

# Nicotine replacement therapy for smoking cessation (Review)

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## ABSTRACT

### Background

The aim of nicotine replacement therapy (NRT) is to replace nicotine from cigarettes. This reduces withdrawal symptoms associated with smoking cessation thus helping resist the urge to smoke cigarettes.

### Objectives

The aims of this review were:

- to determine the effectiveness of the different forms of NRT (chewing gum, transdermal patches, nasal spray, inhalers and tablets) in achieving abstinence from cigarettes, or a sustained reduction in amount smoked;
- to determine whether the effect is influenced by the clinical setting in which the smoker is recruited and treated, the dosage and form of the NRT used, or the intensity of additional advice and support offered to the smoker;
- to determine whether combinations of NRT are more effective than one type alone;
- to determine its effectiveness compared to other pharmacotherapies.

### Search strategy

We searched the Cochrane Tobacco Addiction Group trials register in March 2004.

### Selection criteria

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

### Data collection and analysis

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

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

### Main results

We identified 123 trials; 103 contributing to the primary comparison between NRT and a placebo or non-NRT control group.

The odds ratio (OR) for abstinence with NRT compared to control was 1.77 (95% confidence intervals (CI): 1.66 to 1.88). The ORs for the different forms of NRT were 1.66 (95% CI: 1.52 to 1.81) for gum, 1.81 (95% CI: 1.63 to 2.02) for patches, 2.35 (95% CI: 1.63 to 3.38) for nasal spray, 2.14 (95% CI: 1.44 to 3.18) for inhaled nicotine and 2.05 (95% CI: 1.62 to 2.59) for nicotine sublingual tablet/lozenge. These odds were largely independent of the duration of therapy, the intensity of additional support provided or the setting in which the NRT was offered. In highly dependent smokers there was a significant benefit of 4 mg gum compared with 2 mg gum (OR 2.20, 95% CI: 1.85 to 3.25). There was weak evidence that combinations of forms of NRT are more effective. Higher doses

of nicotine patch may produce small increases in quit rates. Only one study directly compared NRT to another pharmacotherapy. In this study quit rates with bupropion were higher than with nicotine patch or placebo.

### Authors' conclusions

All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) are effective as part of a strategy to promote smoking cessation. They increase the odds of quitting approximately 1.5 to 2 fold regardless of setting.

The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the smoker. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.

## PLAIN LANGUAGE SUMMARY

All forms of nicotine replacement therapy (NRT) can help people quit smoking, almost doubling long term success rates

NRT aims to reduce withdrawal symptoms associated with stopping smoking by replacing nicotine in the blood. NRT is available as chewing gum, patches for the skin, nose spray, inhalers, and tablets. The review of trials found that all these forms of NRT made it more likely that a person's attempt to quit smoking would succeed. There is no evidence that one form of NRT is better than any other. NRT works with or without additional counselling.

## BACKGROUND

Nicotine replacement therapy (NRT) is frequently used as a component of smoking cessation strategies. It reduces many of the physiological and psychomotor withdrawal symptoms usually experienced following smoking cessation and may therefore increase the