg, 6 weeks initial supply, suggested tapering after 3 months, available for 6 months) 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 12 months Validation: CO in all participants, cotinine and carboxyhemaglobin in a subsample of participants	
Notes	No placebo. Arm 3 not included in MA control group - it had a lower quit rate so inclusion would increase the gum treatment effect	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Harackiewicz 1988 (*Continued*)

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

Hasan 2014

Methods	Country: USA Recruitment: hospital
Participants	122 (81 to relevant arms) smokers admitted with a cardiac or pulmonary illness 48% female, average age 55, average cpd 20
Interventions	1. Patch and gum/lozenges as per participant preference. Patch dose dependent on cpd prior to hospitalization; exact dose not specified but participants smoking 10 to 20 cpd on 21 mg/day initially 2. No NRT Level of support: high. 90-min individualized hypnotherapy session with a certified hypnotist and a tobacco treatment specialist, plus self-help materials and counselling (intensive counselling for 30 mins in hospital, with 5 follow-up 15-min phone calls with additional counselling at 1, 2, 4, 8, and 12 weeks after hospital discharge)
Outcomes	7-day PP at 6 months Validation: Urinary cotinine < 15 ng/ml
Notes	New for 2017 update Funding: Norman H. Read Charitable Trust Foundation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "We randomized participants to one of three treatment groups: NRT only (NRT), hypnotherapy only (H), and a group receiving both hypnotherapy and NRT (HNRT)… Randomization assignments were performed in per-

Hasan 2014 (*Continued*)

		muted blocks of three (ratio 1:1:1) with assignments sequentially numbered" Not clear how sequence generated
Allocation concealment (selection bias)	Low risk	Quote: "Randomization assignments were performed in permuted blocks of three (ratio 1:1:1) with assignments sequentially numbered, and schedule was maintained independent of the study by the project coordinator. Randomized assignments were concealed from both patients and research staff until patients had signed the informed consent document and were enrolled in the study"
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Due to the nature of the intervention conditions, counselors could not be blinded to the modality of intervention." "Our analysis is somewhat limited by the fact that comparing two vastly different modalities such as hypnosis and pharmacotherapy represents a randomization challenge, as participants and interventionists cannot be blinded to treatment conditions. " No placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	33.9% lost to follow-up overall. In relevant treatment arms: 14/41 in hypno, 13/38 in hypno-plus-NRT

Hays 1999

Methods	Country: USA (3 sites) Recruitment: community volunteers
Participants	958 smokers, > 15 cpd, motivated to quit 50% female, average age 44, typically smoked 21 to 40 cpd
Interventions	1. Nicotine patches (22 mg, 24 h for 6 weeks) purchased by participants, open-label 2. Nicotine patches (22 mg, 24 h for 6 weeks) 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 and 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 6 months (7-day PP) Validation: CO $\leq$ 8 ppm

Hays 1999 (*Continued*)

Notes	1 and 2 vs 3 in patch vs placebo comparisons Study was supported by Elan Pharmaceutical Research Corp

Risk of bias

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

Herrera 1995

Methods	Country: Venezuela Recruitment: community volunteers
Participants	322 smokers > 10 cpd, scoring ≥ 4 on FTND, no serious illness. Only those who were ready to quit after 4 weeks of behavioural treatment were randomized 43% female, average age ~38, average cpd 33 for high dependence, 16 for low dependence
Interventions	Low-dependence smokers (FTND 4 to 6): 1. 2 mg nicotine gum 2. Placebo gum High-dependence smokers (FTND 7 to 11): 1. 4 mg nicotine gum plus 2. 2 mg nicotine gum Level of support: high for all (12 group sessions over 6 weeks + 6 weekly maintenance sessions) Participants also randomized to starting medication with increasing dose for 1 week before TQD, or to start at full dose on TQD - there was no blinding for this
Outcomes	Sustained abstinence at 2 years (1 year also reported) Validation: expired CO < 6 ppm

Herrera 1995 (*Continued*)

Notes	Low-dependence smokers included in comparison 1 Relapse between 1 and 2 years similar between low-dependence groups. Higher relapse in 4 mg high dependence than 2 mg No information on support or funding

Risk of bias

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

Heydari 2012

Methods	Country: Iran Setting: Smoking cessation clinics
Participants	272 treatment-seeking participants: Brief advice (91), NRT (92), varenicline (89) 41.2% women, mean age 42.5 years, mean FTND 5.5
Interventions	1. NRT: 8 weeks of 15 mg/24 h NRT patches 2. 8 weeks of 1 mg x 2/day varenicline (titrated 1st week) 3. Control group: no pharmacotherapy Level of support: high (all received brief (5 mins) education and counselling at 4 x weekly sessions.)
Outcomes	12 months PPA, in person or by phone, verified by expired CO (cut-off value not given)
Notes	New for 2017 update. Our analyses only include 1 vs 3 Funding: Masih Daneshvari Hospital Research Institute, Tehran Risk of bias and some data extraction taken from Cahill 2016

Risk of bias

Heydari 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Smokers who attended the clinic for help in quitting were divided randomly"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label; blinding of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition: "Participants entered the study of their own accord and none left the study"
Other bias	Unclear risk	Abstinence-by-gender data (Table 2) appears to contain an error for women on NRT at 12 months; we have ignored this finding in favour of the combined-genders data

Heydari 2013

Methods	Country: Iran Recruitment: drug abuse treatment centres
Participants	424 smokers ("habitual smokers" ≥ 1 year), history of drug abuse including opiates or narcotics for ≥ 1 year prior to referral to drug treatment centre 100% male, average age 44, average cpd NS (majority smoked 11 to 30 cpd), mean FTND 5.3
Interventions	1. NRT patch, gum and lozenges over 6 weeks. Step down 30 mg, 20 mg and 10 mg patches, and supply of 4 mg chewing gum and 1 mg pills 2. No pharmacotherapy or placebo Level of support: high (individual behavioural therapy, further detail not provided)
Outcomes	Abstinence at 6 months (type of measure not specified) Validation: exhaled CO (cut off not specified)
Notes	New for 2017 update. Not included in Analysis 4 as only study to be conducted in drug abuse treatment setting Funding: not specified, NRT provided free of charge by Meliora Health Corporation

Risk of bias

Bias	Authors' judgement	Support for judgement

Heydari 2013 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "424 persons were assigned in a simple randomisation process into intervention and control groups using a computer generated list of random numbers"
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "researchers informed clinicians as to the type of treatment to administer to assigned subjects. Clinicians were not blinded…at the point at which treatment was administered"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up at 6 months

Hjalmarson 1984

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	26 groups "were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Low risk	Both therapists and nurse distributing gum were blinded to assignment of groups. Placebo gum was flavoured with capsaicin to mimic nicotine

Hjalmarson 1984 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 dropouts from each cohort during follow-up; they were counted as smokers. 3 more from each cohort relapsed and were retreated, but counted as smokers within the study

Hjalmarson 1994

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects ... were randomized" to 26 groups
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Procedure was blind to both subject and therapist", but where more than 1 household member was enrolled all members got the same treatment (6 couples thus affected, 3 in active and 3 in placebo). At 12 months, 60% of responders correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	By 12 months, 20% had relapsed

Hjalmarson 1997

Methods	Country: Sweden Recruitment: smoking cessation clinic
Participants	247 smokers (> 10 cpd) who had previously made a serious attempt to stop using nicotine gum, and were motivated to quit 64% female, average age 48, average cpd 21
Interventions	1. Nicotine inhaler (recommended minimum 4/day, tapering after 3 months, use permitted to 6 months) 2. Placebo inhaler Level of support: high (8 group meetings over 6 weeks)
Outcomes	Sustained abstinence at 12 months Validation: CO < 10 ppm at 2 and 6 weeks and 3, 6, 12 months
Notes	Study was funded by Pharmacia & Upjohn, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "All numbers were on a list for random allocation to medication"
Allocation concealment (selection bias)	Low risk	Participants received "a subject number consecutively" at the first group session
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The randomization was blinded to both the participant and the therapist", but members of the same household received the same treatment. At 12 month follow-up, 86% of the active group and 90% of placebo group correctly guessed their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and relapsers all counted as failures. Details fully reported

Huber 1988

Methods	Country: Germany Recruitment: community volunteers
Participants	225 smokers (109 contribute to MA) No demographic information

Huber 1988 (*Continued*)

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. 6-month waiting-list control
Outcomes	Abstinence at 12 months Validation: none
Notes	3 vs 2 in comparison 1. No placebo. Quit rates derived from graphs. The nicotine-alone group was not used in the MA; quit rates were higher than intervention 2 Study funding and support not reported

Risk of bias

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

Hughes 1989a

Methods	Country: USA Recruitment: primary care
Participants	315 daily smokers, motivated to quit 56% female, average age 37, average cpd 29
Interventions	1. Nicotine gum (2 mg for 3 to 4 months) 2. Placebo gum Level of support: low (29 to 35 mins at 1st visit including nurse and physician advice and materials, follow-up appointment 1 to 2 weeks later)
Outcomes	Sustained abstinence at 12 months Validation: salivary cotinine < 15 ng/mL or thiocyanate < 1.6 mmol/L

Hughes 1989a (*Continued*)

Notes	Time spent at 1st visit is marginal for inclusion in low-intensity support category Study was funded by National Institute on Drug Abuse; gum supplied by Merrel-Dow Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	A 4th random digit (1 to 9) was added to their 3-digit subject ID number. Only exception was members of same household got the same treatment
Allocation concealment (selection bias)	Low risk	2:1 randomization scheme. Quote: "Subjects were assigned randomly in a double-blind manner"
Blinding (performance bias and detection bias) All outcomes	Low risk	Pharmacists dispensed gum from numbered bins, and were unaware of assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and lost to follow-up were included as smokers. Full details of losses reported

Hughes 1990

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

Hughes 1990 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "in a double-blind manner"; participants guessed which group they had been assigned to
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Subjects unable to be contacted were counted as smokers". Losses not reported

Hughes 1999

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Hughes 1999 (*Continued*)

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

Hughes 2003

Methods	Country: USA Recruitment: community volunteers
Participants	115 smokers with a history of alcohol dependence, motivated to quit, ≥ 30 cpd 68% male, average cpd 30
Interventions	1.Nicotine patch (21 mg, 24 h, 6 weeks + 4 weeks tapering + 2 weeks placebo) 2. Placebo patch 12 weeks Level of support: high (Group behaviour therapy x 6, brief individual counselling x 3)
Outcomes	Sustained abstinence at 6 months (from 2 weeks post-quit) Validation: CO ≤ 10 ppm at each follow-up visit
Notes	Unadjusted ORs used in MA not significant, significant when adjusted for smoking variables Study was supported by GlaxoSmithKline, and funded by National Institute on Drug Abuse

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "Subjects were randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "we assumed that missing data indicated smoking". Losses reported, but not distribution across groups

Hurt 1990

Methods	Country: USA Recruitment: community volunteers
Participants	62 adult smokers (> 20 cpd); only accepted if willing to make a quit attempt 53% female, average age 39, average cpd 30
Interventions	1. Nicotine patch (30 mg 24 h, 6 weeks + option of further 12 weeks ± tapering) 2. Placebo patch (continuing smokers at 6 weeks were offered active patch) Level of support: high (brief advice from nurse co-ordinator at 6 weekly visits)
Outcomes	Sustained abstinence at 12 months (quit by week 6, and all subsequent visits) Validation: CO ≤ 8 ppm
Notes	Study was in part supported by Elan Pharmaceutical Research Corporation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "subjects were assigned randomly"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated; initial double-blind was broken after 6 weeks of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 dropouts from each group in first 6 weeks; smoking status of all dropouts ascertained "at last contact". Early dropouts were excluded from later analyses

Hurt 1994

Methods	Country: USA Recruitment: community volunteers
Participants	240 adult smokers (> 20 cpd), motivated to quit 53% female, average age 43, average cpd 30

Hurt 1994 (*Continued*)

Interventions	1. Nicotine patch (22 mg/24 h, 8 weeks, no tapering) 2. Placebo patch Level of support: high (nurse counselling at 8 weekly visits, weekly phone calls to week 12)
Outcomes	Abstinence at 12 months (no puff since 9-month visit) Validation: CO ≤ 8 ppm
Notes	Study was supported by Lederle Laboratories, NY

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "subjects were randomly assigned to active or placebo patches"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind; no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "subjects with missing information or who dropped out... were considered to be smoking". Dropout rates and reasons fully reported

ICRF 1994

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

ICRF 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Low risk	Quote: "prior random allocation of study numbers to each intervention group and by sequential allocation of a study number to patients on entry"
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and nurses blinded to patches but not to support materials. Participants invited to guess assignment at end of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Disconfirmations and dropouts counted as smokers

Jamrozik 1984

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The codes were balanced to give equal numbers of patients receiving either the active gum ... or a placebo"

Jamrozik 1984 (*Continued*)

Allocation concealment (selection bias)	Low risk	Quote: "allocated to next available of ten alphabetical codes" from lists held in each practice
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatments were "identical in appearance and packaging". "No one doctor or member of staff was likely to see sufficient numbers of patients to be able to break the 10 code system"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up included as failures

Jarvis 1982

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "treated in groups of about ten, taken in order from the waiting list"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Therapists and subjects were blind to the allocation"

Jarvis 1982 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	One sparticipant lost to follow-up counted as a failure
Other bias	High risk	"Placebo" patch contained nicotine

Jensen 1991

Methods	Country: Denmark Recruitment: smoking cessation clinic
Participants	293 adult smokers (> 10 cpd) in relevant arms 54% female, average age 42, average cpd 21 to 22
Interventions	1. Nicotine gum (2 mg for 3 months) 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 week 4)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	12 month data reported in Jensen 1990, used from 2008 Sources of support not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "smokers were randomised to 24 smaller groups and each group was randomly allocated to treatment". No further information
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The study was not blind", because of restrictions on use of silver acetate gum
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21 trial-wide losses reported, but not included in the analyses. Distribution not stated, so not possible to include those lost to follow-up in the final denominator

Johns 2017

Methods	Country: India Recruitment: unclear
Participants	300 (200 to relevant arms) smokers prone to lung cancer (previous lung disease/family history of lung cancer/past cancer treatment/lowered immunity/previous smoking-related cancers/exposure to certain chemicals/radon gas) Other characteristics unknown
Interventions	1. NRT: patch, gum, inhalator, sublingual tablet or nasal spray for 6 weeks (no further detail provided) 2. No NRT Level of behavioural support: low (20 mins intervention, no further detail given)
Outcomes	PP (length NS) at 12 months Validation: CO < 10 ppm
Notes	New for 2017 update Conference abstract only so limited information available, hence only in primary analysis N quit extrapolated from percentages given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	No placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number followed up not reported

Jorenby 1999

Methods	Country: USA (4 sites) Recruitment: community volunteers
Participants	893 smokers, motivated to quit, (> 15 cpd) 52% female, average age 42 to 44, average cpd 25 to 28
Interventions	1. Nicotine patch (21 mg/24 h for 6 weeks, tapered for 2 weeks) and sustained release bupropion 300 mg for 9 weeks from 1 week before quit day 2. Bupropion 300 mg 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. 1 phone call 3 days after quit day
Outcomes	Abstinence at 12 months (primary outcome for study was PP abstinence; this analysis uses continuous abstinence since quit day) Validation: Expired CO < 10 ppm at each clinic visit
Notes	3 vs 4 in main analyses Study was funded by Glaxo Wellcome

Risk of bias

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

Joseph 1996

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

Joseph 1996 (*Continued*)

Notes	Study was funded by Hoechst Marion Roussel	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer-generated schedule" at the Minneapolis VAMC Co-ordinating Center
Allocation concealment (selection bias)	Unclear risk	Participants were randomly assigned in blocks of 10
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses and withdrawals fully reported, as primary and secondary endpoints

Killen 1984

Methods	Country: USA Recruitment: community volunteers	
Participants	64 adult smokers 72% female, average age 44, average cpd 32	
Interventions	1. Nicotine gum (2 mg) for 7 weeks 2. Skills training 3. Skills training plus nicotine gum Level of support: high (group therapy)	
Outcomes	Sustained abstinence at 10½ months Validation: CO	
Notes	1 + 3 vs 2 used in comparison. 3 vs 2 would increase effect Study was funded by the National Institute of Health, and supported by Merrell-Dow Pharmaceuticals Inc	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated

Killen 1984 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Participants "were blocked on sex and Fagerström score and assigned randomly to treatment group". "Therapists were assigned randomly to treatment conditions"
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding reported. "Interpretation of this data is hampered by the lack of a placebo control condition." Unclear if therapists aware of gum allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	11/75 recruited dropped out before full treatment, and are excluded from analyses

Killen 1990

Methods	Country: USA Recruitment: community volunteers who had abstained from smoking for 48 h
Participants	1218 adult smokers 52% female, average age 43, average cpd 25
Interventions	1. Nicotine gum (2 mg, 8 weeks) 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 12 months (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 12 months Study was funded by National Cancer Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly assigned"
Blinding (performance bias and detection bias)	Low risk	Quote: "Assignment to gum condition was double-blind"

Killen 1990 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 deaths removed from final analyses. Participants moving out of the area were removed from the analyses. Unconfirmed claims of abstinence counted as smokers

Killen 1997

Methods	Country: USA Recruitment: community volunteers
Participants	424 smokers ~50% female, average age ~45, average cpd ~23
Interventions	2 x 2 factorial design, comparison between video & self-help manuals and manuals alone collapsed 1. Nicotine patch (21 mg/24 h) for 8 weeks, 14 mg for 4 weeks, 7 mg for 4 weeks 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 12 months (7-day PP at 6 and 12 months) Validation: saliva cotinine < 20 ng/ml with the exception of participants living outside the area
Notes	There was evidence of an interaction between NRT and video/self-help conditions but this does not alter the MA so the conditions are combined from 2007. Both self-help conditions treated as low intensity - classifying video as high intensity would marginally reduce effect in high-intensity subgroup Study was funded by National Heart, Lung, and Blood Institute, and supported by Hoechst Marion Roussel Inc and Blue Shield Management

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Participants "were randomized to treatment conditions"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Assignment to the patch condition was double-blind"; participants invited to

Killen 1997 (*Continued*)

		guess assignment at 6 month follow-up
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants leaving the area (10) were excluded from analyses; all other unconfirmed claims of abstinence were counted as failures

Kornitzer 1995

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

Risk of bias

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

Kralikova 2009

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

Risk of bias

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

Leischow 1996a

Methods	Country: USA Recruitment: community volunteers
Participants	222 smokers (> 20 cpd). (2 excluded from analysis having received incorrect prescription) 55% female, average age 44, average cpd 26
Interventions	1. Nicotine Inhaler (10 mg). Advised to use 4 to 20 cartridges/day for 3 months. After this tapering was encouraged until 6 months 2. Placebo inhaler Participants received advice and watched a video showing proper use of the inhaler

Leischow 1996a (*Continued*)

	Level of support: high (brief individual smoking cessation support at each study visit, 10 in all)
Outcomes	Sustained abstinence at 12 months Validation: CO < 10 ppm at each follow-up
Notes	Study was funded by Pharmacia Upjohn, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "the randomization code was generated by computer"
Allocation concealment (selection bias)	Low risk	Quote: "subjects were sequentially and randomly assigned"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts reported at 12-month visit. Losses to follow-up counted as failures

Lerman 2015

Methods	Country: USA and Canada Recruitment: community (multicentre)
Participants	1246 (826 to relevant arms) smokers of at least 10 cpd for at least 6 months 44% female, average age 46, average cpd 18, mean FTND 5.3
Interventions	1. NRT patch, 11 weeks. 21 mg for 6 weeks, 14 mg for 2 weeks, 7 mg for 3 weeks 2. Placebo Level of support: high (1 h in-person pre-quit group behavioural counselling, brief (~15 minute) telephone counselling at weeks 0, 1, 4, 8)
Outcomes	7-day PP at 12 months Validation: CO < 8 ppm
Notes	New for 2017 update Funding: National Institute on Drug Abuse, National Cancer Institute, National Human Genome Research Institute, National Institute on General Medical Sciences, Abramson Cancer Center at the University of Pennsylvania, Commonwealth of Pennsylvania Department of Health, Canadian Institutes of Health Research, Canada Foundation for Innovation, Ontario Ministry of Research and Innovation. Pfizer Inc. provided varenicline and placebo pills at no cost

	N quit extrapolated from percentages given As combination of group and indiv. support, not included in support subgroup analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not specified Quote: "biostatistician, independent of study investigators, developed the randomisation procedure which was integrated into a centralised data management system. Subjects were randomised to the treatment arms in a 1:1:1 ratio. Randomisation was stratified by baseline NMR status and study site, and blocked in blocks of 12 patients (4/treatment block) to ensure approximate balance"
Allocation concealment (selection bias)	Low risk	Allocation was done by centralised data management system
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinding of researchers and participants "participants, study investigators, and personnel…were masked to treatment arm allocation and NMR status". Data were only unmasked following collection of all 6-month follow-up data
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 50% followed up by 12 months (280/418 I, 264/408 C)

Lewis 1998

Methods	Country: USA Recruitment: hospitalised patients willing to make a quit attempt
Participants	185 smokers (≥ 10 cpd), motivated to quit 46% female, average age 43 to 44, cpd 23 to 24
Interventions	1. Minimal intervention, 2 to 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 weeks 3. As 2. plus nicotine patch (22 mg/ 24 h for 3 weeks, tapered to 11 mg for 3 weeks) Level of support: low (since initial support was brief and further contacts in 2 were by phone
Outcomes	PP abstinence at 6 months Validation: CO ≤ 10 ppm

Lewis 1998 (*Continued*)

Notes	3 vs 1 + 2 used in MAs Study was funded by Elan Pharmaceutical Research Corporation

Risk of bias

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

Llivina 1988

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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated

Llivina 1988 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Quote: "asignados al azar"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "doble ciego"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and withdrawals reported (Tabla 2)

Malcolm 1980

Methods	Country: UK Recruitment: community volunteers
Participants	194 smokers 40% to 43% female, average age 44 to 46, average cpd 25 to 26
Interventions	1. Nicotine gum (2 mg) at least 10/day for at least 3 months 2. Placebo gum 3. Control Level of support: high (weekly individual counselling for 1 month)
Outcomes	Sustained abstinence at 6 months Validation: venous carboxyhaemoglobin $\leq$ 1.6%
Notes	Study was supported by AB Leo & Company, Helsinborg, Sweden

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Quote: "randomly allocated"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "The trial was double blind between the gum groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only the 1-month quitters were followed up at 6 months (77/82 participants)
Other bias	Unclear risk	16 participants with dentures who could not chew gum were allocated to Controls but analysed separately

McGovern 1992

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

Risk of bias

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

Molyneux 2003

Methods	Country: UK Recruitment: hospital
Participants	274 smokers (182 in relevant arms) admitted to medical and surgical wards, smoked in last 28 days 60% male, average age 60, median cpd 17, 81% had previous quit attempt
Interventions	1. Choice of NRT products (15 mg 16-h patch/2 mg or 4 mg gum, 10 mg inhalator/2 mg sublingual tablet, 0.5 mg spray), Brief (20 min) bedside counselling from a research doctor or nurse 2. Brief counselling only 3. Usual care, no smoking advice (not used in MA) Level of support: low

Molyneux 2003 (*Continued*)

Outcomes	Continuous abstinence at 12 months Validation: CO < 10 ppm
Notes	No placebo. 63% chose patch, 13% inhalator, 11% gum, 8% tablets and 1% nasal spray, 4% declined use Study was supported by Pharmacia Consumer Healthcare, Sweden

Risk of bias

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

Moolchan 2005

Methods	Country: USA Recruitment: community volunteers
Participants	120 adolescent (age 13 to 17) smokers (≥ 10 cpd), motivated to quit 70% female, average age 15, average cpd 19
Interventions	1. Nicotine patch (21 mg, or 14 mg for < 20 cpd) for 6 weeks + placebo gum 2. Nicotine gum (4 mg, or 2 mg for < 24 cpd) for 6 weeks + placebo patch 3. Double placebo Level of support: high (11 x 45-min individual counselling over 12 weeks)
Outcomes	PP abstinence at 6 months Validation: CO and cotinine
Notes	Placebo group contributes twice to MA - too small to affect total Sustained abstinence at 3 and 6 months could be derived from text, relative effect greater

Moolchan 2005 (*Continued*)

	since no quitters on placebo Study was funded by National Institute on Drug Abuse, and supported by GlaxoSmithKline

Risk of bias

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

Mori 1992

Methods	Country: Japan Recruitment: hospital
Participants	364 smokers with smoking-related illness. Number of cpd not stated. Motivation to quit probably not required
Interventions	1. Nicotine gum 2 mg for 3 months 2. Placebo gum Level of support: low
Outcomes	Abstinence (not defined) at 6 months Validation: serum thiocyanate
Notes	"Supported partially by FISss 90/0431 and SEPAR". Trial report was abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Mori 1992 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated

Nakamura 1990

Methods	Country: Japan Recruitment: community volunteers
Participants	60 adult smokers. Average cpd 31
Interventions	1. Nicotine gum (2 mg, 2 months or longer) 2. Non-placebo control group received counselling Level of support: high
Outcomes	Sustained abstinence at 6 months Validation: CO
Notes	Study was supported by Merrell-Dow Pharmaceuticals

Risk of bias

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

NCT00534404

Methods	Country: USA Recruitment: not specified
Participants	2485 (1658 in relevant arms) smokers of at least 10 cpd
Interventions	1. NRT patch, 8 weeks. 21 mg for 4 weeks, 14 mg for 2 weeks, 7 mg for 2 weeks 2. No NRT Level of support: low (internet assisted tobacco treatment)
Outcomes	6 months prolonged abstinence at 9 months Validation: none
Notes	New for 2017 update Funding: not specified Data from clinical trials registry so limited information available, for this reason not included in setting subgroup

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Not specified but as not placebo-controlled presumably unblinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 50% participants followed up (687/830 I, 586/828 C)

Nebot 1992

Methods	Country: Spain Recruitment: primary care
Participants	425 unselected smokers. 60% to 70% smoking > 15 cpd
Interventions	A. Brief counselling from physician B. Physician counselling plus nicotine gum C. Health education from nurse Level of support: low
Outcomes	PP abstinence at 12 months Validation: CO

Nebot 1992 (*Continued*)

Notes	Study was supported by the Fondo de Investigaciones Sanitarias de la Seguridad Social

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not applicable; "each PCT was randomly allocated to perform the three different interventions successively". No information about avoidance of selection bias
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not applicable
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Only those quit at 2 months were followed up at 12 months. All non-responders were included as failures
Other bias	Unclear risk	Unequal assignments to the 3 groups, with nurse and NRT groups outnumbered 1:2 by the medical advice group

Niaura 1994

Methods	Country: USA Recruitment: outpatient settings and physician referrals (primary care subgroup)
Participants	77 low-dependence (FTND $\leq$ 6) and 96 high-dependence smokers 50% female, average age 42, average cpd 29, FTND 4.7 for low dependence, 8.0 for high dependence
Interventions	1. Nicotine gum 2 mg, ad lib for up to 4 months (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 12 months 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 point estimate would be higher if inclusion restricted to the high-dependence group Study was supported by National Cancer Institute and National Heart, Lung, and Blood Institute

Niaura 1994 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants stratified on level of nicotine dependence. "Within each of the high- and low-dependence groups, subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	No placebo - not relevant. But therapist and participant were blinded to FTQ score (level of dependency), and to match or mismatch status for gum use
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates fully reported

Niaura 1999

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Niaura 1999 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Counselors were kept blind to the relapse prevention condition to which subjects were assigned". Participants not blinded, and no placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported

Ockene 1991

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

Risk of bias

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

Ockene 1991 (*Continued*)

		staff)

Oncken 2007

Methods	Country: USA Recruitment: community volunteers
Participants	152 post-menopausal women (≥ 10 cpd) Average cpd 22, average age 54/56.6
Interventions	1. Nicotine patch (21 mg for 13 weeks including 4 weeks tapering) 2. Placebo patch Level of support: high (7 visits including 4 x 2-h group counselling, 1 pre-TQD)
Outcomes	PP abstinence at 16 months (12 months post-EOT) Validation: CO < 8 ppm
Notes	Study was supported by The Patrick and Catherine Weldon Donaghue Foundation, The University of Connecticut Center on Aging, University of Connecticut General Clinical Research Center and the National Institute for Health. Pharmaceuticals supplied by GlaxoSmithKline

Risk of bias

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

Oncken 2008

Methods	Country: USA Recruitment: volunteers from antenatal clinics
Participants	194 pregnant women smoking at least 1 cpd Average age 25, average cpd 10 in week before study enrolment, average cpd 18 prepregnancy, mean FTND < 4

Oncken 2008 (*Continued*)

Interventions	1. 2 mg nicotine gum (first 6 weeks: instructed to chew 1 piece for every cigarette usually smoked per day, not exceeding 20, followed by 6-week tapering period) 2. Placebo gum, dosing and duration as above Level of support: high. In-person and telephone individual smoking cessation counselling
Outcomes	Abstinence at 32 to 34 weeks of gestation and 7-day PP at 6 to12 weeks post-partum (abstinence at 6 weeks post-quit date also reported) Validation: CO and urinary cotinine
Notes	Varying lengths of follow-up. Longest follow-up used in primary analysis NRT group had significantly higher birth weight and gestational age than placebo group. NRT group significantly more likely to attend follow-up visits Funded by the National Institutes of Health.

Risk of bias

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

Ortega 2011

Methods	Country: Spain Recruitment: hospital inpatients
Participants	1843 hospital inpatients who identified as smokers 88% male, average age 62, average 56 packs/year
Interventions	1. Nicotine patch or gum (max 12 weeks; participant's choice) + CBT 2. CBT only 3. Declined to participate Level of support: high (standardized 30- to 45-min sessions every 3 days until participant discharged from hospital; post-discharge participant could have telephone or in-person

Ortega 2011 (*Continued*)

	sessions at 1 week, 15 days, 2, 3, 6, and 12 months)
Outcomes	Continuous abstinence from quit day at 12 months Validation: 34% of participants verified with CO measurement
Notes	No placebo. Groups 1 and 2 included in primary analysis under 'choice of NRT'. "No significant outcome differences between NRT types" (personal communication from author) 717 declined to participate but followed up at 12 months Funding not reported

Risk of bias

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

Otero 2006

Methods	Country: Brazil Recruitment: community volunteers
Participants	1199 smokers (includes 254 non-attenders), motivated to quit 63% female, average age 42, 46% smoked > 20 cpd
Interventions	Factorial design with multiple levels of behavioural support 1. Nicotine patch (21 mg, 14 mg for FTND < 5) 8 weeks including tapering + behavioural support 2. Cognitive behavioural support only Level of support: Mixed - low = single 20-min session. High = 1, 2, 3 or 4 weekly 1-h sessions. Maintenance or recycling sessions provided at 3, 6, 12 months

Otero 2006 (*Continued*)

Outcomes	PP abstinence at 12 months Validation: none
Notes	Contributes to both high- and low-support subgroups No placebo Study was supported by the Institute for Global Tobacco Control and the Fogarty International Center of the National Institutes of Health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated. Randomization was stratified by age and sex by an independent specialist
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	29% of control group participants asked for nicotine patch after the 3-month follow-up which might have increased control group quit rates at 12 months
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated

Page 1986

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

Risk of bias

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

Paoletti 1996

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

Risk of bias

Bias	Authors' judgement	Support for judgement

Paoletti 1996 (*Continued*)

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

Perng 1998

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

Risk of bias

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

Piper 2009

Methods	Country: USA Participants: community volunteers
Participants	1504 smokers motivated to quit 58% female, average age 45, average cpd 21.4
Interventions	1. Nicotine lozenge 2 or 4 mg for 12 weeks (based on dose-for-dependence level as in instructions) 2. Nicotine patch (24 h, 21, 14, and 7 mg titrated down over 8 week period post-quit) 3. Bupropion SR (150 mg bid, 1 week pre-quit, 8 weeks post-quit) 4. Lozenge + patch (duration and dosage as above) 5. Bupropion + lozenge (duration and dosage as above) 6. Placebo (5 groups matched to above 5 interventions) Level of support: high. All participants received 7 one-to-one 10- to 20-min counselling sessions
Outcomes	7-day PP abstinence at 6 months; initial cessation Validation: CO < 10 ppm
Notes	Placebo outcomes not reported by subgroup; outcomes generated by applying overall percentage of events in placebo group to individual subgroups. 1, 2, 4 and 6 included in primary analysis Analyses conducted using ITT Most of the funding from National Institute on Drug Abuse and National Center for Research Resources. Medication provided to participants at no extra cost by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was double-blind and used a block randomization scheme with sex and self-reported race as the blocking variables."
Allocation concealment (selection bias)	Low risk	Quote: "Staff did not know to which type (s) of medication a participant would be assigned until the moment of randomization, and study staff were blinded to whether the medication was active or placebo."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double blind." "Study staff were blinded to whether the medication was active or placebo". Type of medication (i.e. patch, gum, pill) would have been apparent to both groups

Piper 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	90 dropouts (out of 1504). Analyses conducted using ITT. Individuals with missing data considered to be smoking

Pirie 1992

Methods	Country: USA Recruitment: community volunteers
Participants	417 women smokers, average cpd 25 to 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: 2 mg ad lib Level of support: high
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	3 and 4 compared to 1 and 2 Study was funded by the National Cancer Institute

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomized to one of four groups"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No placebo. No detail reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up. Moved away completed assessments by phone or mail

Pollak 2007

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

Risk of bias

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

Prapavessis 2007

Methods	Country: New Zealand Recruitment: community volunteers
Participants	121 women smokers (> 10 cpd) (excludes dropouts not starting programme)
Interventions	NRT as adjunct to either CBT or exercise programmes, collapsed for this review 1. Nicotine patch (21 mg/24 h for 10 weeks, no weaning) 2. No patch Level of support: high (36 x 45-min session over 12 weeks of group CBT or supervised vigorous exercise, starting 6 weeks before TQD)
Outcomes	Continuous abstinence since TQD at 12 months from end of programme Validation: CO < 10 ppm, cotinine < 10 ng/mL
Notes	No placebo Study was funded by the National Heart Foundation of New Zealand, and supported by GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Using a computer-generated program, participants were then randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Analyses were conducted by intent to treat". Missing data on smoking abstinence were counted as failures. % losses reported

Puska 1979

Methods	Country: Finland Recruitment: community volunteers
Participants	229 adult smokers, 80% smoking > 5 cpd
Interventions	1. Nicotine gum (4 mg) for 3 weeks 2. Placebo gum for 3 weeks Level of support: high (group therapy)

Puska 1979 (*Continued*)

Outcomes	PP abstinence at 6 months Validation: none	
Notes	Study was supported by AB Leo and Co, Helsinborg, Sweden	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Neither the subjects nor the course leaders were aware who received active and who placebo gum"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up were reported, but were not included in the analyses

Richmond 1993

Methods	Country: Australia Recruitment: primary care	
Participants	450 adult smokers (350 in included arms) Average cpd 15 to 21	
Interventions	1. Smokescreen programme plus nicotine gum, dose and duration not stated 2. Smokescreen programme alone 3. Brief advice and gum (not included in MA) Level of support: high (5 visits during first 3 months)	
Outcomes	Continuous abstinence (from week 1) at 12 months Validation: expired CO < 14 ppm	
Notes	No placebo Continuous abstinence rates from Richmond 1993 paper used from 2007. Group 3 not included Study was funded by the Department of Health, Housing and Community Services, Community Health Anti-Tuberculosis Association, Glaxo Australia, and the Drug and Alcohol Directorate, NSW Department of Health	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Richmond 1993 (*Continued*)

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

Richmond 1994

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Treatment and control patches were arranged in random order by Marion Merrell Dow, Sydney, then issued sequentially to patients as they attended"; married couples were assigned to same condition
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind

Richmond 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up included as failures. Dropout rates fully reported

Roto 1987

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts classified as smokers

Russell 1983

Methods	Country: UK Recruitment: primary care - consecutive attenders admitting to being cigarette smokers and consenting to participate at 6 general practices
Participants	2106 unselected adult smokers average cpd 17.5

Russell 1983 (*Continued*)

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 months and 12 months 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 point estimate Only 53% of group 3 tried the gum Use of quit rates adjusted for estimated validation failure and protocol violation would increase relative effect of gum Study was funded by the Medical Research Council, and the AB Leo Research Foundation, Sweden

Risk of bias

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

Sachs 1993

Methods	Country: USA Recruitment: community volunteers
Participants	220 adult smokers average cpd 28 to 29
Interventions	1. Nicotine patch (15 mg/16 h, 12 weeks + 6 weeks tapering) 2. Placebo patch Level of support: high (physician advice, 8 visits during treatment period)

Sachs 1993 (*Continued*)

Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	Study was funded by National Institute on Drug Abuse, Kabi Pharmacia AB and Parke-Davis

Risk of bias

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

Scherphof 2014

Methods	Country: Netherlands Recruitment: schools
Participants	265 adolescents (12 to 18 years old), smoking ≥ 7 cpd, motivated to quit 52.9% female, mean age 16.5, mean cpd 16.7
Interventions	1. 24-h patch, dose and length depending on baseline cpd. If > 20 cpd, 3 weeks 21 mg/day, 3 weeks 14 mg/day; 3 weeks 7 mg/day; if < 20 cpd, 3 weeks 14 mg/day, 3 weeks 7 mg/day 2. Control: placebo patch control, otherwise identical to intervention Level of support: low (one-off "short behavioral intervention aimed at quitting smoking (e.g. preparations and expectations)" at study start)
Outcomes	30-day PP abstinence at 12 months Verification: salivary cotinine measured using a NicAlert saliva strip (Nymox)
Notes	New for 2017 update Funding: ZonMw - The Netherlands Organization for Health Research and Development; Novartis provided study medication and placebo Risk of bias and some data extraction from Fanshawe 2017

Risk of bias

Scherphof 2014 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomized according to a computer-generated randomization list by the pharmacy of the University Medical Centre to either (1) active study medication (nicotine patch) or (2) an identically appearing placebo (placebo patch)."
Allocation concealment (selection bias)	Unclear risk	Quote: "participants and research assistants were blind to treatment allocation"; however, does not specify how this occurred
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo-controlled, but no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up not reported by trial arm, but 10.1% overall at 12 months

Schneider 1983a

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

Risk of bias

Bias	Authors' judgement	Support for judgement

Schneider 1983a (*Continued*)

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

Schneider 1983b

Methods	Country: USA Recruitment: community volunteers
Participants	36 heavy smokers (> 1 pack/day) no demographic details
Interventions	Study B (pilot dispensary study): 1. Nicotine gum, (2 mg, duration not stated) 2. Placebo gum Level of support: low (weekly laboratory visits for 5 weeks but no support provided)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	Reported in same papers as Schneider 1983a. Shared study ID until 2008 Study was funded by National Institute on Drug Abuse and by the Medical Research Service of the Veterans Administration

Risk of bias

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

Schneider 1995

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

Risk of bias

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

Schneider 1996

Methods	Country: USA Recruitment: community volunteers
Participants	223 adult smokers (≥10 cpd) 37% female, average age 44, average cpd 29/26 (significantly higher in active group)
Interventions	1. Nicotine inhaler (4 to 20 inhalers per day) for up to 6 months, with weaning from 3 months 2. Placebo inhaler Level of support: high (repeated clinic visits for assessment)
Outcomes	Sustained abstinence at 12 months Validation: CO and salivary cotinine

Schneider 1996 (*Continued*)

Notes	Study was funded by Veteran Affairs and by Pharmacia & Upjohn (Sweden)

Risk of bias

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

Schnoll 2010

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

Segnan 1991

Methods	Country: Italy Recruitment: primary care - consecutive patients attending 44 general practices
Participants	923 practice attenders aged 20 to 60 average cpd not stated Therapists: GPs who had undergone a 3-h training session
Interventions	1. Advice and leaflet 2. Repeated counselling (follow-up at 1, 3, 6, 9 months) 3. Repeated counselling plus prescription for nicotine gum unless contraindicated, dose not stated, up to 3 months

Segnan 1991 (*Continued*)

	4. Repeated counselling plus spirometry Level of support: high
Outcomes	Sustained abstinence at 12 months Validation: urinary cotinine
Notes	3 vs 1 + 2 + 4. Study was supported by SIMG (Italian Association of General Practice), and by Serono SPA

Risk of bias

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

Shiffman 2002 (2 mg)

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

Shiffman 2002 (2 mg) (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "smokers were randomized" after stratification for dependency by time to first cigarette of the day
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only abstainers were followed up. "Participants who did not appear for a visit were counted as treatment failures". Losses fully reported

Shiffman 2002 (4 mg)

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

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See above (Shiffman 2002 (2 mg))
Allocation concealment (selection bias)	Unclear risk	See above

Shiffman 2002 (4 mg) (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See above

Shiffman 2009 (2 mg)

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "using a 1:1 computer-generated randomization scheme, balanced across study sites and generated separately for the 2- and 4-mg groups"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double-blind", method not specified

Shiffman 2009 (2 mg) (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Those who had not succeeded at 28 days follow-up not followed up at 6 months. All missing data considered to be smoking

Shiffman 2009 (4 mg)

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

Risk of bias

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

Stapleton 1995

Methods	Country: UK Setting: primary care
Participants	1200 smokers considered by GP to be highly dependent and motivated to give up average cpd 23 to 24
Interventions	1. Nicotine patch standard dose (15 mg/16 h for 18 weeks) 2. Nicotine patch with dose increase to 25 mg at 1 week if required 3. Placebo patch group The nicotine patch groups were further randomized to gradual tapering or abrupt withdrawal at week 12 Level of support: high (physician advice and brief support at 1, 3, 6, 12 weeks)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	The dose increase after 1 week did not affect cessation, 1 + 2 vs 3 in comparison 1 Study was funded by Kabi Pharmacia (Sweden)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "a computer generated list, complied in blocks of six (four active, two placebo)"
Allocation concealment (selection bias)	Low risk	Numbered packages
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Both subjects and their doctors or nurses were blind to whether the dose increase was real or placebo". Study conduct throughout was monitored by clinical research associates of the pharmaceutical company
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analyses, with losses/failures included as smokers. Number of dropouts not specified

Stein 2013

Methods	Country: USA Recruitment: methadone-maintained treatment centres in New England
Participants	315 adult methadone-maintained smokers, smoking 10+ cpd, willing to set a quit date within the 1st week Mean age 39.9, 47.6% female, 78.5% white, mean cpd 20, mean FTND 5.7

Stein 2013 (*Continued*)

Interventions	1. Combination NRT: 24-week course of NRT patch (42 mg for > 30 cpd, 21 mg if < 30 cpd), + ad lib nicotine gum (4 mg) as needed 2. Varenicline: 24-week course of varenicline tablets, 1st week titrated 3. Placebo: 24-week course of identical tablets and regimen Level of support: high (all received standardized 15-min session of advice to quit (5As model) and made monthly visits for support and top-up medication)
Outcomes	7-day PP at 6 months (continuous abstinence also reported from 2 weeks to 6 months but unclear if this was biochemically verified) Validation: CO < 8 ppm; urinary cotinine in varenicline and placebo participants claiming abstinence
Notes	New for 2017 update. Analysis uses only 1 v 3 Funding: NCI grant RO1 CA129226; MDS supported by a NIDA mid-career investigator award K24 DA000512 Risk of bias and some data extraction from Cahill 2016

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Quote: Participants were randomized to treatment after completing the baseline assessment". No further information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"; research assistants were "blind to participant group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	26/133 NRT and 10/45 placebo lost to follow-up

Sutherland 1992

Methods	Country: UK Recruitment: smoking cessation clinic
Participants	227 smokers, motivated to quit. Average cpd 25 to 27
Interventions	1. Nicotine nasal spray, maximum 40 mg/day 2. Placebo spray Level of support: High (4 weeks group support)
Outcomes	Sustained abstinence at 12 months Validation: CO

Sutherland 1992 (*Continued*)

Notes	Follow-up beyond 1 year reported in Stapleton 1998 Study was funded by the Medical Research Council and by the Imperial Cancer Research Fund

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They drew a card marked A or P for allocation to active or placebo group"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Subjects and therapists were blind to spray assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up briefly reported

Sønderskov 1997

Methods	Country: Denmark Recruitment: customers seeking to buy nicotine patches OTC at 42 pharmacies
Participants	522 smokers of > 10 cpd. Smokers of > 20 cpd used a higher-dose patch than lower-rate smokers 50% female, average age 39
Interventions	1. Nicotine patch (24 h). > 20/day smokers used 21 mg for 4 weeks, 14 mg for 4 weeks, 7 mg for 4 weeks. Smokers of < 20/day used 14 mg for first 8 weeks, 7 mg for 4 weeks 2. Placebo patches Level of support: Low (brief instructions on patch use at baseline, visit to collect further patches at 4 and 8 weeks, no behavioural support)
Outcomes	Abstinence at 6 months - no reported smoking in the last 4 weeks, by telephone interview with neutral independent assessor Validation: none
Notes	Study was partly funded by Ciba-Geigy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized sequential treatment packages", stratified by smoking level

Sønderskov 1997 (*Continued*)

Allocation concealment (selection bias)	Low risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo patches contained "a pharmacologically negligible amount of nicotine". "The blinding procedure was not broken until all the main results were tabulated"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Participants lost to follow-up (n = 19) were classified as smokers". Losses and reasons fully reported

TNSG 1991

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

Risk of bias

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

TNSG 1991 (*Continued*)

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

Tuisku 2016

Methods	Country: Finland Recruitment: community
Participants	180 (in relevant arms) 18 to 26 years old, smoked daily for at least past month, smoked > 100 cigarettes in life, light smokers (as per Heaviness of Smoking Index based on cpd and time to first cigarette) only included in this review 52% female, median age 21, median cpd 10
Interventions	1. NRT patch (10 mg/16 h) for 8 weeks 2. Placebo Level of support: high (individual smoking cessation counselling of 30 mins (and planned for week 52))
Outcomes	7-day PP at 6 months (Methods section also states 12 months follow-up but results not reported) Validation: none
Notes	New for 2017 update Funding: Ministry of Social Affairs and Health, Finland; Finnish Research Foundation of the Pulmonary Disease; Finnish Medical Society Duodecim Participants were assessed as light or heavy smokers. Light smokers were randomized to placebo or 10 mg NRT patches. Heavy smokers were randomized to varenicline or 15 mg NRT patches. First comparison is eligible for inclusion in this review (NRT vs no NRT). Second comparison is not (NRT vs varenicline). Cannot combine NRT 15 mg group with 10 mg group - different populations randomized

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After assessment… at the baseline visit, simple randomisation with a computer-generated random list… was used to allocate study subjects into the different treatment groups"
Allocation concealment (selection bias)	Unclear risk	Not specified

Tuisku 2016 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "The placebo patch was not identical to the nicotine patch" "the study was not conducted in a blinded manner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts: 22/86 for placebo, 18/94 for NRT
Other bias	High risk	12-month cessation measured but not reported

Tønnesen 1988

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants stratified by dependence, then "subjects on each list were then randomly assigned to treatment in blocks of two"
Allocation concealment (selection bias)	Unclear risk	Not stated

Tønnesen 1988 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Gum was packaged and produced to be indistinguishable between 2 mg, 4 mg and placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who attended 1st counselling session were included in analyses, regardless of attendance or level of gum use. Only 2/173 were lost to follow-up

Tønnesen 1991

Methods	Country: Denmark Recruitment: community volunteers
Participants	289 smokers (≥ 10 cpd) 70% female, average age 45, average cpd 22
Interventions	1. Nicotine patch (15 mg/16 h for 12 weeks with tapering) 2. Placebo patch Level of support: high (7 clinic visits including a few minutes of advice)
Outcomes	Sustained abstinence at 12 months (also reported 24 months in Tønnesen 1992, 3 years in Mikkelsen 1994) Validation: CO
Notes	Classification of support corrected to high in 2008 update Study was supported in part by Kabi Pharmacia Therapeutics

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "subjects were sequentially and randomly assigned to either active treatment or placebo according to a computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	Quote: "Patches were packaged and labeled with consecutive numbers"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebo patches were identical to the active patches in appearance, packaging and labeling, but contained no nicotine" Blinding code was broken after week 26

Tønnesen 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	All who attended the 1st session were included in the analyses. Losses to follow-up were included as smokers

Tønnesen 1993

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The randomization code for assignment to either active or placebo inhaler was generated by a computer program"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The placebo inhaler contained only the additive and was identical in appearance to the active inhaler". Participants were asked at 12 months to guess their assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Subjects unavailable for follow-up were assumed to be smokers". Relapsers were dropped from the study, but were all contacted at 1 year. 6 were lost to follow-up and 7 excluded for protocol violations

Tønnesen 2000

Methods	Country: Denmark Recruitment: referrals to lung clinic
Participants	446 smokers ≥ 10 cpd 52% female, average age 49, average cpd 18
Interventions	1. 5 mg nicotine patch (placebo) 2. 15 mg (16 h) nicotine patch for 12 weeks (up to 9 months on request) 3. Nicotine inhaler (4 to 12/day ad lib) 4. Combination, 15 mg patch and inhaler Level of support: high (Physician advice at baseline, brief (15 minute) nurse counselling at 2, 6 weeks, 3, 6, 9, 12 months)
Outcomes	Sustained abstinence at 12 months, (from week 2, paper also reports PP and with-slips rates) Validation: CO < 10 ppm at all visits
Notes	In main comparison for patch vs placebo but not inhaler Study funding and support not reported

Risk of bias

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

Tønnesen 2006

Methods	Country: Denmark Recruitment: lung clinic patients and newspaper adverts
Participants	370 smokers (at least 1 cpd) with COPD (Mean FEV1 was 56% of predicted) 52% female, average age 61, average cpd 20 (8% < 7/day), 71% had previously tried NRT
Interventions	2 x 2 factorial trial of lozenge and behavioural support 1. Nicotine sublingual tablet (2 mg), recommended dose depended on baseline cpd, from min 3 to max 40 per day 2. Placebo

Tønnesen 2006 (*Continued*)

	Level of support: high: Either 4 clinic visits (0, 2 weeks, 6, 12 months) and 6 phone calls, total time 2½ h, or 7 visits (0, 2, 4, 8, 12 weeks) and 5 calls, total 4½ h
Outcomes	Sustained abstinence at 12 months (from 2 weeks) Validation: CO < 10 ppm at all visits
Notes	New for 2008 update Behavioural support arms collapsed. Both involved multiple clinic visits Study was funded by the Danish Medical Research Council, and supported by Pfizer Consumer Healthcare (Sweden)

Risk of bias

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

Tønnesen 2012

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

Tønnesen 2012 (*Continued*)

Notes	Funded by McNeil AB, Sweden Setting: smoking cessation clinics

Risk of bias

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

Villa 1999

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

Villa 1999 (*Continued*)

Notes	No placebo	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Los participantes fueron distribuidos aleatoriamente"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated

Wallstrom 2000

Methods	Country: Sweden Recruitment: community volunteers	
Participants	247 smokers (≥ 10 cpd), motivated to quit 59% female, average age 45, average cpd 1 to 20	
Interventions	1. Nicotine sublingual tablet, 2 mg. Recommended dosage 1/h for smokers with FTND < 7, 2/h for scores ≥ 7. After 3 months treatment, tapering period of 3 months if necessary 2. Placebo tablet Level of support: high (brief 5-mins counselling at study visits (0, 1, 2, 3, 6 weeks, 3, 6 months)	
Outcomes	Sustained abstinence at 12 months (from week 2, paper also reports with-slips rates) Validation: CO < 10 ppm	
Notes	Study was supported by Pharmacia & Upjohn Consumer Health Care	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomized... using a computer program"
Allocation concealment (selection bias)	Unclear risk	Not stated

Wallstrom 2000 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All medication was dispensed by staff who were not involved in treating the subjects"; placebo tablets identical, but without nicotine and with capsaicin
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Analyses were based on ITT. Losses not reported in detail

Ward 2013

Methods	Country: Syria Recruitment: primary care centres (3 clinics were operated by NGOs for low-middle income patients, 4th clinic is private)
Participants	269 smokers (≥ 5 cpd, > 1 year) 22% female, average age 40, average cpd 28, mean FTND 5.8
Interventions	1. Nicotine patch, 24 h for 6 weeks. Participants who smoked ≥ 10 cpd given 2 weeks at 21 mg, 2 weeks 14 mg, 2 weeks 7 mg. Participants who smoked 5 to 9 cpd given 4 weeks 14 mg, 2 weeks 7 mg 2. Placebo on same schedule Level of support: high (3 x 30 mins individual face-to-face counselling plus 5 x 10-min phone calls, from 4 days prior to TQD to 45 days post-TQD)
Outcomes	Prolonged abstinence at 12 months Validation: CO < 10 ppm
Notes	New for 2017 update N quit extrapolated from percentages given Funding: "This work was supported by PHS grant 1R01DA024876"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not specified: "random permuted blocks stratified according to clinic and patient gender"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation assignments were contained in opaque, sequentially-numbered envelopes and were maintained in the biostatistics unit of the SCTS, a facility geographically separated from the clinics. A statistician, not otherwise involved in the trial, made each allocation after receiving a request from a cessation coordinator,

Ward 2013 (*Continued*)

		prepared the treatment package, including patches, and had it delivered to the clinic. Patients, interventionists and data collectors were blind to allocation"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Patients, interventionists and data collectors were blind to allocation" placebo-controlled: "62% of those on NRT correctly guessed treatment group, compared to 40% on placebo". However, no effect detected so judged as low risk of bias for this domain
Incomplete outcome data (attrition bias) All outcomes	Low risk	85% I and 79% C follow-up at 12 months

Wennike 2003b

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

Westman 1993

Methods	Country: USA Recruitment: community volunteers
Participants	158 smokers motivated to quit (excludes 1 participant who used nicotine gum throughout) 57% female, average age 41, average cpd 30
Interventions	1. Nicotine patch (25 mg/24 h, 6 weeks 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 6 months (from 2 weeks post-TQD) Validation: CO < 8 ppm
Notes	Study was supported by TBS Laboratories, Piscataway, NJ
Risk of bias	

Westman 1993 (*Continued*)

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

Wisborg 2000

Methods	Country: Denmark Recruitment: volunteers, antenatal clinic
Participants	250 pregnant women who continued to smoke after 1st trimester Average age 28, average cpd 14; 43% primiparous
Interventions	1. Nicotine patch (15 mg/16 h, tapering to 10 mg, 11 weeks total) 2. Placebo patch Level of support: high. 4 x 15- to 20-min sessions of midwife counselling at 0, 4,11 weeks from enrolment, and 4 weeks before expected delivery
Outcomes	Abstinence at 4 weeks prior to delivery and at 1 year post-partum (telephone interview) . (Rates at 3 months post-partum also reported) Validation: Cotinine < 26 ng/ml at 4 weeks pre-delivery visit only
Notes	First long-term study of nicotine patch in pregnancy. Compliance with patch use was low. Only 17% of active and 8% of placebo used all patches. Data used in Analysis 5.1 from 2012 is abstinence at 4th prenatal visit rather than continuous abstinence from 2nd to 4th prenatal visit, for consistency with Coleman 2015. The effect estimate is not altered Study was funded by the Danish Cancer Society and the Department of Health, and supported by Pharmacia & Upjohn

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization. Quote: "Pharmacia & Upjohn ... generated the randomization

Wisborg 2000 (*Continued*)

		list, supplied the patches with randomization numbers, and kept the code between patch number and the specific treatment until data collection was finished"
Allocation concealment (selection bias)	Low risk	Quote: "Women ... were assigned consecutive numbers on the randomization list"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Treatment status was not known by the women or the midwife throughout the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data reported, and included as smokers. Analyses were ITT

Wittchen 2011

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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Generated by the study center"; used to put 4 different coloured questionnaires in random order

Wittchen 2011 (*Continued*)

Allocation concealment (selection bias)	High risk	No concealment Quote: "questionnaires were distributed consecutively to all attending patients on the target days by nurses. Thus, the assignment of patients was entirely dependent on the consecutive attendance of patients and the random assignment of a color. Doctors were not allowed to interfere with this study procedure." But numbers allocated to groups very uneven and discussion states: "Random checks of this procedure [randomization] and quality assurance tests by study monitors revealed that in some cases in the latter part of the study treatment was based on patient and physician preferences. "
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor providers were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of dropouts between groups; participants lost to follow-up considered smokers for MA

Zelman 1992

Methods	Country: USA Recruitment: community volunteers
Participants	116 smokers (excludes 10 early treatment dropouts evenly distributed across conditions) 54% female, average age 29 to 35, average cpd 25 to 27
Interventions	1. Rapid smoking + support counselling 2. Rapid smoking + skills training 3. Nicotine gum 2 mg, average 10 pieces/day, duration not stated + skills training 4. Nicotine gum + support counselling Level of support: high (6 x 60- to 75-min group sessions over 2 weeks, starting on quit day)
Outcomes	Sustained abstinence at 12 months (not more than 2 consecutive days of smoking) Validation: Independent observer report
Notes	No placebo. Group support variants collapsed; 3 and 4 compared to 1 and 2 Study was funded by National Institutes of Health
Risk of bias	

Zelman 1992 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "subjects were randomly assigned"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Placebos not used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Early dropout rates reported, but not included in the analyses. 4 12-month dropouts included as smokers

AE = adverse event; ALA = American Lung Association; C = control; CBT = cognitive behavioural therapy; CO = carbon monoxide in exhaled air; cpd = cigarettes per day; COPD = chronic obstructive pulmonary disease; EOT = end of treatment; FTND = Fagerström Test for Nicotine Dependence; FTQ = Fagerström Tolerance Questionnaire; I = intervention; ITT = intention to treat; MA = meta-analysis; RTQ = reduce-to-quit; OTC = over-the-counter; PP = point prevalence; SC = smoking cessation; TQD = target quit date

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

Study	Reason for exclusion
Adelman 2009	Study of nicotine nasal spray in adolescents. 12 weeks follow-up
Allen 2005	Short-term study of effect of nicotine patch on weight change during early abstinence
Allen 2011	Trial of NRT for reduction of agitation and aggression in smokers with schizophrenia
Aubin 2006	Short-term study of the effect of different types of nicotine patch on sleep and smoking urges
Batra 2005	Trial of nicotine gum for smoking reduction in people not making a quit attempt. See Cochrane Review of harm reduction interventions, Lindson-Hawley 2016
Berlin 2011	Trial of standard NRT dosing vs dose adaptation according to salivary cotinine
Bock 2010	Trial of computer software quit programme, treatment group offered free NRT. Control group could also use NRT (unsubsidized)
Bolliger 2000a	Trial of nicotine inhaler for smoking reduction in people not making a quit attempt. See Cochrane Review of harm reduction interventions, Lindson-Hawley 2016
Bolliger 2007	Pilot study, not powered to detect efficacy differences between gum, inhaler and mouth spray

(*Continued*)

Brantmark 1973a	Double-blind gum/placebo only for 1st week of clinic, then both groups offered active gum during 6-month follow-up period
Caldwell 2016	All arms received pharmacotherapy
Carpenter 2003	Compared 2 methods of reducing smoking. Control group also offered NRT if a quit attempt planned
Carpenter 2011	Measured effect of providing NRT samples on participants not initially motivated to quit. Participants were encouraged but not required to make a practice quit attempt. Intervention participants were provided with up to 2 boxes of nicotine lozenges
Chan 2010	Measured effect of counselling + 2 weeks free NRT. No data on whether control group also using NRT; unclear if outcome due to counselling or free NRT
Chan 2011	Measured effect of adherence counselling as opposed to effect of NRT itself
Chou 2004	Only 3 months follow-up
Christen 1984	Only 15 weeks follow-up
Cohen 1989a	Primarily a trial of training dentists. Included in Cochrane Review of training of health professionals (Carson 2012)
Cohen 1989b	Primarily a trial of training doctors. Included in Cochrane Review of training of health professionals (Carson 2012)
Croghan 2007	Provides a short-term comparison between nicotine patch, bupropion, and combination therapy. Initial failures randomized to retreatment so no long-term control group
Cummings 2011	Compared provision of free NRT, but participants able to use additional NRT as desired
Dey 1999	Compared free and paid prescription for nicotine patch. Only 14 weeks follow-up
Donny 2009	Endpoint not cessation
Ebbert 2009	Study of NRT for smokeless tobacco users
Ebbert 2010	Study of mailed NRT for smokeless tobacco users
Elan Pharm 88-02	No long-term follow-up. Long-term follow-up for 1 site included as Hurt 1990
Elan Pharm 90-03	No long-term follow-up. Long-term follow-up for 1 site included as Fiore 1994a
Etter 2004	Trial of a choice of NRT products for smoking reduction in people not making a quit attempt. See Cochrane Review of harm reduction interventions, Lindson-Hawley 2016
Fagerström 1993	Endpoint withdrawal symptoms, not cessation

(*Continued*)

Fagerström 1997	Short-term cross-over trial of different types of NRT. For 2 weeks smokers could choose a method, for other 2 they were randomly assigned to one of gum, patch, spray, inhaler or tablet. Smoking reduction assessed
Fagerström 2000	Short-term cross-over trial comparing 2 nicotine delivery devices
Ferguson 2012	Study of offer of free NRT via NHS Quitline services. Control group had access to and used free NRT and other stop-smoking medications at high levels; study conditions were very similar for both groups
Finland unpublished	Only 3-month follow-up. Comparison of patch and 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 6 months
Garvey 2006	Not enough information currently available (abstract only)
Glover 1992	Follow-up less than 6 months
Gross 1989	Study of weight gain. Abstinence outcomes not reported
Guo 2006	Only 3 months follow-up
Hajek 1999	Follow-up less than 6 months
Hanson 2003	Follow-up only 10 weeks; 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, Lindson-Hawley 2016
Hoch 2006	Not enough information currently available (abstract only)
Hotham 2006	RCT of nicotine patch as adjunct to counselling for pregnant smokers. Only 20 people in each condition, with high withdrawal and low compliance
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 1983a for main outcomes
Jibrail 2010	Only 12 weeks follow-up. Study of NRT for smoking abstinence and relationship between c-reactive protein and depressed mood during nicotine abstinence
Kapur 2001	Only 12 weeks follow-up. Trial of nicotine patch in pregnant smokers. 30 participants

(*Continued*)

Korberly 1999	Insufficient data in unpublished abstracts to include
Kozak 1995	Open-label study in which smokers with higher nicotine dependence scores were given higher patch doses
Kras 2010	Study of NRT and hypericum perforatum extract. Only 10 weeks follow-up
Krumpe 1989	Only 10 weeks follow-up
Krupski 2016	All arms received pharmacotherapy
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 weeks follow-up reported in abstract
Leischow 1996b	Only 10 weeks follow-up
Levin 1994	Only 9 weeks follow-up
Lin 1996	Only 8 weeks follow-up
Marsh 2005	Only 3 months follow-up, safety study comparing 4 mg lozenge to 4 mg gum
McCarthy 2006	Only 3 months follow-up, study of withdrawal symptoms
McRobbie 2010	Short-term cross-over study assessing withdrawal symptoms and user satisfaction
Meier 1990	Short-term follow-up. Compared dependence individualized to standard dose patch
Merz 1993	Only 3 months follow-up
Miller 2009	1377 low-income smokers with quitline and subsidized NRT. Participants informed what group they would be in when first invited to participate
Millie 1989	Only 2 months follow-up
Minneker 1989	Only 9 weeks follow-up
Molander 2000	Cross-over study with 2-day smoke-free periods
Mooney 2005	All participants used nicotine gum
Mulligan 1990	Only 6 weeks follow-up
Nackaerts 2009	Insufficient data in published abstract to include (longest follow-up reported in abstract 1m); NRT delivered for maximum 7 days

(*Continued*)

NCT00000437	3-month follow-up only. Thank you to Barbara Mason for confirming
Okuyemi 2007	Intervention combined nicotine gum and multiple sessions of motivational interviewing
Oncken 2009	Study of short-term effects of NRT in pregnant smokers
Piper 2016	All arms received pharmacotherapy
Pomerleau 2003	Compared extended treatment (18 weeks) to 10-week treatment with nicotine patch. No follow-up beyond 18 weeks
Rennard 2006	Trial of nicotine inhaler for smoking reduction in people not making a quit attempt. See Cochrane Review of harm reduction interventions, Lindson-Hawley 2016
Rey 2009	All study participants received nicotine nasal spray. Comparison between different types of instructional guidance for dosing
Rigotti 2009	Assessed effectiveness of adding NRT to rimonabant which has not been licensed for smoking cessation and results may not be generalizable
Roddy 2006	Only 13 weeks 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 week)
Rose 1990	Only 3 weeks follow-up
Rubinstein 2008	Only 12 weeks follow-up
Sachs 1995	Only 6 weeks follow-up
Schlam 2016	All arms received pharmacotherapy
Schneider 2004	Short-term cross-over study
Schneider 2008	Outcome was craving and withdrawal, not abstinence
Schnoll 2015	All arms received pharmacotherapy
Shahab 2011	Short-term cross-over trial of withdrawal symptom relief
Shiffman 2000a	Compared 10 and 6 weeks of patch treatment without longer follow-up. Main outcome was craving and withdrawal
Shiffman 2000b	Comparison between 24-h and 16-h patches. Assessment of craving and abstinence over 2 weeks
Shiffman 2002a	Only 10 weeks follow-up

(*Continued*)

Shiffman 2002b	Not a randomized trial. Compared prescription and OTC patch in different populations using different methods
Shiffman 2006	Only 6 weeks follow-up. High-dose (35 mg) patch
Stapleton 2011	Only 12 weeks follow-up
Sun 2009	Only 3 months follow-up
Sussman 2004	Presents Project EX program for adolescent tobacco use cessation. Mentions trial of nicotine gum vs herbal gum but insufficient detail provided
Sutherland 1999	Only 3 months follow-up. Comparison of patch and nasal spray (n = 104) versus patch alone (n = 138) or nasal spray alone (n = 138). Used in a sensitivity analysis of combination therapies
Sutherland 2005	Only 12 weeks 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
Tsukahara 2010	Follow-up less than 6 months. Direct comparison of varenicline and nicotine patch for smoking cessation
Tundulawessa 2010	Only 4 weeks follow-up
Tzivoni 1998	Follow-up less than 6 months
Tønnesen 1996	All study participants received nicotine nasal spray. Comparison between ad lib and fixed schedule dosing
Uyar 2005	Unpublished, insufficient detail in abstract on nicotine patch dose, length of treatment, level of support
Velicer 2006	Participants were sent nicotine patches if they were assessed as potentially ready to quit. They did not have to set a quit date
Vial 2002	Treatment groups differed from control in amount of counselling as well as use of NRT
Vikhireva 2003	Trial of free choice of NRT product vs assigned NRT product from the outcome; no control group
Warner 2005	Goal of intervention was relief of stress and withdrawal postoperatively
Wennike 2003a	Trial of nicotine gum for smoking reduction in people not making a quit attempt. See Cochrane Review of harm reduction interventions, Lindson-Hawley 2016
Williams 2007	Only short-term outcomes reported in conference abstract. Trial terminated early when no benefit of higher dose detected in interim analysis

(*Continued*)

Wiseman 2005	2-week cross-over study
Working Group 1994	Follow-up less than 6 months

h = hour; OTC = over the counter;

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

NCT01010477

Trial name or title	Double-blind, placebo-controlled trial of nicotine nasal spray as an aid for smoking cessation in schizophrenia
Methods	RCT
Participants	60 individuals with schizophrenia
Interventions	Nicotine nasal spray or placebo spray with behavioural intervention
Outcomes	Abstinence at 12 months
Starting date	August 2009
Contact information	Mia H Zimmerman, hanosma@umdnj.edu
Notes	

NCT01484340

Trial name or title	A smoking cessation trial in HIV-infected patients in South Africa (JHU)
Methods	RCT
Participants	HIV-infected patients in South Africa
Interventions	1. intensive anti-smoking counseling + NRT (patches) 2. intensive anti-smoking counseling only
Outcomes	6-month and 12-month cessation, CO-validated
Starting date	March 2014
Contact information	Johns Hopkins University
Notes	

NCT02918500

Trial name or title	Effect of pre-op NRT on peri-operative complications and long-term abstinence: a pilot trial in patients undergoing CABG surgery
Methods	Single site, double-blind RCT
Participants	Smokers of > 5 cpd scheduled for CABG surgery
Interventions	1. NRT patch 2. Placebo
Outcomes	Smoking cessation (CO-validated) at time of surgery and 6 month post-op; peri-operative complications
Starting date	Oct 2017
Contact information	Evyanne Wooding, ewooding@ottawaheart.ca
Notes	

CABG = coronary artery bypass graft; RCT = randomized controlled trial

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	133	64640	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.49, 1.61]
1.1 Gum	56	22581	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.40, 1.60]
1.2 Patch	51	25754	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.53, 1.75]
1.3 Inhalator	4	976	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.36, 2.67]
1.4 Intranasal spray	4	887	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [1.49, 2.73]
1.5 Tablets/lozenges	8	4439	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.32, 1.74]
1.6 Oral spray	1	479	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.24, 4.94]
1.7 Choice of NRT product	7	8288	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.25, 1.52]
1.8 Patch and inhalator	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.57, 1.99]
1.9 Patch and lozenge	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.01, 3.31]
1.10 Patch and gum	2	259	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.64, 2.06]
1.11 Patch, gum and lozenge	1	424	Risk Ratio (M-H, Fixed, 95% CI)	15.0 [2.00, 112.54]

Comparison 2. Subgroup: Definition of abstinence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine gum. Smoking cessation	56	22581	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.40, 1.60]
1.1 Sustained 12 months	32	13737	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [1.31, 1.56]
1.2 Sustained 6 months	8	4187	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [2.14, 3.59]
1.3 PP/uncertain 12 months	8	2501	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.12, 1.55]
1.4 PP/uncertain 6 months	8	2156	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.20, 1.68]
2 Nicotine patch: Smoking cessation	49	23976	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.52, 1.75]
2.1 Sustained 12 months	21	7622	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.34, 1.74]
2.2 Sustained 6 months	9	8613	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.51, 1.92]
2.3 PP/uncertain 12 months	9	3856	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.44, 1.93]
2.4 PP/uncertain 6 months	10	3885	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.32, 2.04]

Comparison 3. Subgroup: Level of behavioural support

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine gum. Smoking cessation	55	21759	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.40, 1.61]
1.1 Low intensity support	17	11257	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.46, 1.88]
1.2 High intensity individual support	18	6891	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.18, 1.49]
1.3 High intensity group-based support	20	3611	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [1.40, 1.76]
2 Nicotine patch. Smoking cessation	49	23657	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.56, 1.79]
2.1 Low intensity support	15	7310	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.54, 2.02]
2.2 High intensity individual support	25	12709	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.47, 1.81]
2.3 High intensity group-based support	10	3638	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [1.43, 1.90]

Comparison 4. Subgroup: Recruitment/treatment setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Community volunteer (treatment provided in medical setting)	65	24597	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.53, 1.72]
1.1 Nicotine gum	28	8336	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.28, 1.53]
1.2 Nicotine patch	27	11214	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.59, 1.91]
1.3 Nicotine inhalator	2	443	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [0.98, 3.27]
1.4 Nicotine tablet/lozenge	7	3405	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.61, 2.36]
1.5 Nicotine intranasal spray	2	412	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.16, 2.95]
1.6 Combination of NRT	1	308	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.01, 3.31]
1.7 Nicotine oral spray	1	479	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [1.24, 4.94]
2 Smoking clinic	12	3300	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.48, 1.96]
2.1 Nicotine gum	6	1283	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.30, 1.91]
2.2 Nicotine inhalator	2	533	Risk Ratio (M-H, Fixed, 95% CI)	1.96 [1.30, 2.95]
2.3 Nicotine intranasal spray	2	475	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [1.44, 3.20]
2.4 Nicotine patch	2	1009	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [1.18, 2.19]
3 Primary care	24	11974	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.33, 1.69]
3.1 Nicotine gum	16	7277	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.35, 1.85]
3.2 Nicotine patch	7	4419	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.15, 1.71]
3.3 Choice of NRT products	1	278	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.83, 2.30]
4 Hospitals	13	7037	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.24, 1.55]
4.1 Nicotine gum	3	2194	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.86, 1.43]
4.2 Nicotine patch	6	2492	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.10, 1.78]
4.3 Combination of NRT	2	326	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.64, 1.52]
4.4 Choice of NRT products	2	2025	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.36, 1.86]

5 Community volunteer (treatment provided in 'over-the-counter' setting)	9	13163	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.26, 1.55]
5.1 Nicotine gum	2	3297	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [2.60, 5.52]
5.2 Nicotine patch	5	3542	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.38, 2.55]
5.3 Tablets/lozenges	1	1034	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.32]
5.4 Choice of product	1	5290	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [1.03, 1.37]
6 Antenatal clinic	4	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.92, 1.62]
6.1 Nicotine gum	1	194	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.50, 2.65]
6.2 Nicotine patch	2	1300	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.85, 1.66]
6.3 Choice of NRT products	1	181	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.69, 3.03]

Comparison 5. NRT in pregnancy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Smoking cessation	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Abstinence at end of pregnancy	6	2129	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [1.04, 1.69]
1.2 Abstinence at longest post partum follow-up	4	1675	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.90, 1.86]

Comparison 6. Palpitations in NRT vs placebo users

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

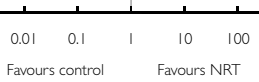
Analysis 1.1. Comparison 1 Any type of NRT versus placebo/no NRT control, Outcome 1 Smoking cessation at 6+ months follow up.

Review: Nicotine replacement therapy versus control 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		1.3 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		1.1 %	1.54 [1.13, 2.10]
Blondal 1989	30/92	22/90		0.7 %	1.33 [0.84, 2.13]
Br Thor Society 1983	39/410	111/1208		1.7 %	1.04 [0.73, 1.46]
Campbell 1987	13/424	9/412		0.3 %	1.40 [0.61, 3.25]
Campbell 1991	21/107	21/105		0.6 %	0.98 [0.57, 1.69]
Clavel 1985	24/205	6/222		0.2 %	4.33 [1.81, 10.38]
Clavel-Chapelon 1992	47/481	42/515		1.2 %	1.20 [0.81, 1.78]
Cooper 2005	17/146	15/147		0.5 %	1.14 [0.59, 2.20]
Fagerström 1982	30/50	23/50		0.7 %	1.30 [0.90, 1.90]
Fagerström 1984	28/96	5/49		0.2 %	2.86 [1.18, 6.94]
Fee 1982	23/180	15/172		0.5 %	1.47 [0.79, 2.71]
Fortmann 1995	110/552	84/522		2.6 %	1.24 [0.96, 1.60]
Garc a 1989	21/68	5/38		0.2 %	2.35 [0.96, 5.72]
Garvey 2000	75/405	17/203		0.7 %	2.21 [1.34, 3.64]
Gilbert 1989	11/112	9/111		0.3 %	1.21 [0.52, 2.81]
Gross 1995	37/131	6/46		0.3 %	2.17 [0.98, 4.79]
Hall 1985	18/41	10/36		0.3 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		0.4 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		0.8 %	0.90 [0.56, 1.44]
Harackiewicz 1988	12/99	7/52		0.3 %	0.90 [0.38, 2.15]
Herrera 1995	30/76	13/78		0.4 %	2.37 [1.34, 4.18]
Hjalmarson 1984	31/106	16/100		0.5 %	1.83 [1.07, 3.13]
Huber 1988	13/54	11/60		0.3 %	1.31 [0.64, 2.68]



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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
Hughes 1989a	23/210	6/105		0.2 %	1.92 [0.81, 4.56]
Hughes 1990	15/59	5/19		0.2 %	0.97 [0.40, 2.31]
Jamrozik 1984	10/101	8/99		0.2 %	1.23 [0.50, 2.98]
Jarvis 1982	22/58	9/58		0.3 %	2.44 [1.23, 4.85]
Jensen 1991	49/211	19/82		0.8 %	1.00 [0.63, 1.59]
Killen 1984	16/44	6/20		0.3 %	1.21 [0.56, 2.63]
Killen 1990	129/600	112/617		3.4 %	1.18 [0.94, 1.49]
Llivina 1988	61/113	28/103		0.9 %	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		1.3 %	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		0.7 %	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		0.2 %	1.16 [0.42, 3.17]
Niaura 1994	5/84	4/89		0.1 %	1.32 [0.37, 4.77]
Niaura 1999	1/31	2/31		0.1 %	0.50 [0.05, 5.23]
Ockene 1991	40/402	33/420		1.0 %	1.27 [0.82, 1.97]
Oncken 2008	11/100	9/94		0.3 %	1.15 [0.50, 2.65]
Page 1986	9/93	13/182		0.3 %	1.35 [0.60, 3.05]
Pirie 1992	75/206	50/211		1.5 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		0.6 %	1.35 [0.82, 2.21]
Richmond 1993	17/200	14/150		0.5 %	0.91 [0.46, 1.79]
Roto 1987	19/54	7/60		0.2 %	3.02 [1.38, 6.61]
Russell 1983	81/729	78/1377		1.6 %	1.96 [1.46, 2.64]
Schneider 1983a	9/30	6/30		0.2 %	1.50 [0.61, 3.69]
Schneider 1983b	1/13	3/23		0.1 %	0.59 [0.07, 5.11]
Segnan 1991	22/294	37/629		0.7 %	1.27 [0.76, 2.12]
Shiffman 2009 (2 mg)	24/819	9/817		0.3 %	2.66 [1.24, 5.69]
Shiffman 2009 (4 mg)	101/830	24/831		0.7 %	4.21 [2.73, 6.51]
T nnesen 1988	23/60	12/53		0.4 %	1.69 [0.94, 3.06]
Villa 1999	11/21	10/26		0.3 %	1.36 [0.72, 2.57]

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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
Zelman 1992	23/58	18/58		0.5 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**10596**	**11985**		**34.1 %**	**1.49 [1.40, 1.60]**
Total events: 1732 (NRT), 1196 (Control)					
Heterogeneity: Chi^2 = 91.05, df = 55 (P = 0.002); I^2 =40%					
Test for overall effect: Z = 11.56 (P < 0.00001)					
2 Patch					
Abelin 1989	17/100	11/99		0.3 %	1.53 [0.76, 3.10]
Ahluwalia 1998	35/205	24/205		0.7 %	1.46 [0.90, 2.36]
Anthenelli 2016	320/2038	191/2035		5.8 %	1.67 [1.41, 1.98]
Buchkremer 1988	11/42	16/89		0.3 %	1.46 [0.74, 2.86]
Campbell 1996	24/115	17/119		0.5 %	1.46 [0.83, 2.57]
Cinciripini 1996	12/32	7/32		0.2 %	1.71 [0.78, 3.79]
Coleman 2012	49/521	40/529		1.2 %	1.24 [0.83, 1.86]
Cummins 2016	44/637	38/633		1.2 %	1.15 [0.76, 1.75]
Cunningham 2016	14/500	5/499		0.2 %	2.79 [1.01, 7.70]
Daughton 1991	28/106	4/52		0.2 %	3.43 [1.27, 9.28]
Daughton 1998	25/184	16/185		0.5 %	1.57 [0.87, 2.84]
Davidson 1998	33/401	16/401		0.5 %	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		0.3 %	1.67 [0.82, 3.40]
Fiore 1994b	10/57	4/55		0.1 %	2.41 [0.80, 7.24]
Gallagher 2007	1/60	4/60		0.1 %	0.25 [0.03, 2.17]
Glavas 2003a	13/56	9/56		0.3 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		0.4 %	2.42 [1.33, 4.39]
Hays 1999	62/636	14/322		0.6 %	2.24 [1.28, 3.94]
Heydari 2012	23/92	6/91		0.2 %	3.79 [1.62, 8.88]
Hughes 1999	171/779	34/260		1.5 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		0.3 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		0.2 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		0.5 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		1.6 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		0.3 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		1.1 %	0.82 [0.51, 1.30]

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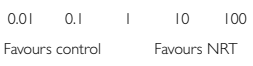
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Killen 1997	23/212	21/212		0.6 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		0.4 %	0.95 [0.47, 1.94]
Lerman 2015	69/418	50/408		1.5 %	1.35 [0.96, 1.89]
Lewis 1998	6/62	7/123		0.1 %	1.70 [0.60, 4.84]
Moolchan 2005	9/34	2/40		0.1 %	5.29 [1.23, 22.85]
NCT00534404	194/830	109/828		3.3 %	1.78 [1.43, 2.20]
Oncken 2007	19/57	28/95		0.6 %	1.13 [0.70, 1.83]
Otero 2006	193/597	122/602		3.7 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.1 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.1 %	3.20 [0.96, 10.71]
Piper 2009	90/262	8/37		0.4 %	1.59 [0.84, 3.00]
Prapavessis 2007	13/59	7/62		0.2 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		0.4 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		0.3 %	2.65 [1.35, 5.19]
Scherphof 2014	6/136	8/129		0.2 %	0.71 [0.25, 1.99]
Stapleton 1995	77/800	19/400		0.8 %	2.03 [1.24, 3.30]
S nderskov 1997	20/251	14/267		0.4 %	1.52 [0.78, 2.94]
TNSG 1991	111/537	31/271		1.3 %	1.81 [1.25, 2.62]
Tuisku 2016	19/94	13/86		0.4 %	1.34 [0.70, 2.54]
T nnesen 1991	24/145	6/144		0.2 %	3.97 [1.67, 9.43]
T nnesen 2000	9/104	2/109		0.1 %	4.72 [1.04, 21.32]
Ward 2013	17/134	16/135		0.5 %	1.07 [0.56, 2.03]
Westman 1993	16/78	2/80		0.1 %	8.21 [1.95, 34.51]
Wisborg 2000	19/124	18/126		0.5 %	1.07 [0.59, 1.94]
Subtotal (95% CI)	**13773**	**11981**		**35.4 %**	**1.64 [1.53, 1.75]**
Total events: 2160 (NRT), 1131 (Control)					
Heterogeneity: Chi^2 = 65.44, df = 50 (P = 0.07); I^2 =24%					
Test for overall effect: Z = 14.23 (P < 0.00001)					
3 Inhalator					
Hjalmarson 1997	35/123	22/124		0.7 %	1.60 [1.00, 2.57]
Leischow 1996a	12/110	6/110		0.2 %	2.00 [0.78, 5.14]
Schneider 1996	15/112	9/111		0.3 %	1.65 [0.75, 3.62]
T nnesen 1993	22/145	7/141		0.2 %	3.06 [1.35, 6.93]



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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
Subtotal (95% CI)	**490**	**486**	◆	**1.3 %**	**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 Intranasal spray					
Blondal 1997	20/79	13/78		0.4 %	1.52 [0.81, 2.84]
Hjalmarson 1994	34/125	18/123		0.6 %	1.86 [1.11, 3.11]
Schneider 1995	23/128	10/127		0.3 %	2.28 [1.13, 4.60]
Sutherland 1992	30/116	11/111		0.3 %	2.61 [1.38, 4.95]
Subtotal (95% CI)	**448**	**439**	◆	**1.6 %**	**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)					
5 Tablets/lozenges					
Dautzenberg 2001	25/211	18/222		0.5 %	1.46 [0.82, 2.60]
Fraser 2014	151/518	139/516		4.2 %	1.08 [0.89, 1.32]
Glover 2002	22/120	12/121		0.4 %	1.85 [0.96, 3.56]
Piper 2009	87/260	8/36		0.4 %	1.51 [0.80, 2.84]
Shiffman 2002 (2 mg)	82/459	44/458		1.3 %	1.86 [1.32, 2.62]
Shiffman 2002 (4 mg)	67/450	28/451		0.8 %	2.40 [1.57, 3.65]
T nnesen 2006	26/185	5/185		0.2 %	5.20 [2.04, 13.25]
Wallstrom 2000	28/123	19/124		0.6 %	1.49 [0.88, 2.52]
Subtotal (95% CI)	**2326**	**2113**	◆	**8.5 %**	**1.52 [1.32, 1.74]**
Total events: 488 (NRT), 273 (Control)					
Heterogeneity: Chi^2 = 24.39, df = 7 (P = 0.00097); I^2 =71%					
Test for overall effect: Z = 5.97 (P < 0.00001)					
6 Oral spray					
T nnesen 2012	44/318	9/161		0.4 %	2.48 [1.24, 4.94]
Subtotal (95% CI)	**318**	**161**	◆	**0.4 %**	**2.48 [1.24, 4.94]**
Total events: 44 (NRT), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.010)					
7 Choice of NRT product					
Graham 2017	366/2630	312/2660		9.4 %	1.19 [1.03, 1.37]
Johns 2017	27/100	16/100		0.5 %	1.69 [0.97, 2.93]
Kralikova 2009	39/209	9/105		0.4 %	2.18 [1.10, 4.32]
Molyneux 2003	10/91	4/91		0.1 %	2.50 [0.81, 7.68]

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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
Ortega 2011	305/924	193/919		5.9 %	1.57 [1.35, 1.84]
Pollak 2007	24/122	8/59		0.3 %	1.45 [0.69, 3.03]
Wittchen 2011	22/103	27/175		0.6 %	1.38 [0.83, 2.30]
Subtotal (95% CI)	**4179**	**4109**		**17.2 %**	**1.37 [1.25, 1.52]**
Total events: 793 (NRT), 569 (Control)					
Heterogeneity: Chi^2 = 10.41, df = 6 (P = 0.11); I^2 =42%					
Test for overall effect: Z = 6.34 (P < 0.00001)					
8 Patch and inhalator					
Hand 2002	20/136	15/109		0.5 %	1.07 [0.57, 1.99]
Subtotal (95% CI)	**136**	**109**		**0.5 %**	**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)					
9 Patch and lozenge					
Piper 2009	107/267	9/41		0.5 %	1.83 [1.01, 3.31]
Subtotal (95% CI)	**267**	**41**		**0.5 %**	**1.83 [1.01, 3.31]**
Total events: 107 (NRT), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.048)					
10 Patch and gum					
Hasan 2014	13/40	15/41		0.4 %	0.89 [0.49, 1.62]
Stein 2013	11/133	1/45		0.0 %	3.72 [0.49, 28.03]
Subtotal (95% CI)	**173**	**86**		**0.5 %**	**1.15 [0.64, 2.06]**
Total events: 24 (NRT), 16 (Control)					
Heterogeneity: Chi^2 = 2.00, df = 1 (P = 0.16); I^2 =50%					
Test for overall effect: Z = 0.46 (P = 0.64)					
11 Patch, gum and lozenge					
Heydari 2013	15/212	1/212		0.0 %	15.00 [2.00, 112.54]
Subtotal (95% CI)	**212**	**212**		**0.0 %**	**15.00 [2.00, 112.54]**
Total events: 15 (NRT), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.63 (P = 0.0084)					
Total (95% CI)	**32918**	**31722**		**100.0 %**	**1.55 [1.49, 1.61]**
Total events: 5574 (NRT), 3315 (Control)					
Heterogeneity: Chi^2 = 220.20, df = 135 (P<0.00001); I^2 =39%					
Test for overall effect: Z = 21.25 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 23.05, df = 10 (P = 0.01), I^2 =57%					

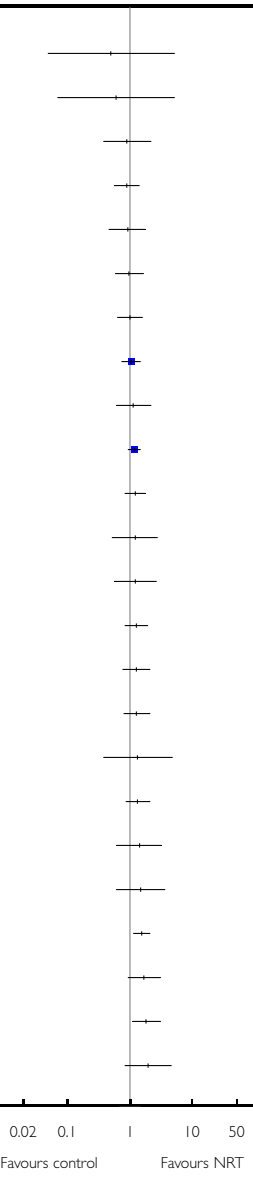
Analysis 2.1. Comparison 2 Subgroup: Definition of abstinence, Outcome 1 Nicotine gum. Smoking cessation.

Review: Nicotine replacement therapy versus control 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 12 months					
Niaura 1999	1/31	2/31		0.2 %	0.50 [0.05, 5.23]
Schneider 1983b	1/13	3/23		0.2 %	0.59 [0.07, 5.11]
Harackiewicz 1988	12/99	7/52		0.8 %	0.90 [0.38, 2.15]
Hall 1996	24/98	28/103		2.4 %	0.90 [0.56, 1.44]
Richmond 1993	17/200	14/150		1.4 %	0.91 [0.46, 1.79]
Campbell 1991	21/107	21/105		1.9 %	0.98 [0.57, 1.69]
Jensen 1991	49/211	19/82		2.4 %	1.00 [0.63, 1.59]
Br Thor Society 1983	39/410	111/1208		5.0 %	1.04 [0.73, 1.46]
Cooper 2005	17/146	15/147		1.3 %	1.14 [0.59, 2.20]
Killen 1990	129/600	112/617		9.8 %	1.18 [0.94, 1.49]
Clavel-Chapelon 1992	47/481	42/515		3.6 %	1.20 [0.81, 1.78]
Gilbert 1989	11/112	9/111		0.8 %	1.21 [0.52, 2.81]
Killen 1984	16/44	6/20		0.7 %	1.21 [0.56, 2.63]
Ockene 1991	40/402	33/420		2.9 %	1.27 [0.82, 1.97]
Segnan 1991	22/294	37/629		2.1 %	1.27 [0.76, 2.12]
Zelman 1992	23/58	18/58		1.6 %	1.28 [0.78, 2.10]
Niaura 1994	5/84	4/89		0.3 %	1.32 [0.37, 4.77]
Blondal 1989	30/92	22/90		2.0 %	1.33 [0.84, 2.13]
Campbell 1987	13/424	9/412		0.8 %	1.40 [0.61, 3.25]
Schneider 1983a	9/30	6/30		0.5 %	1.50 [0.61, 3.69]
Pirie 1992	75/206	50/211		4.4 %	1.54 [1.14, 2.08]
T nnesen 1988	23/60	12/53		1.1 %	1.69 [0.94, 3.06]
Hjalmarson 1984	31/106	16/100		1.5 %	1.83 [1.07, 3.13]
Hughes 1989a	23/210	6/105		0.7 %	1.92 [0.81, 4.56]



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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
Russell 1983	81/729	78/1377		4.8 %	1.96 [1.46, 2.64]
Llivina 1988	61/113	28/103		2.6 %	1.99 [1.39, 2.84]
Garvey 2000	75/405	17/203		2.0 %	2.21 [1.34, 3.64]
Herrera 1995	30/76	13/78		1.1 %	2.37 [1.34, 4.18]
Jarvis 1982	22/58	9/58		0.8 %	2.44 [1.23, 4.85]
Fagerström 1984	28/96	5/49		0.6 %	2.86 [1.18, 6.94]
Moolchan 2005	8/46	2/40		0.2 %	3.48 [0.78, 15.44]
Clavel 1985	24/205	6/222		0.5 %	4.33 [1.81, 10.38]
Subtotal (95% CI)	**6246**	**7491**		**61.3 %**	**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 6 months					
Hughes 1990	15/59	5/19		0.7 %	0.97 [0.40, 2.31]
Page 1986	9/93	13/182		0.8 %	1.35 [0.60, 3.05]
Gross 1995	37/131	6/46		0.8 %	2.17 [0.98, 4.79]
Garc a 1989	21/68	5/38		0.6 %	2.35 [0.96, 5.72]
Nakamura 1990	13/30	5/30		0.4 %	2.60 [1.06, 6.39]
Shiffman 2009 (2 mg)	24/819	9/817		0.8 %	2.66 [1.24, 5.69]
Malcolm 1980	6/73	3/121		0.2 %	3.32 [0.86, 12.85]
Shiffman 2009 (4 mg)	101/830	24/831		2.1 %	4.21 [2.73, 6.51]
Subtotal (95% CI)	**2103**	**2084**		**6.4 %**	**2.77 [2.14, 3.59]**
Total events: 226 (Nicotine gum), 70 (Control)					
Heterogeneity: Chi^2 = 12.78, df = 7 (P = 0.08); I^2 =45%					
Test for overall effect: Z = 7.70 (P < 0.00001)					
3 PP/uncertain 12 months					
McGovern 1992	51/146	40/127		3.8 %	1.11 [0.79, 1.56]
Nebot 1992	5/106	13/319		0.6 %	1.16 [0.42, 3.17]
Fortmann 1995	110/552	84/522		7.7 %	1.24 [0.96, 1.60]
Huber 1988	13/54	11/60		0.9 %	1.31 [0.64, 2.68]
Villa 1999	11/21	10/26		0.8 %	1.36 [0.72, 2.57]
Fee 1982	23/180	15/172		1.4 %	1.47 [0.79, 2.71]
Hall 1985	18/41	10/36		0.9 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		1.3 %	2.05 [1.20, 3.52]

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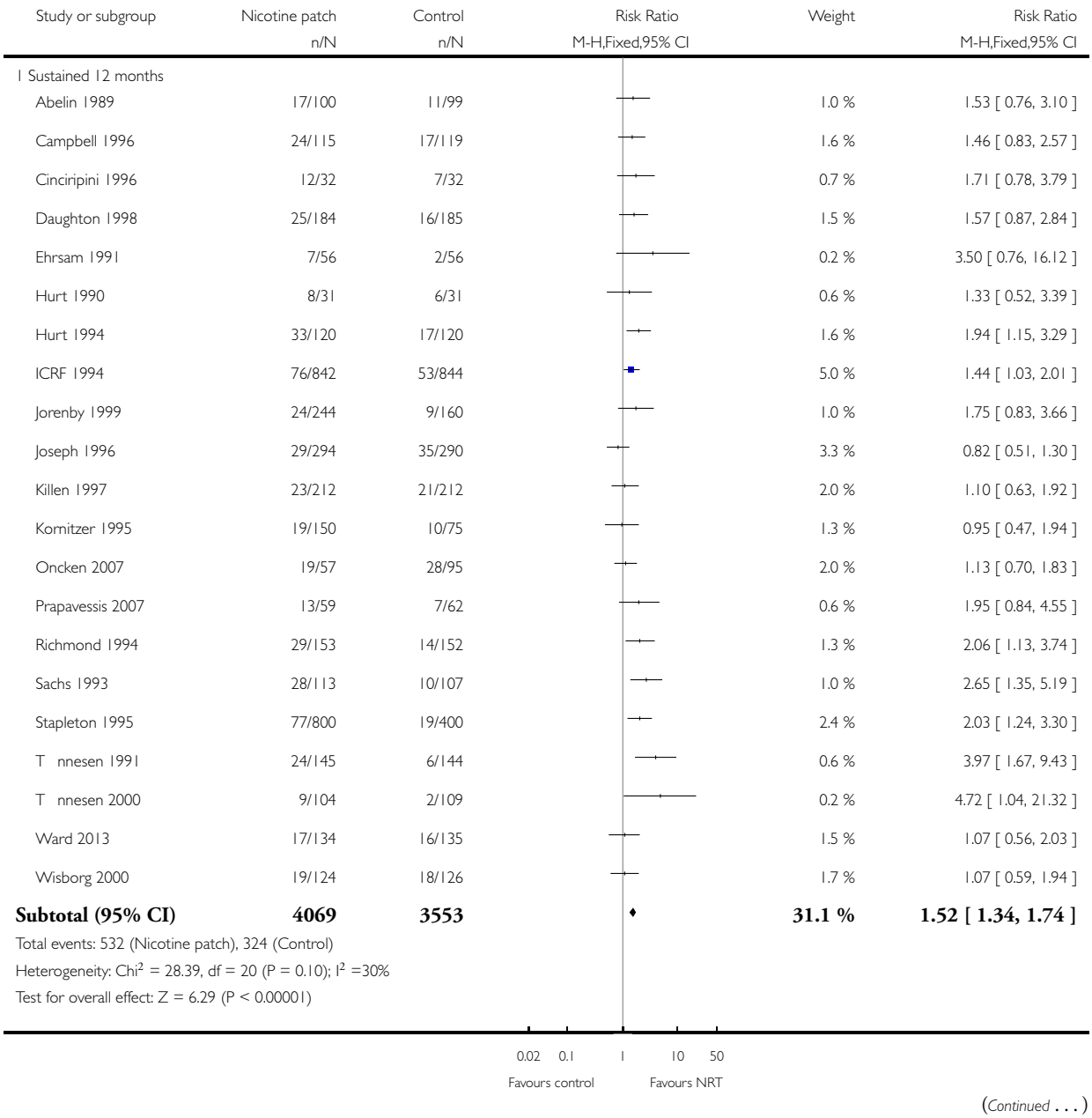
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**1171**	**1330**	♦	**17.4 %**	**1.31 [1.12, 1.55]**
Total events: 261 (Nicotine gum), 197 (Control)					
Heterogeneity: Chi^2 = 4.30, df = 7 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 3.27 (P = 0.0011)					
4 PP/uncertain 6 months					
Oncken 2008	11/100	9/94		0.8 %	1.15 [0.50, 2.65]
Jamrozik 1984	10/101	8/99		0.7 %	1.23 [0.50, 2.98]
Ahluwalia 2006	53/378	42/377		3.7 %	1.26 [0.86, 1.84]
Fagerström 1982	30/50	23/50		2.0 %	1.30 [0.90, 1.90]
Puska 1979	29/116	21/113		1.9 %	1.35 [0.82, 2.21]
Mori 1992	30/178	22/186		1.9 %	1.42 [0.86, 2.37]
Areechon 1988	56/99	37/101		3.3 %	1.54 [1.13, 2.10]
Roto 1987	19/54	7/60		0.6 %	3.02 [1.38, 6.61]
Subtotal (95% CI)	**1076**	**1080**	♦	**15.0 %**	**1.42 [1.20, 1.68]**
Total events: 238 (Nicotine gum), 169 (Control)					
Heterogeneity: Chi^2 = 4.81, df = 7 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 4.07 (P = 0.000047)					
Total (95% CI)	**10596**	**11985**	♦	**100.0 %**	**1.49 [1.40, 1.60]**
Total events: 1732 (Nicotine gum), 1196 (Control)					
Heterogeneity: Chi^2 = 91.05, df = 55 (P = 0.002); I^2 =40%					
Test for overall effect: Z = 11.56 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 25.26, df = 3 (P = 0.00), I^2 =88%					

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

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 2 Subgroup: Definition of abstinence

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 Sustained 12 months					
Abelin 1989	17/100	11/99		1.0 %	1.53 [0.76, 3.10]
Campbell 1996	24/115	17/119		1.6 %	1.46 [0.83, 2.57]
Cinciripini 1996	12/32	7/32		0.7 %	1.71 [0.78, 3.79]
Daughton 1998	25/184	16/185		1.5 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.2 %	3.50 [0.76, 16.12]
Hurt 1990	8/31	6/31		0.6 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		1.6 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		5.0 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		1.0 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	35/290		3.3 %	0.82 [0.51, 1.30]
Killen 1997	23/212	21/212		2.0 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		1.3 %	0.95 [0.47, 1.94]
Oncken 2007	19/57	28/95		2.0 %	1.13 [0.70, 1.83]
Prapavessis 2007	13/59	7/62		0.6 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.3 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		1.0 %	2.65 [1.35, 5.19]
Stapleton 1995	77/800	19/400		2.4 %	2.03 [1.24, 3.30]
T nnesen 1991	24/145	6/144		0.6 %	3.97 [1.67, 9.43]
T nnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Ward 2013	17/134	16/135		1.5 %	1.07 [0.56, 2.03]
Wisborg 2000	19/124	18/126		1.7 %	1.07 [0.59, 1.94]
Subtotal (95% CI)	**4069**	**3553**		**31.1 %**	**1.52 [1.34, 1.74]**
Total events: 532 (Nicotine patch), 324 (Control)					
Heterogeneity: Chi^2 = 28.39, df = 20 (P = 0.10); I^2 =30%					
Test for overall effect: Z = 6.29 (P < 0.00001)					

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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
2 Sustained 6 months					
Ahluwalia 1998	35/205	24/205		2.3 %	1.46 [0.90, 2.36]
Anthenelli 2016	320/2038	191/2035		18.1 %	1.67 [1.41, 1.98]
Coleman 2012	49/521	40/529		3.8 %	1.24 [0.83, 1.86]
Daughton 1991	28/106	4/52		0.5 %	3.43 [1.27, 9.28]
Davidson 1998	33/401	16/401		1.5 %	2.06 [1.15, 3.69]
Hughes 1999	171/779	34/260		4.8 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		0.8 %	1.44 [0.65, 3.20]
TNSG 1991	111/537	31/271		3.9 %	1.81 [1.25, 2.62]
Westman 1993	16/78	2/80		0.2 %	8.21 [1.95, 34.51]
Subtotal (95% CI)	**4726**	**3887**		**35.9 %**	**1.70 [1.51, 1.92]**
Total events: 776 (Nicotine patch), 350 (Control)					
Heterogeneity: Chi^2 = 10.01, df = 8 (P = 0.26); I^2 =20%					
Test for overall effect: Z = 8.59 (P < 0.00001)					
3 PP/uncertain 12 months					
Buchkremer 1988	11/42	16/89		1.0 %	1.46 [0.74, 2.86]
Glavas 2003a	13/56	9/56		0.9 %	1.44 [0.67, 3.10]
Hays 1999	62/636	14/322		1.8 %	2.24 [1.28, 3.94]
Heydari 2012	23/92	6/91		0.6 %	3.79 [1.62, 8.88]
Lerman 2015	69/418	50/408		4.8 %	1.35 [0.96, 1.89]
Otero 2006	193/597	122/602		11.5 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.4 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.3 %	3.20 [0.96, 10.71]
Scherphof 2014	6/136	8/129		0.8 %	0.71 [0.25, 1.99]
Subtotal (95% CI)	**2067**	**1789**		**21.9 %**	**1.66 [1.44, 1.93]**
Total events: 401 (Nicotine patch), 232 (Control)					
Heterogeneity: Chi^2 = 12.71, df = 8 (P = 0.12); I^2 =37%					
Test for overall effect: Z = 6.76 (P < 0.00001)					
4 PP/uncertain 6 months					
Cummins 2016	44/637	38/633		3.6 %	1.15 [0.76, 1.75]
Cunningham 2016	14/500	5/499		0.5 %	2.79 [1.01, 7.70]
Fiore 1994a	15/44	9/44		0.9 %	1.67 [0.82, 3.40]
Fiore 1994b	10/57	4/55		0.4 %	2.41 [0.80, 7.24]
Glavas 2003b	29/80	12/80		1.1 %	2.42 [1.33, 4.39]
Lewis 1998	6/62	7/123		0.4 %	1.70 [0.60, 4.84]

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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
Moolchan 2005	9/34	2/40		0.2 %	5.29 [1.23, 22.85]
Piper 2009	90/262	8/37		1.3 %	1.59 [0.84, 3.00]
S nderskov 1997	20/251	14/267		1.3 %	1.52 [0.78, 2.94]
Tuisku 2016	19/94	13/86		1.3 %	1.34 [0.70, 2.54]
Subtotal (95% CI)	**2021**	**1864**		**11.0 %**	**1.64 [1.32, 2.04]**
Total events: 256 (Nicotine patch), 112 (Control)					
Heterogeneity: Chi^2 = 8.82, df = 9 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 4.49 (P < 0.00001)					
Total (95% CI)	**12883**	**11093**		**100.0 %**	**1.63 [1.52, 1.75]**
Total events: 1965 (Nicotine patch), 1018 (Control)					
Heterogeneity: Chi^2 = 61.81, df = 48 (P = 0.09); I^2 =22%					
Test for overall effect: Z = 13.32 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.59, df = 3 (P = 0.66), I^2 =0.0%					

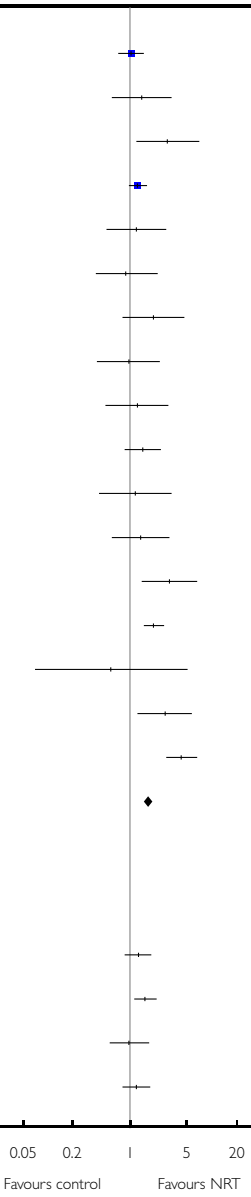
Analysis 3.1. Comparison 3 Subgroup: Level of behavioural support, Outcome 1 Nicotine gum. Smoking cessation.

Review: Nicotine replacement therapy versus control 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		5.1 %	1.04 [0.73, 1.46]
Campbell 1987	13/424	9/412		0.8 %	1.40 [0.61, 3.25]
Fagerström 1984	28/96	5/49		0.6 %	2.86 [1.18, 6.94]
Fortmann 1995	110/552	84/522		7.9 %	1.24 [0.96, 1.60]
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 1989a	23/210	6/105		0.7 %	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		0.7 %	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		4.9 %	1.96 [1.46, 2.64]
Schneider 1983b	1/13	3/23		0.2 %	0.59 [0.07, 5.11]
Shiffman 2009 (2 mg)	24/819	9/817		0.8 %	2.66 [1.24, 5.69]
Shiffman 2009 (4 mg)	101/830	24/831		2.2 %	4.21 [2.73, 6.51]
Subtotal (95% CI)	**4885**	**6372**		**30.4 %**	**1.66 [1.46, 1.88]**
Total events: 531 (Nicotine gum), 413 (Control)					
Heterogeneity: Chi^2 = 42.62, df = 16 (P = 0.00032); I^2 =62%					
Test for overall effect: Z = 7.74 (P < 0.00001)					
2 High intensity individual support					
Ahluwalia 2006	53/378	42/377		3.8 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		3.3 %	1.54 [1.13, 2.10]
Campbell 1991	21/107	21/105		1.9 %	0.98 [0.57, 1.69]
Clavel-Chapelon 1992	47/481	42/515		3.7 %	1.20 [0.81, 1.78]



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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
Cooper 2005	17/146	15/147		1.4 %	1.14 [0.59, 2.20]
Fagerström 1982	30/50	23/50		2.1 %	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		2.5 %	1.00 [0.63, 1.59]
Killen 1990	129/600	112/617		10.1 %	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]
Oncken 2008	11/100	9/94		0.8 %	1.15 [0.50, 2.65]
Richmond 1993	17/200	14/150		1.5 %	0.91 [0.46, 1.79]
Schneider 1983a	9/30	6/30		0.5 %	1.50 [0.61, 3.69]
Segnan 1991	22/294	37/629		2.2 %	1.27 [0.76, 2.12]
Subtotal (95% CI)	**3465**	**3426**		**37.9 %**	**1.32 [1.18, 1.49]**
Total events: 605 (Nicotine gum), 414 (Control)					
Heterogeneity: Chi^2 = 17.42, df = 17 (P = 0.43); I^2 =2%					
Test for overall effect: Z = 4.80 (P < 0.00001)					
3 High intensity group-based support					
Blondal 1989	30/92	22/90		2.0 %	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		1.4 %	1.47 [0.79, 2.71]
Garc a 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		1.3 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		2.5 %	0.90 [0.56, 1.44]
Herrera 1995	37/76	17/78		1.5 %	2.23 [1.38, 3.61]
Hjalmarson 1984	31/106	16/100		1.5 %	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		0.8 %	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		2.7 %	1.99 [1.39, 2.84]
McGovern 1992	51/146	40/127		3.9 %	1.11 [0.79, 1.56]

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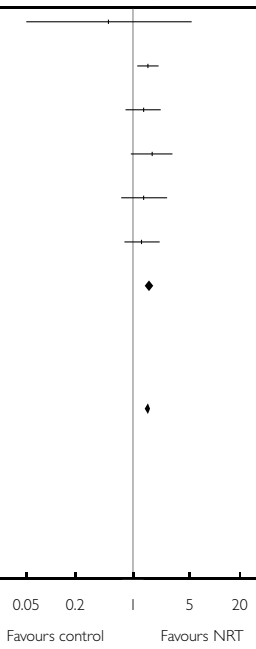
Study or subgroup	Nicotine gum n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Niaura 1999	1/31	2/31		0.2 %	0.50 [0.05, 5.23]
Pirie 1992	75/206	50/211		4.5 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		1.9 %	1.35 [0.82, 2.21]
T nnesen 1988	23/60	12/53		1.2 %	1.69 [0.94, 3.06]
Villa 1999	11/21	10/26		0.8 %	1.36 [0.72, 2.57]
Zelman 1992	23/58	18/58		1.6 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**1844**	**1767**		**31.7 %**	**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)	**10194**	**11565**		**100.0 %**	**1.50 [1.40, 1.61]**
Total events: 1699 (Nicotine gum), 1167 (Control)					
Heterogeneity: Chi^2 = 90.90, df = 54 (P = 0.001); I^2 =41%					
Test for overall effect: Z = 11.60 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 7.36, df = 2 (P = 0.03), I^2 =73%					



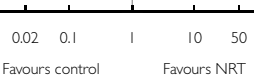
Analysis 3.2. Comparison 3 Subgroup: Level of behavioural support, Outcome 2 Nicotine patch. Smoking cessation.

Review: Nicotine replacement therapy versus control 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		1.0 %	1.53 [0.76, 3.10]
Cunningham 2016	14/500	5/499		0.5 %	2.79 [1.01, 7.70]
Daughton 1991	28/106	4/52		0.5 %	3.43 [1.27, 9.28]
Daughton 1998	25/184	16/185		1.5 %	1.57 [0.87, 2.84]
Davidson 1998	33/401	16/401		1.5 %	2.06 [1.15, 3.69]
Glavas 2003a	13/56	9/56		0.8 %	1.44 [0.67, 3.10]
Glavas 2003b	29/80	12/80		1.1 %	2.42 [1.33, 4.39]
Hays 1999	62/636	14/322		1.7 %	2.24 [1.28, 3.94]
Killen 1997	23/212	21/212		1.9 %	1.10 [0.63, 1.92]
Lewis 1998	6/62	7/123		0.4 %	1.70 [0.60, 4.84]
NCT00534404	194/830	109/828		10.1 %	1.78 [1.43, 2.20]
Otero 2006	57/189	39/194		3.6 %	1.50 [1.05, 2.14]
Paoletti 1996	15/60	4/60		0.4 %	3.75 [1.32, 10.64]
Scherphof 2014	6/136	8/129		0.8 %	0.71 [0.25, 1.99]
S nderskov 1997	20/251	14/267		1.3 %	1.52 [0.78, 2.94]
Subtotal (95% CI)	**3803**	**3507**		**27.1 %**	**1.76 [1.54, 2.02]**
Total events: 542 (Nicotine patch), 289 (Control)					
Heterogeneity: Chi^2 = 13.90, df = 14 (P = 0.46); I^2 =0.0%					
Test for overall effect: Z = 8.30 (P < 0.00001)					
2 High intensity individual support					
Ahluwalia 1998	35/205	24/205		2.2 %	1.46 [0.90, 2.36]
Anthenelli 2016	320/2038	191/2035		17.7 %	1.67 [1.41, 1.98]
Campbell 1996	24/115	17/119		1.6 %	1.46 [0.83, 2.57]
Coleman 2012	49/521	40/529		3.7 %	1.24 [0.83, 1.86]
Ehrsam 1991	7/56	2/56		0.2 %	3.50 [0.76, 16.12]
Fiore 1994b	10/57	4/55		0.4 %	2.41 [0.80, 7.24]



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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
Gallagher 2007	1/60	4/60		0.4 %	0.25 [0.03, 2.17]
Heydari 2012	23/92	6/91		0.6 %	3.79 [1.62, 8.88]
Hurt 1990	8/31	6/31		0.6 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		1.6 %	1.94 [1.15, 3.29]
ICRF 1994	76/842	53/844		4.9 %	1.44 [1.03, 2.01]
Jorenby 1999	24/244	9/160		1.0 %	1.75 [0.83, 3.66]
Joseph 1996	29/294	34/290		3.2 %	0.84 [0.53, 1.34]
Kornitzer 1995	19/150	10/75		1.2 %	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		0.3 %	3.20 [0.96, 10.71]
Piper 2009	90/262	8/37		1.3 %	1.59 [0.84, 3.00]
Sachs 1993	28/113	10/107		1.0 %	2.65 [1.35, 5.19]
Stapleton 1995	77/800	19/400		2.4 %	2.03 [1.24, 3.30]
Tuisku 2016	19/94	13/86		1.3 %	1.34 [0.70, 2.54]
T nnesen 1991	24/145	6/144		0.6 %	3.97 [1.67, 9.43]
T nnesen 2000	9/104	2/109		0.2 %	4.72 [1.04, 21.32]
Ward 2013	17/134	16/135		1.5 %	1.07 [0.56, 2.03]
Westman 1993	16/78	2/80		0.2 %	8.21 [1.95, 34.51]
Wisborg 2000	19/124	18/126		1.7 %	1.07 [0.59, 1.94]
Subtotal (95% CI)	**6743**	**5966**		**49.5 %**	**1.63 [1.47, 1.81]**
Total events: 975 (Nicotine patch), 516 (Control)					
Heterogeneity: Chi^2 = 42.61, df = 24 (P = 0.01); I^2 =44%					
Test for overall effect: Z = 9.40 (P < 0.00001)					
3 High intensity group-based support					
Buchkremer 1988	11/42	16/89		1.0 %	1.46 [0.74, 2.86]
Cinciripini 1996	12/32	7/32		0.6 %	1.71 [0.78, 3.79]
Fiore 1994a	15/44	9/43		0.8 %	1.63 [0.80, 3.32]
Hughes 1999	171/779	34/260		4.7 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		0.8 %	1.44 [0.65, 3.20]
Oncken 2007	19/57	28/95		1.9 %	1.13 [0.70, 1.83]
Otero 2006	136/408	83/408		7.7 %	1.64 [1.29, 2.07]
Prapavessis 2007	13/59	7/62		0.6 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.3 %	2.06 [1.13, 3.74]

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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
TNSG 1991	111/537	31/271		3.8 %	1.81 [1.25, 2.62]
Subtotal (95% CI)	**2172**	**1466**		**23.4 %**	**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)	**12718**	**10939**		**100.0 %**	**1.67 [1.56, 1.79]**
Total events: 2047 (Nicotine patch), 1042 (Control)					
Heterogeneity: Chi^2 = 61.01, df = 49 (P = 0.12); I^2 =20%					
Test for overall effect: Z = 14.27 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.87, df = 2 (P = 0.65), I^2 =0.0%					

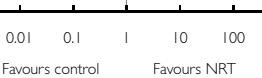
Analysis 4.1. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 1 Community volunteer (treatment provided in medical setting).

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 1 Community volunteer (treatment provided in medical setting)

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 Nicotine gum					
Ahluwalia 2006	53/378	42/377		2.9 %	1.26 [0.86, 1.84]
Areechon 1988	56/99	37/101		2.5 %	1.54 [1.13, 2.10]
Blondal 1989	30/92	22/90		1.5 %	1.33 [0.84, 2.13]
Clavel 1985	24/205	6/222		0.4 %	4.33 [1.81, 10.38]
Clavel-Chapelon 1992	47/481	42/515		2.8 %	1.20 [0.81, 1.78]
Cooper 2005	17/146	15/147		1.0 %	1.14 [0.59, 2.20]
Fortmann 1995	110/552	84/522		5.9 %	1.24 [0.96, 1.60]



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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
Garvey 2000	75/405	17/203		1.5 %	2.21 [1.34, 3.64]
Gross 1995	37/131	6/46		0.6 %	2.17 [0.98, 4.79]
Hall 1985	18/41	10/36		0.7 %	1.58 [0.84, 2.97]
Hall 1987	30/71	14/68		1.0 %	2.05 [1.20, 3.52]
Hall 1996	24/98	28/103		1.9 %	0.90 [0.56, 1.44]
Herrera 1995	30/76	13/78		0.9 %	2.37 [1.34, 4.18]
Huber 1988	13/54	11/60		0.7 %	1.31 [0.64, 2.68]
Hughes 1990	15/59	5/19		0.5 %	0.97 [0.40, 2.31]
Killen 1984	16/44	6/20		0.6 %	1.21 [0.56, 2.63]
Killen 1990	129/600	112/617		7.5 %	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		2.9 %	1.11 [0.79, 1.56]
Moolchan 2005	8/46	2/40		0.1 %	3.48 [0.78, 15.44]
Nakamura 1990	13/30	5/30		0.3 %	2.60 [1.06, 6.39]
Niaura 1999	1/31	2/31		0.1 %	0.50 [0.05, 5.23]
Pirie 1992	75/206	50/211		3.4 %	1.54 [1.14, 2.08]
Puska 1979	29/116	21/113		1.4 %	1.35 [0.82, 2.21]
Schneider 1983a	9/30	6/30		0.4 %	1.50 [0.61, 3.69]
Schneider 1983b	1/13	3/23		0.1 %	0.59 [0.07, 5.11]
Villa 1999	11/21	10/26		0.6 %	1.36 [0.72, 2.57]
Zelman 1992	23/58	18/58		1.2 %	1.28 [0.78, 2.10]
Subtotal (95% CI)	**4302**	**4034**		**43.7 %**	**1.40 [1.28, 1.53]**
Total events: 951 (NRT), 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 Nicotine patch					
Anthenelli 2016	320/2038	191/2035		13.0 %	1.67 [1.41, 1.98]
Buchkremer 1988	11/42	16/89		0.7 %	1.46 [0.74, 2.86]
Cinciripini 1996	12/32	7/32		0.5 %	1.71 [0.78, 3.79]
Daughton 1991	28/106	4/52		0.4 %	3.43 [1.27, 9.28]
Fiore 1994a	15/44	9/44		0.6 %	1.67 [0.82, 3.40]
Fiore 1994b	10/57	4/55		0.3 %	2.41 [0.80, 7.24]
Glavas 2003a	13/56	9/56		0.6 %	1.44 [0.67, 3.10]

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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
Glavas 2003b	29/80	12/80		0.8 %	2.42 [1.33, 4.39]
Hughes 1999	171/779	34/260		3.5 %	1.68 [1.19, 2.36]
Hughes 2003	13/61	8/54		0.6 %	1.44 [0.65, 3.20]
Hurt 1990	8/31	6/31		0.4 %	1.33 [0.52, 3.39]
Hurt 1994	33/120	17/120		1.2 %	1.94 [1.15, 3.29]
Jorenby 1999	24/244	9/160		0.7 %	1.75 [0.83, 3.66]
Killen 1997	23/212	21/212		1.4 %	1.10 [0.63, 1.92]
Kornitzer 1995	19/150	10/75		0.9 %	0.95 [0.47, 1.94]
Moolchan 2005	9/34	2/40		0.1 %	5.29 [1.23, 22.85]
Oncken 2007	19/57	28/95		1.4 %	1.13 [0.70, 1.83]
Otero 2006	193/597	122/602		8.3 %	1.60 [1.31, 1.94]
Paoletti 1996	15/60	4/60		0.3 %	3.75 [1.32, 10.64]
Perng 1998	9/30	3/32		0.2 %	3.20 [0.96, 10.71]
Piper 2009	90/262	8/37		1.0 %	1.59 [0.84, 3.00]
Prapavessis 2007	13/59	7/62		0.5 %	1.95 [0.84, 4.55]
Richmond 1994	29/153	14/152		1.0 %	2.06 [1.13, 3.74]
Sachs 1993	28/113	10/107		0.7 %	2.65 [1.35, 5.19]
TNSG 1991	111/537	31/271		2.8 %	1.81 [1.25, 2.62]
T nnesen 1991	24/145	6/144		0.4 %	3.97 [1.67, 9.43]
Westman 1993	16/78	2/80		0.1 %	8.21 [1.95, 34.51]
Subtotal (95% CI)	**6177**	**5037**		**42.3 %**	**1.74 [1.59, 1.91]**
Total events: 1285 (NRT), 594 (Control)					
Heterogeneity: Chi^2 = 29.29, df = 26 (P = 0.30); I^2 =11%					
Test for overall effect: Z = 11.94 (P < 0.00001)					
3 Nicotine inhalator					
Leischow 1996a	12/110	6/110		0.4 %	2.00 [0.78, 5.14]
Schneider 1996	15/112	9/111		0.6 %	1.65 [0.75, 3.62]
Subtotal (95% CI)	**222**	**221**		**1.0 %**	**1.79 [0.98, 3.27]**
Total events: 27 (NRT), 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)					
4 Nicotine tablet/lozenge					
Dautzenberg 2001	25/211	18/222		1.2 %	1.46 [0.82, 2.60]
Glover 2002	22/120	12/121		0.8 %	1.85 [0.96, 3.56]

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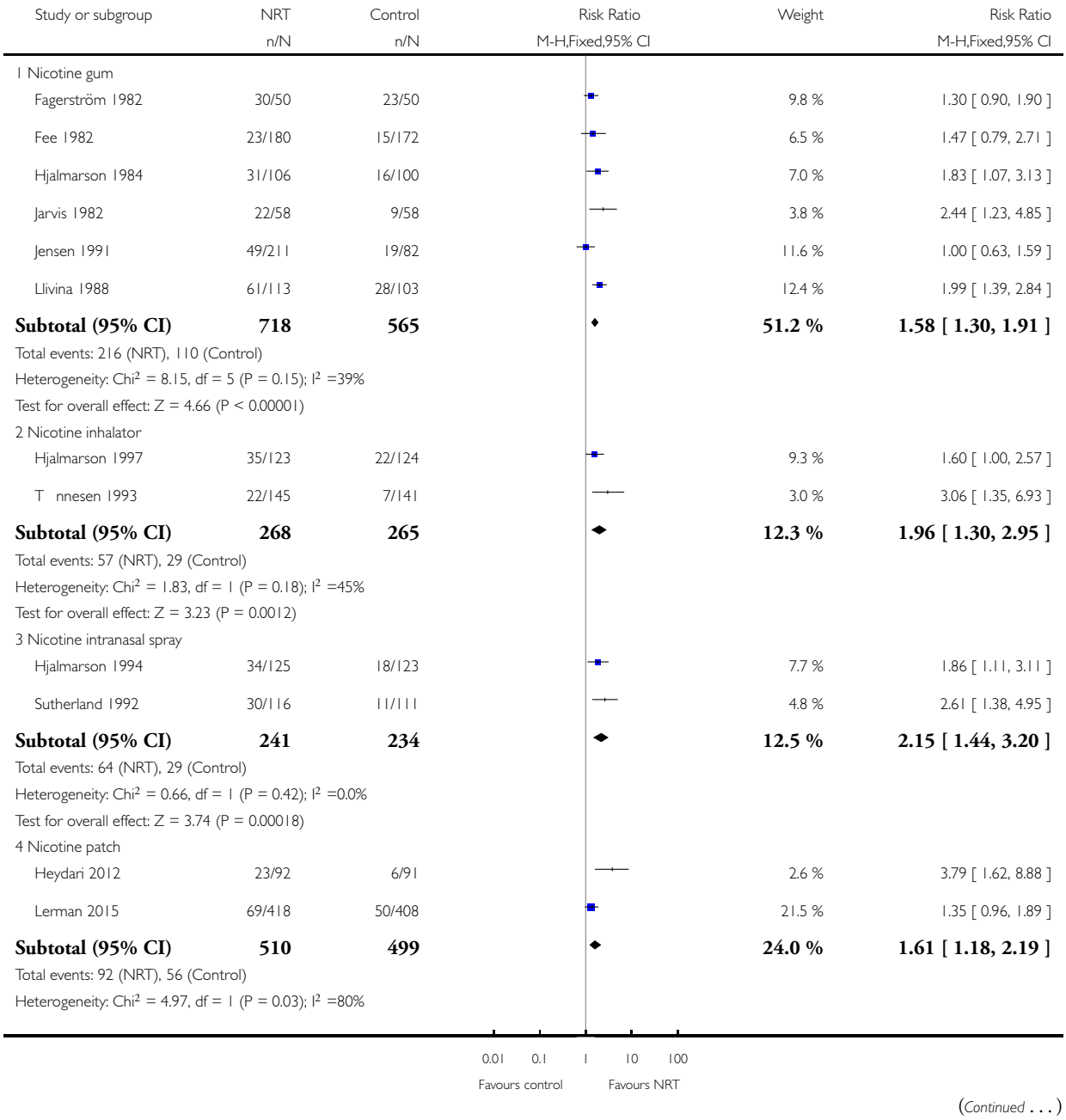
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Piper 2009	87/260	8/36		1.0 %	1.51 [0.80, 2.84]
Shiffman 2002 (2 mg)	82/459	44/458		3.0 %	1.86 [1.32, 2.62]
Shiffman 2002 (4 mg)	67/450	28/451		1.9 %	2.40 [1.57, 3.65]
T nnesen 2006	26/185	5/185		0.3 %	5.20 [2.04, 13.25]
Wallstrom 2000	28/123	19/124		1.3 %	1.49 [0.88, 2.52]
Subtotal (95% CI)	**1808**	**1597**		**9.5 %**	**1.95 [1.61, 2.36]**
Total events: 337 (NRT), 134 (Control)					
Heterogeneity: Chi^2 = 7.88, df = 6 (P = 0.25); I^2 =24%					
Test for overall effect: Z = 6.81 (P < 0.00001)					
5 Nicotine intranasal spray					
Blondal 1997	20/79	13/78		0.9 %	1.52 [0.81, 2.84]
Schneider 1995	23/128	10/127		0.7 %	2.28 [1.13, 4.60]
Subtotal (95% CI)	**207**	**205**		**1.6 %**	**1.85 [1.16, 2.95]**
Total events: 43 (NRT), 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)					
6 Combination of NRT					
Piper 2009	107/267	9/41		1.1 %	1.83 [1.01, 3.31]
Subtotal (95% CI)	**267**	**41**		**1.1 %**	**1.83 [1.01, 3.31]**
Total events: 107 (NRT), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.048)					
7 Nicotine oral spray					
T nnesen 2012	44/318	9/161		0.8 %	2.48 [1.24, 4.94]
Subtotal (95% CI)	**318**	**161**		**0.8 %**	**2.48 [1.24, 4.94]**
Total events: 44 (NRT), 9 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.57 (P = 0.010)					
Total (95% CI)	**13301**	**11296**		**100.0 %**	**1.62 [1.53, 1.72]**
Total events: 2794 (NRT), 1414 (Control)					
Heterogeneity: Chi^2 = 89.74, df = 67 (P = 0.03); I^2 =25%					
Test for overall effect: Z = 15.92 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 18.68, df = 6 (P = 0.00), I^2 =68%					

Analysis 4.2. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 2 Smoking clinic.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 2 Smoking clinic



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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
Test for overall effect: Z = 3.01 (P = 0.0026)					
Total (95% CI)	**1737**	**1563**	♦	**100.0 %**	**1.70 [1.48, 1.96]**
Total events: 429 (NRT), 224 (Control)					
Heterogeneity: Chi^2 = 18.11, df = 11 (P = 0.08); I^2 =39%					
Test for overall effect: Z = 7.34 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.46, df = 3 (P = 0.48), I^2 =0.0%					

Analysis 4.3. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 3 Primary care.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 3 Primary care

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 Nicotine gum					
Campbell 1987	13/424	9/412		2.3 %	1.40 [0.61, 3.25]
Fagerström 1984	28/96	5/49		1.7 %	2.86 [1.18, 6.94]
Garc a 1989	21/68	5/38		1.6 %	2.35 [0.96, 5.72]
Gilbert 1989	11/112	9/111		2.3 %	1.21 [0.52, 2.81]
Harackiewicz 1988	12/99	7/52		2.3 %	0.90 [0.38, 2.15]
Hughes 1989a	23/210	6/105		2.0 %	1.92 [0.81, 4.56]
Jamrozik 1984	10/101	8/99		2.0 %	1.23 [0.50, 2.98]
Nebot 1992	5/106	13/319		1.6 %	1.16 [0.42, 3.17]
Niaura 1994	5/84	4/89		1.0 %	1.32 [0.37, 4.77]
Ockene 1991	40/402	33/420		8.1 %	1.27 [0.82, 1.97]
Page 1986	9/93	13/182		2.2 %	1.35 [0.60, 3.05]

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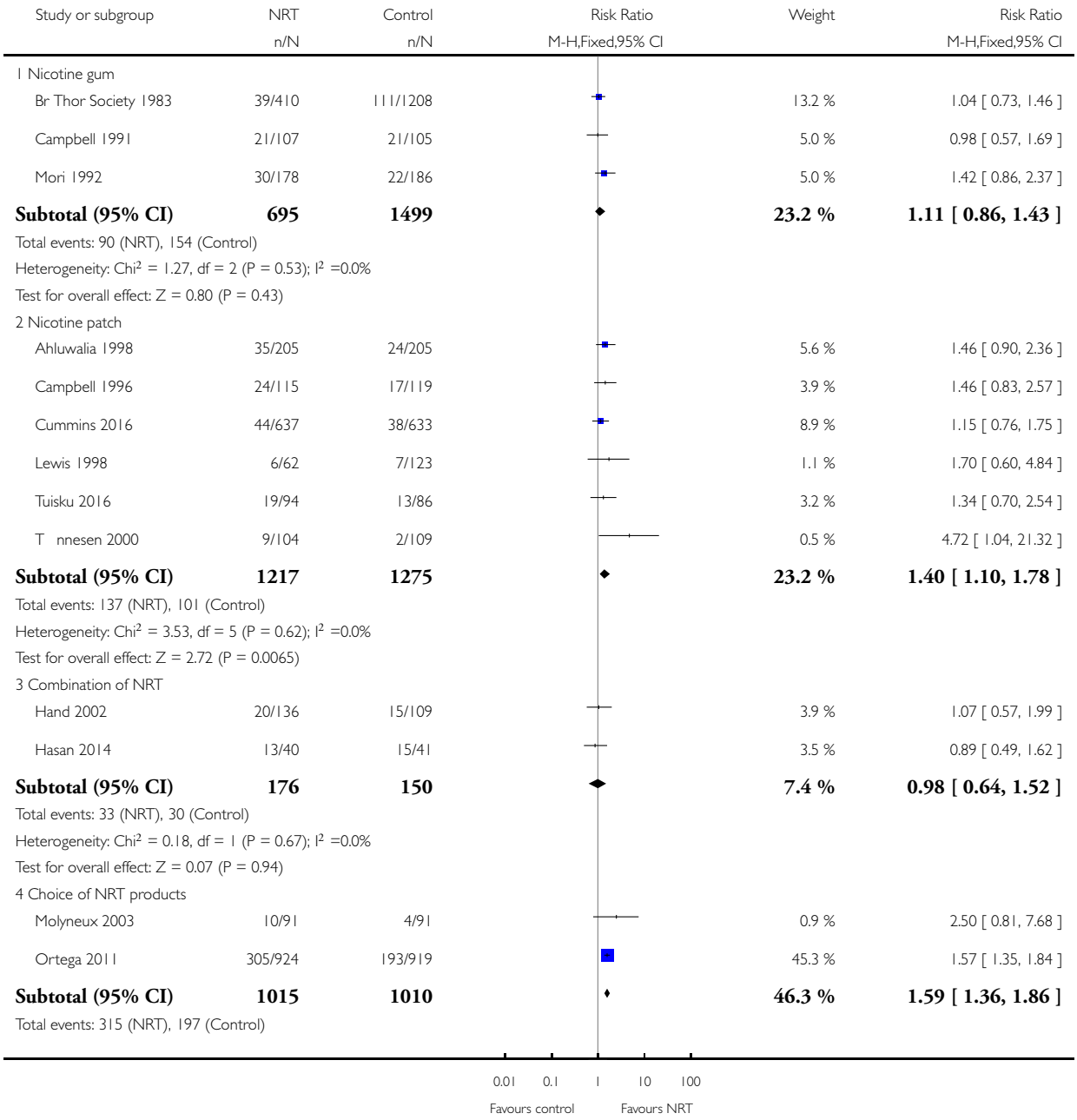
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Richmond 1993	17/200	14/150		4.0 %	0.91 [0.46, 1.79]
Roto 1987	19/54	7/60		1.7 %	3.02 [1.38, 6.61]
Russell 1983	81/729	78/1377		13.5 %	1.96 [1.46, 2.64]
Segnan 1991	22/294	37/629		5.9 %	1.27 [0.76, 2.12]
T nnesen 1988	23/60	12/53		3.2 %	1.69 [0.94, 3.06]
Subtotal (95% CI)	**3132**	**4145**		**55.3 %**	**1.58 [1.35, 1.85]**
Total events: 339 (NRT), 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)					
2 Nicotine patch					
Abelin 1989	17/100	11/99		2.8 %	1.53 [0.76, 3.10]
Daughton 1998	25/184	16/185		4.0 %	1.57 [0.87, 2.84]
Ehrsam 1991	7/56	2/56		0.5 %	3.50 [0.76, 16.12]
ICRF 1994	76/842	53/844		13.3 %	1.44 [1.03, 2.01]
Joseph 1996	29/294	35/290		8.8 %	0.82 [0.51, 1.30]
Stapleton 1995	77/800	19/400		6.3 %	2.03 [1.24, 3.30]
Ward 2013	17/134	16/135		4.0 %	1.07 [0.56, 2.03]
Subtotal (95% CI)	**2410**	**2009**		**39.7 %**	**1.40 [1.15, 1.71]**
Total events: 248 (NRT), 152 (Control)					
Heterogeneity: Chi^2 = 9.66, df = 6 (P = 0.14); I^2 =38%					
Test for overall effect: Z = 3.37 (P = 0.00075)					
3 Choice of NRT products					
Wittchen 2011	22/103	27/175		5.0 %	1.38 [0.83, 2.30]
Subtotal (95% CI)	**103**	**175**		**5.0 %**	**1.38 [0.83, 2.30]**
Total events: 22 (NRT), 27 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.26 (P = 0.21)					
Total (95% CI)	**5645**	**6329**		**100.0 %**	**1.50 [1.33, 1.69]**
Total events: 609 (NRT), 439 (Control)					
Heterogeneity: Chi^2 = 25.30, df = 23 (P = 0.33); I^2 =9%					
Test for overall effect: Z = 6.63 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.95, df = 2 (P = 0.62), I^2 =0.0%					

Analysis 4.4. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 4 Hospitals.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 4 Hospitals



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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: Chi² = 0.65, df = 1 (P = 0.42); I² =0.0%					
Test for overall effect: Z = 5.90 (P < 0.00001)					
Total (95% CI)	**3103**	**3934**	◆	**100.0 %**	**1.39 [1.24, 1.55]**
Total events: 575 (NRT), 482 (Control)					
Heterogeneity: Chi² = 14.16, df = 12 (P = 0.29); I² =15%					
Test for overall effect: Z = 5.78 (P < 0.00001)					
Test for subgroup differences: Chi² = 8.43, df = 3 (P = 0.04), I² =64%					

Analysis 4.5. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 5 Community volunteer (treatment provided in 'over-the-counter' setting).

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 5 Community volunteer (treatment provided in 'over-the-counter' setting)

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 Nicotine gum					
Shiffman 2009 (2 mg)	24/819	9/817		1.7 %	2.66 [1.24, 5.69]
Shiffman 2009 (4 mg)	101/830	24/831		4.4 %	4.21 [2.73, 6.51]
Subtotal (95% CI)	**1649**	**1648**	◆	**6.1 %**	**3.79 [2.60, 5.52]**
Total events: 125 (NRT), 33 (Control)					
Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² =6%					
Test for overall effect: Z = 6.95 (P < 0.00001)					
2 Nicotine patch					
Cunningham 2016	14/500	5/499		0.9 %	2.79 [1.01, 7.70]
Davidson 1998	33/401	16/401		2.9 %	2.06 [1.15, 3.69]
Hays 1999	62/636	14/322		3.4 %	2.24 [1.28, 3.94]
Scherphof 2014	6/136	8/129		1.5 %	0.71 [0.25, 1.99]

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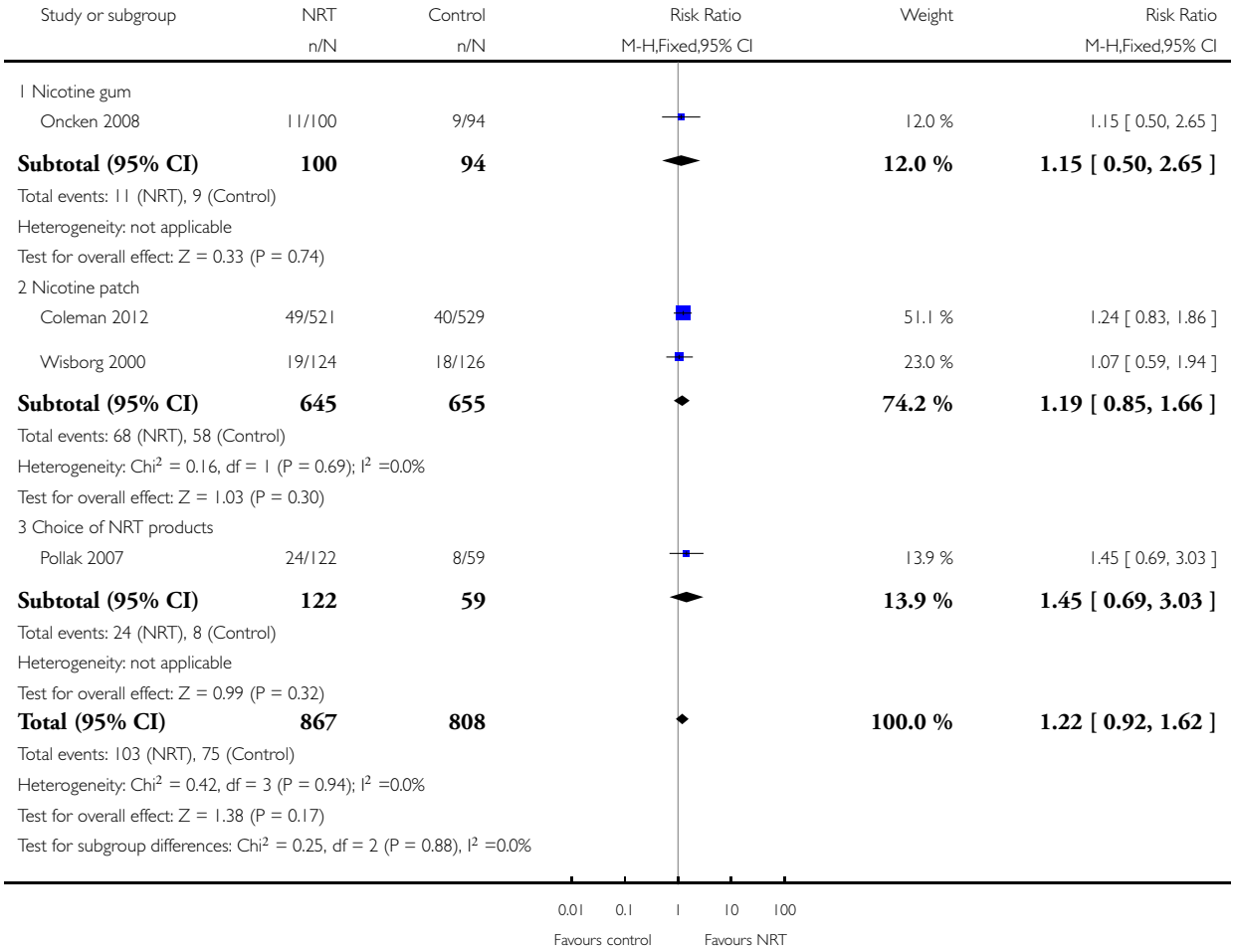
Study or subgroup	NRT n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
S nderskov 1997	20/251	14/267		2.5 %	1.52 [0.78, 2.94]
Subtotal (95% CI)	**1924**	**1618**		**11.3 %**	**1.88 [1.38, 2.55]**
Total events: 135 (NRT), 57 (Control)					
Heterogeneity: Chi^2 = 4.87, df = 4 (P = 0.30); I^2 =18%					
Test for overall effect: Z = 4.00 (P = 0.000062)					
3 Tablets/lozenges					
Fraser 2014	151/518	139/516		25.6 %	1.08 [0.89, 1.32]
Subtotal (95% CI)	**518**	**516**		**25.6 %**	**1.08 [0.89, 1.32]**
Total events: 151 (NRT), 139 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.79 (P = 0.43)					
4 Choice of product					
Graham 2017	366/2630	312/2660		57.0 %	1.19 [1.03, 1.37]
Subtotal (95% CI)	**2630**	**2660**		**57.0 %**	**1.19 [1.03, 1.37]**
Total events: 366 (NRT), 312 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.38 (P = 0.018)					
Total (95% CI)	**6721**	**6442**		**100.0 %**	**1.40 [1.26, 1.55]**
Total events: 777 (NRT), 541 (Control)					
Heterogeneity: Chi^2 = 47.15, df = 8 (P<0.00001); I^2 =83%					
Test for overall effect: Z = 6.38 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 41.41, df = 3 (P = 0.00), I^2 =93%					

Analysis 4.6. Comparison 4 Subgroup: Recruitment/treatment setting, Outcome 6 Antenatal clinic.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 4 Subgroup: Recruitment/treatment setting

Outcome: 6 Antenatal clinic

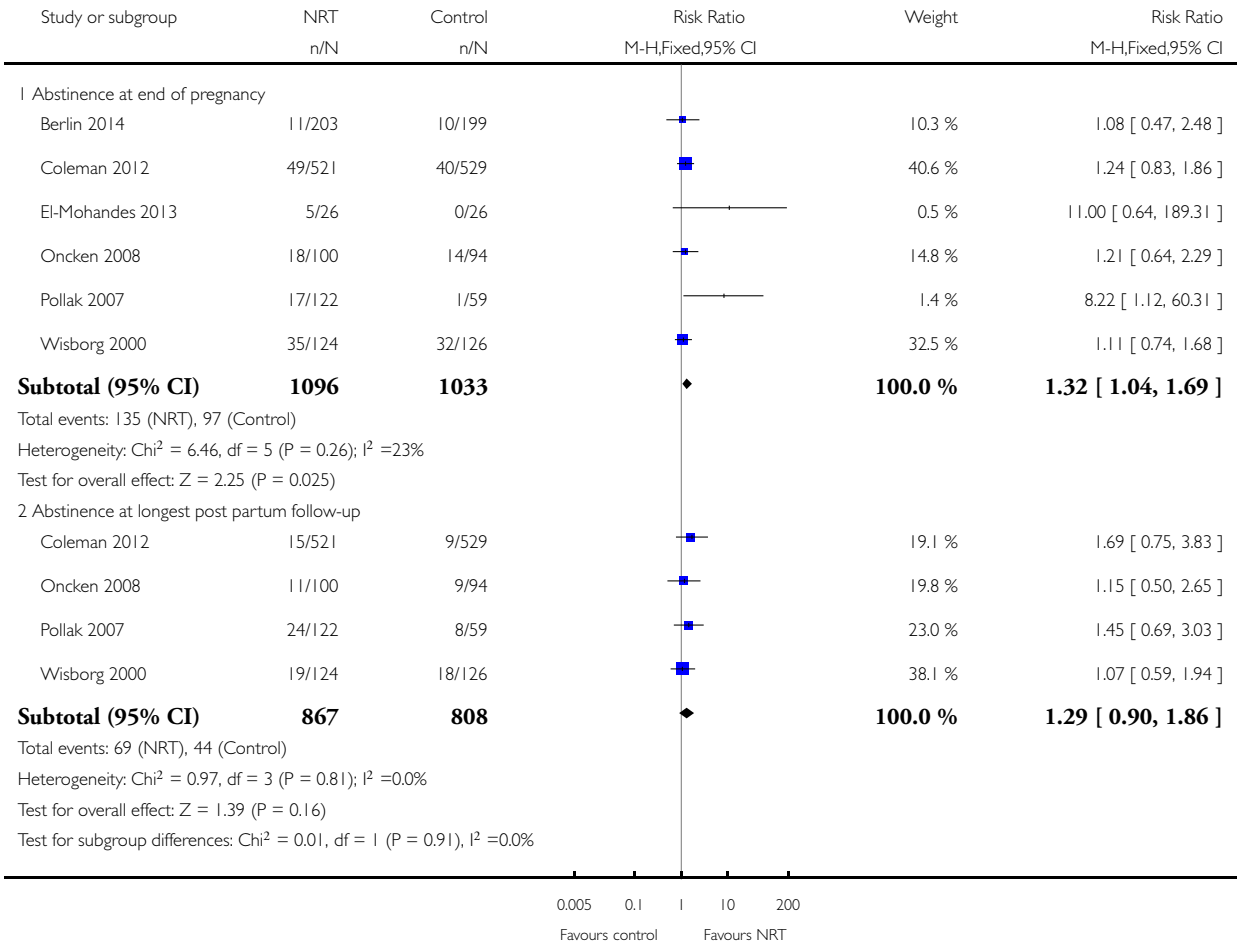


Analysis 5.1. Comparison 5 NRT in pregnancy, Outcome 1 Smoking cessation.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 5 NRT in pregnancy

Outcome: 1 Smoking cessation



Analysis 6.1. Comparison 6 Palpitations in NRT vs placebo users, Outcome 1 Palpitations/chest pains.

Review: Nicotine replacement therapy versus control for smoking cessation

Comparison: 6 Palpitations in NRT vs placebo users

Outcome: 1 Palpitations/chest pains

Study or subgroup	NRT n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Bolliger 2000b	1/200	2/200		3.2 %	0.50 [0.04, 5.53]
Brantmark 1973b	3/46	4/42		6.3 %	0.66 [0.14, 3.15]
Bullen 2010	9/249	1/246		1.6 %	9.19 [1.16, 73.07]
CEASE 1999	69/2861	6/714		15.2 %	2.92 [1.26, 6.74]
Gourlay 1995	5/179	3/143		5.3 %	1.34 [0.32, 5.71]
Hays 1999	5/321	2/322		3.2 %	2.53 [0.49, 13.15]
Hjalmarson 1994	9/116	2/107		3.1 %	4.42 [0.93, 20.92]
Oncken 2007	1/57	1/95		1.2 %	1.68 [0.10, 27.37]
Schneider 1995	23/128	10/127		13.4 %	2.56 [1.17, 5.63]
Schnoll 2010	0/182	2/134		4.7 %	0.15 [0.01, 3.05]
Shiffman 2009 (4 mg)	6/1649	6/1648		9.7 %	1.00 [0.32, 3.11]
Sutherland 1992	26/111	15/103		19.4 %	1.79 [0.89, 3.62]
S nderskov 1997	1/255	4/267		6.3 %	0.26 [0.03, 2.33]
T nnesen 1988	1/114	0/47		1.1 %	1.26 [0.05, 31.38]
Wennike 2003b	6/205	4/206		6.3 %	1.52 [0.42, 5.48]
Total (95% CI)	**6673**	**4401**		**100.0 %**	**1.88 [1.37, 2.57]**

Total events: 165 (NRT), 62 (Placebo)

Heterogeneity: Chi^2 = 15.50, df = 14 (P = 0.35); I^2 =10%

Test for overall effect: Z = 3.93 (P = 0.000084)

Test for subgroup differences: Not applicable

ADDITIONAL TABLES

Table 1. Nicotine replacement therapies available in the UK

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

Information extracted from British National Formulary
* 35 mg/24-hour and 53.5 mg/24-hour patches available in other regions.

APPENDICES

Appendix 1. Specialized Register search strategy

#1 NRT: TI,AB,KY,XKY,MH,EMT
#2 (nicotine NEAR2 patch*):TI,AB,KY,XKY,MH,EMT
#3 (nicotine NEAR2 gum):TI,AB,KY,XKY,MH,EMT
#4 (nicotine NEAR2 nasal spray):TI,AB,KY,XKY,MH,EMT
#5 (nicotine NEAR2 lozenge*):TI,AB,KY,XKY,MH,EMT
#6 (nicotine NEAR2 tablet*):TI,AB,KY,XKY,MH,EMT
#7 (nicotine NEAR2 sublingual):TI,AB,KY,XKY,MH,EMT
#8 (nicotine NEAR2 inhal*):TI,AB,KY,XKY,MH,EMT
#9 (nicotine NEAR2 replacement):TI,AB,KY,XKY,MH,EMT
#10 (nicotine NEAR3 therap*):TI,AB,KY,XKY,MH,EMT
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
The specialised register was transferred from Reference Manager to the CRS in May 2012. This is the search used for the CRS: KY, XKY, MH & EMT are keyword fields.

Appendix 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

(*Continued*)

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

(*Continued*)

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
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 adverse events
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

Appendix 3. Main adverse events by study

Adverse Event	*RCTs* ***P = patch, G = gum, S = spray, I = inhalator, L = lozenge, T = tablet.*** ***EX = excluded study***	*Active n events*	*Active total*	*Control n events*	*Control total*	*Notes*
Headache	Anthenelli 2016 (P)	233	2022	199	2014	Totals are numbers assessed for adverse events
	Areechon 1988 (G)	1	98	0	101	-
	Berlin 2014 (P)	12	203	9	199	-
	Blondal 1989 (G)	14	92	14	92	From %
	Coleman 2012 (P)	25	521	16	529	Pregnant women

(*Continued*)

	Daughton 1991 (P) 24 h 16 h	8 3	51 55	5	52	-
	Gourlay 1995 (P)	8	315	13	314	-
	Harackiewicz 1988 (G)	6	99	8	85	First 6 weeks
	Hays 1999 (P)	24	321	24	322	Excludes pay group
	Hjalmarson 1994 (S)	27	116	18	107	First 2 weeks
	Hurt 1994 (P)	14	120	21	120	-
	Jarvis 1982 (G)	14	47	17	44	-
	Jorenby 1999 (P)	69 63	243 244	52	159	P vs placebo P + B vs placebo
	Lerman 2015 (P)	139	418	169	408	Number of events summed over time, not number of people
	Lewis 1998 (P)	1	62	1	62	-
	Llivina 1988 (G)	11	113	8	101	From %
	Paoletti 1996 (P)	19	147 (LC15 + HC25)	15	150 (LCP + HC15)	Active vs placebo (Pl + Pl or lowA+Pl)
	Puska 1979 (G)	20	80	14	74	From %; missing data removed from denominator
	Sachs 1993 (P)	7	113	5	107	-
	Schneider 1995 (S)	41	128	32	127	From %

(*Continued*)

	Shiffman 2002 (2 mg) (L) Shiffman 2002 (4 mg) (L)	23 36	459 450	27 15	458 451	From %
	Stapleton 1995 (P)	84	761	30	364	-
	Stein 2013 (P)	10	104	6	33	-
	Sutherland 1992 (S)	49	111	41	103	-
	Tønnesen 1991 (P)	6	145	6	144	From %
	Ward 2013 (P)	< 5%	134	< 5%	135	-
	EX Batra 2005 (G)	43	184	52	180	-
	EX CEASE 1999 (P) 25 mg 15 mg	80 76	1430 1431	28	714	-
	EX Ebbert 2009 (L)	10	136	7	134	Smokeless (from %)
	EX Hanson 2003 (P)	27	50	34	50	adolescents
	EX Mulligan 1990 (P)	1	39	0	36	-
	EX Rigotti 2009 (P)	31	367	22	362	All were on rimonabant
	EX Schnoll 2010 (P)	0	182	2	134	At 12 weeks
	EX Stapleton 2011 (S)	320	506	154	255	-
Dizziness/lightheadedness	Ahluwalia 1998 (P)	0	174	1	168	-

(*Continued*)

	Anthenelli 2016 (P)	85	2022	66	2014	Totals are numbers assessed for adverse events
	Areechon 1988 (G)	2	98	0	101	-
	Berlin 2014 (P)	< 5%	203	< 5%	199	-
	Daughton 1991 (P) 24 h 16 h	7 4	51 55	6	52	-
	Gourlay 1995 (P)	5	315	4	314	-
	Harackiewicz 1988 (G)	9	99	12	85	First 6 weeks
	Hjalmarson 1994 (S)	24	116	16	107	First 2 weeks
	Hughes 1989a (G)	71	210	18	105	From %
	Jarvis 1982 (G)	15	47	11	44	
	Jorenby 1999 (P)	8 20	243 244	10	159	P vs placebo P + B vs placebo
	Lerman 2015 (P)	42	418	56	408	Number of events summed over time, not number of people
	Lewis 1998 (P)	0	62	1	62	-
	Puska 1979 (G)	16	80	16	74	From %;
	Sachs 1993 (P)	1	113	0	107	-
	Schneider 1995 (S)	61	128	69	127	From %
	Stapleton 1995 (P)	46	761	24	364	-

(*Continued*)

	Stein 2013 (P)	5	104	1	33	-
	Sutherland 1992 (S)	61	111	50	103	-
	Tønnesen 1991 (P)	6	145	0	144	From %
	Ward 2013 (P)	<5%	134	<5%	135	-
	EX Hanson 2003 (P)	20	50	22	50	adolescents
	EX Mulligan 1990 (P)	1	39	0	36	-
	EX Oncken 2009 (P, S)	P3 S0	7 7	3	7	Pregnant women
	EX Rigotti 2009 (P)	25	367	16	362	All were on rimonabant
	EX Schnoll 2010 (P)	2	182	1	134	At 12 weeks
	EX Stapleton 2011 (S)	308	506	139	255	-
Nausea/ vomiting	Ahluwalia 1998 (P)	1	174	3	168	-
	Anthenelli 2016 (P) Nausea	199	2022	137	2014	Totals are numbers assessed for adverse events
	Areechon 1988 (G)	2	98	2	101	-
	EX Batra 2005 (G)	19	184	11	180	-
	Berlin 2014 (P) Nausea Vomiting Total	4 5 9	203	3 8 11	199	-

(*Continued*)

	Campbell 1996 (P)	14	115	4	119	-
	Coleman 2012 (P)	16	521	19	529	Pregnant women
	Dautzenberg 2001 (L)	7	214	11	222	-
	Garvey 2000 (G)	11	209	1	69	(2 mg + 4 mg) %
	Glover 2002 (T)	14	120	3	121	-
	Gourlay 1995 (P)	10	315	7	314	-
	Harackiewicz 1988 (G)	17	99	6	85	First 6 weeks
	Hays 1999 (P)	19	321	16	322	Excludes pay group
	Heydari 2012 (P) Nausea	0	92	0	91	-
	Hjalmarson 1994 (S)	16	116	7	107	First 2 weeks
	Hughes 1989a (G)	69	210	18	105	From %
	Hurt 1994 (P)	6	120	3	120	-
	Jarvis 1982 (G)	20	47	9	44	-
	Jorenby 1999 (P) P P + B	19 28	243 244	8	159	-
	Lerman 2015 (P) nausea vomiting	88 10	418	111 16	408	Number of events summed over time, not number of people
	Lewis 1998 (P)	4	62	3	62	P + counselling vs Pl + counselling

(*Continued*)

	Richmond 1994 (P)	9	156	2	157	From %
	Sachs 1993 (P)	4	113	10	107	-
	Schneider 1995 (S)	24	128	11	127	From %
	Schneider 1996 (I)	14	112	13	111	-
	Shiffman 2002 (2 mg) (L) Shiffman 2002 (4 mg) (L)	56 68	459 450	22 24	458 451	From %
	Stapleton 1995 (P) (= Russell 1993)	34	761	12	364	-
	Stein 2013 (P) Nausea	9	104	2	33	-
	Sutherland 1992 (S)	26	111	20	103	-
	Tønnesen 1988 (G) 2 mg 4 mg	1 0	87 27	0	47	-
	Tønnesen 1991 (P)	6	145	1	144	From %
	Tønnesen 1993 (I)	1	145	1	141	severe
	Wallstrom 2000 (T)	30	123	9	124	From %
	Ward 2013 (P)	< 5%	134	< 5%	135	-
	EX Bolliger 2000a (I)	9	200	8	200	-
	EX CEASE 1999 (P) 25 mg 15 mg	104 77	1430 1431	26	714	-

(*Continued*)

	EX McRobbie 2010 (L,G,S)	L17 G15 S16	45 45 45	2	47	-
	EX Rennard 2006 (I)	11	215	5	214	-
	EX Rigotti 2009 (P)	54	367	36	362	All were on rimonabant
	EX Roddy 2006 (P)	2	49	3	49	"Dizziness, nausea or headache"
	EX Schnoll 2010 (P)	1	182	1	134	At 12 weeks (i.e. 4 weeks on placebo or patch)
	EX Stapleton 2011 (S)	336	506	168	255	-
	EX Tsukahara 2010 (P)	4	16	0	16	V vs Gum, no placebo
Gastro-intestinal symptoms	Berlin 2014 (P) Reflux Pyrosis Total	8 4 12	203	5 4 9	199	-
	Campbell 1991 (G)	3	107	7	103	From %
	Daughton 1991 (P) 24 h 16 h	1 4	51 55	0	52	-
	Dautzenberg 2001 (L)	2	214	8	222	-
	Glover 2002 (T)	11	120	6	121	-
	Harackiewicz 1988 (G)	23	99	8	85	First 6 weeks
	Hjalmarson 1984 (G)	25	92	11	91	-

(*Continued*)

	Hurt 1994 (P)	4	120	6	120	-
	Hughes 1989a (G)	65	210	18	105	-
	Jarvis 1982 (G)	24	47	12	44	-
	Joseph 1996 (P)	5	294	6	290	-
	Lerman 2015 (P) Gas Abdominal pain Constipation Diarrhoea Flatulence Indigestion	199 53 100 54 154 81	418	211 41 111 77 159 92	408	Number of events summed over time, not number of people
	Lewis 1998 (P)	1	62	2	62	-
	Llivina 1988 (G)	11	113	6	101	From %
	Paoletti 1996 (P)	16	147 (LC15+HC25)	11	150 (LCP+HC15)	(Pl+Pl or lowA+Pl)
	Puska 1979 (G)	12	80	13	74	From %
	Sachs 1993 (P)	2	113	4	107	-
	Shiffman 2002 (2 mg) (L) Shiffman 2002 (4 mg) (L)	16 24	459 450	10 17	458 451	From %
	Shiffman 2009 (2 mg) (G) Shiffman 2009 (4 mg) (G)	213 216	819 830	118 120	817 831	From %
	Schneider 1996 (I)	16	112	11	111	-
	Sønderskov 1997 (P)	7	255	9	267	First 4 wks
	Stein 2013 (P) Diarrhoea	0	104	1	33	-

(*Continued*)

	Tønnesen 1988 (G) 2 mg 4 mg	11 4	87 27	5	47	-
	Wallstrom 2000 (T)	22	123	11	124	From %
	Ward 2013 (P)	< 5%	134	< 5%	135	-
	EX Batra 2005 (G)	12	184	5	180	-
	Bullen 2010 (P, G) serious non-serious	24 19	249 249	12 26	246 249	-
	EX Ebbert 2010 (L)	3	30	0	30	Smokeless (from %)
	EX Ebbert 2009 (L)	15	136	1	134	Smokeless (from %)
	EX Molander 2000 (T)	1	20	1	20	-
	EX Mulligan 1990 (P)	3	39	0	36	-
	EX Oncken 2009 (P, S)	P3 S0	7 7	1	7	Pregnant women
	EX Tsukahara 2010 (P)	14	16	1	16	V vs Gum, no placebo
Sleep/dream problems	Ahluwalia 1998 (P)	0	174	0	168	In first week
	Anthenelli 2016 (P) Insomnia Initial insomnia Sleep disorder Nightmare	195 20 45 56	2022	139 6 42 17	2014	Totals are numbers assessed for adverse events
	Berlin 2014 (P)	7	203	5	199	-

(*Continued*)

	Dautzenberg 2001 (L)	2	214	3	222	-
	Gourlay 1995 (P)	43	315	19	314	-
	Hays 1999 (P)	30	321	20	322	Excludes pay group
	Heydari 2012 (P) Abnormal dreams	0	92	0	91	-
	Hurt 1994 (P)	9	120	5	120	-
	ICRF 1994 (P) Mild Moderate Severe	45 95 32	842	10 40 13	844	-
	Jorenby 1999 (P) P P+B	73 116	243 244	31	159	-
	Joseph 1996 (P)	10	294	6	290	-
	Lerman 2015 (P) Sleep Abnormal dreams	203 182	418	190 132	408	Number of events summed over time, not number of people
	Llivina 1988 (G)	7	113	10	101	From %
	Oncken 2007 (P)	5	57	2	95	-
	Paoletti 1996 (P)	19	147 (LC15+HC25)	36	150 (LCP+HC15)	(Pl+Pl or lowA+Pl)
	Perng 1998 (P)	2	30	0	32	-
	Puska 1979 (G)	26	80	20	74	From %;
	Richmond 1994 (P)	41	156	25	157	From %
	Sachs 1993 (P)	4	113	5	107	-

(*Continued*)

	Stein 2013 (P) Insomnia/sleep problems/ awakening Dreaming or nightmares	38 19	104	12 8	33	-
	Ward 2013 (P)	11	134	14	135	-
	EX CEASE 1999 (P) 25 mg 15 mg	70 77	1430 1431	42	714	-
	EX Ebbert 2009 (L)	15	136	1	134	Smokeless (from %)
	EX Ebbert 2010 (L)	0	30	3	30	Smokeless (from %)
	EX Hanson 2003 (P)	30	50	23	50	Adolescents
	EX Mulligan 1990 (P)	2	39	0	36	-
	EX Rigotti 2009 (P)	35	367	11	362	All were on rimonabant
	EX Schnoll 2010 (P)	2	182	6	134	At12 weeks
	EX Tsukahara 2010 (P)	6	16	2	16	V vs Gum
CV (palpitations, chest pain)	Berlin 2014 (P) palpitations CV other	< 5% < 5%	203	< 5% < 5%	199	-
	Gourlay 1995 (P)	5	179	3	143	-
	Hays 1999 (P)	5	321	2	322	Excludes pay group
	Hjalmarson 1994 (S)	9	116	2	107	First 2 weeks

(*Continued*)

	Lerman 2015 (P) Chest pain Palpitations Irregular heartbeat	18 35 11	418	26 50 19	408	Number of events summed over time, not number of people, therefore excluded from meta-analysis 6.1
	Oncken 2007 (P)	1	57	1	95	-
	Schneider 1995 (S)	23	128	10	127	From %
	Shiffman 2009 (2 mg) (G) Shiffman 2009 (4 mg) (G)	3 3	819 830	3 3	817 831	From %
	Sønderskov 1997 (P) "cardiac"	1	255	4	267	First 4 weeks
	Sutherland 1992 (S)	26	111	15	103	-
	Tønnesen 1988 (G) 2 mg 4 mg	0 1	87 27	0	47	-
	Ward 2013 (P) Palpitations CV other	< 5% < 5%	134	< 5% < 5%	135	-
	EX Bolliger 2000a (I)	1	200	2	200	-
	EX Brantmark 1973a (G)	3	46	4	42	-
	EX Bullen 2010 (P,G)	9	249	1	246	-
	EX CEASE 1999 (P) 25 mg 15 mg	32 37	1430 1431	6	714	-

(*Continued*)

	EX Schnoll 2010 (P)	0	182	2	134	At12 weeks (i. e. 4 weeks on placebo or patch)
	EX Wennike 2003a (G)	6	205	4	206	-
Wisborg 2000 states 5 women had palpitations, but no distribution info						
Skin reactions	Abelin 1989 (P)	12	156	1	155	Combined studies
	Ahluwalia 1998 (P)	8	174	5	168	-
	Anthenelli 2016 (P)	109	2022	16	2014	Totals are numbers assessed for adverse events
	Berlin 2014 (P)	23	203	8	199	-
	Buchkremer 1988 (P)	6	42	6	43	From %
	Campbell 1996 (P)	54	115	40	119	-
	Coleman 2012 (P)	97	521	28	529	Pregnant women
	Daughton 1991 (P)	1 3	51 (24 h) 55 (16 h)	1	52	-
	Dautzenberg 2001	0	214	2	222	-
	Davidson 1998 (P)	100	401	52	401	From %
	Gourlay 1995 (P)	44	315	27	314	-
	Hays 1999 (P)	124	321	48	322	Excludes pay group
	Hurt 1990 (P)	19	31	10	31	Over 6 weeks

(*Continued*)

	Hurt 1994 Mild Moderate Severe	68 5 1	120	24 3 0	120	-
	ICRF 1994 (P) Mild Moderate Severe	18 75 40	842	8 26 9	844	-
	Jorenby 1999 (P) P P+B	45 37	243 244	11	159	-
	Joseph 1996 (P)	6	294	3	290	-
	Kornitzer 1995 (P,G)	9 7	149 150	1	75	P+G vs Pl P+PlG vs Pl
	Lerman 2015 (P) Redness Swelling/rash	68 48	418	32 44	408	Number of events summed over time, not number of people
	Lewis 1998 (P)	16	62	11	62	-
	Oncken 2007 (P)	8	57	2	95	-
	Paoletti 1996 (P)	59	147 (LC15+HC25)	30	150 (LCP+HC15)	Active vs placebo (Pl+Pl or lowA+Pl)
	Perng 1998 (P)	7	30	5	32	-
	Richmond 1994 (P)	36	156	19	157	From %
	Sønderskov 1997 (P)	75	255	49	267	First 4 weeks
	Stapleton 1995 (P)	108	761	18	364	-

(*Continued*)

	Stein 2013 (P) Flushing or sweating	30	104	11	33	-
	Ward 2013 (P)	12	134	16	135	-
	EX Bullen 2010 (P,G)	6 5	249 249	8 3	246 246	Skin SAEs
	EX CEASE 1999 (P) 25 mg 15 mg	206 185	1430 1431	36	714	-
	EX Hanson 2003 (P)	31	50	24	50	adolescents
	EX Levin 1994 (P)	24	31	21	31	-
	EX Mulligan 1990 (P)	10	39	10	36	-
	EX Oncken 2009 (P, S)	P3 S0	7 7	0	7	Pregnant women
	EX Roddy 2006 (P)	16	49	7	49	-
	EX Rose 1990 (P) mod. severe	12 4	33	0 0	32	From %
	Ex Schnoll 2010 (P)	1	182	1	134	@12wks
	EX Tsukahara 2010 (P)	0	16	9	16	V vs Gum, no placebo
Oral/nasal reactions	Areechon 1988 (G)	1	98	2	101	-
	Berlin 2014 (P)	< 5%	203	< 5%	199	-
	Campbell 1991 (G)	9	107	6	105	From %

(*Continued*)

	Dautzenberg 2001 (L)	5	214	0	222	-
	Garvey 2000 (G)	2	209	0	69	(2 mg + 4 mg)
	Glover 2002 (T)	24	120	23	121	Weeks 1 to 2
	Harackiewicz 1988 (G)	34	99	1	85	First 6 wks
	Hjalmarson 1984 (P)	24	92	14	91	-
	Hjalmarson 1994 (S)	85	116	40	107	First 2 wks
	Hughes 1989a (G)	160	210	56	105	From %
	Jarvis 1982 (G)	28	47	23	44	-
	Jorenby 1999 (P) P P+B	16 25	243 244	10	159	-
	Lerman 2015 (P)	173	418	160	408	Number of events summed over time, not number of people
	Llivina 1988 (G)	13	113	4	101	From %
	Perng 1998 (P)	4	30	0	32	-
	Schneider 1995 (S)	125	128	65	127	From %
	Schneider 1996 (I)	47	112	26	111	-
	Shiffman 2002 (2 mg) (L) Shiffman 2002 (4 mg) (L)	12 23	459 450	12 18	458 451	From %

(*Continued*)

	Stein 2013 (P) Dry mouth Change in taste	17 14	104	4 1	33	-
	Sutherland 1992 (S)	105	111	67	103	-
	Tønnesen 1988 (G) 2 mg 4 mg	20 8	87 27	11	47	-
	Tønnesen 1993 (I)	72	145	24	141	From %
	Wallstrom 2000 (T)	66	123	62	124	From %
	Ward 2013 (P)	< 5%	134	< 5%	135	-
	EX Adelman 2009 (S)	7	20	0	20	Open-label, no spray for controls
	EX Batra 2005 (G)	8	184	33	180	-
	EX Bolliger 2000a (I)	14	200	4	200	-
	EX Brantmark 1973a (G)	6	46	3	42	-
	EX McRobbie 2010 (L,G,S)	L8 G6 S16	45 45 45	2	47	-
	EX Molander 2000 (T)	5	20	0	20	-
	EX Oncken 2009 (P, S)	P1 S2	7 7	0	7	Pregnant women
	EX Rigotti 2009 (P)	23	367	24	362	All were on rimonabant
	EX Stapleton 2011 (S)	194	506	135	255	-

(*Continued*)

Hiccups	Berlin 2014 (P)	< 5%	203	< 5%	199	-
	Blondal 1989 (G)	13	90	0	92	-
	Glover 2002 (T)	18	120	1	121	-
	Harackiewicz 1988 (G)	8	99	1	85	First 6 weeks
	Hjalmarson 1984 (P)	7	92	0	91	-
	Hughes 1989a (G)	103	210	22	105	From %
	Jarvis 1982 (G)	14	47	2	44	-
	Schneider 1996 (I)	3	112	0	111	-
	Shiffman 2002 (2 mg) (L) Shiffman 2002 (4 mg) (L)	16 38	459 450	0 0	458 451	From %
	Tønnesen 1988 (G) 2 mg 4 mg	2 4	87 27	0	47	-
	Wallstrom 2000 (T)	14	123	0	124	From %
	Ward 2013 (P)	< 5%	134	< 5%	135	-
	EX Batra 2005 (G)	28	184	3	180	-
	EX Brantmark 1973a (G)	11	46	2	42	-
	EX McRobbie 2010 (L,G,S)	L17 G15 S16	45 45 45	2	47	-
	EX Molander 2000 (T)	1	20	0	20	-

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: 1 November 2017.

Date	Event	Description
4 September 2018	Amended	CENTRAL search date corrected

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 2, 1996

Date	Event	Description
8 November 2017	New citation required but conclusions have not changed	No changes to conclusions for NRT versus control (other comparisons moved elsewhere). Review marked as stable. Changes to authorship
8 November 2017	New search has been performed	Searches updated, 18 new studies added. Review split into NRT versus control and NRT versus NRT
19 September 2012	New citation required but conclusions have not changed	Additional author. No major changes to conclusions.
19 September 2012	New search has been performed	Searches updated, 18 new studies added. Table of adverse events added
22 June 2011	Amended	Additional table converted to appendix to correct pdf format
16 April 2008	Amended	Converted to new review format.
1 November 2007	New citation required and conclusions have changed	New studies added, some comparisons reorganised, effect measure changed from odds ratio to risk ratio. Minor changes made to the conclusions about the evidence for combinations of NRT types. Authors changed
7 April 2004	New citation required and minor changes	Twelve new studies added, no changes to main conclusions.

CONTRIBUTIONS OF AUTHORS

For the most recent version of this review: JHB and SC screened studies. Data extraction and risk of bias assessment was conducted by SC, WY and JHB. The review text was updated by JHB, SC and WY with review and suggestions from all other authors.

DECLARATIONS OF INTEREST

CB was involved in a trial on pre-cessation use of NRT (Bullen 2010)

SCC none known

JHB none known

TL none known

WY none known

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NOTES

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

INDEX TERMS

Medical Subject Headings (MeSH)

*Tobacco Use Cessation Products; Administration, Cutaneous; Administration, Inhalation; Chewing Gum; Nicotine [administration & dosage]; Nicotinic Agonists [administration & dosage]; Randomized Controlled Trials as Topic; Smoking Cessation [*methods; statistics & numerical data]; Smoking Prevention [*methods; statistics & numerical data]; Tablets; Time Factors

MeSH check words

Female; Humans; Male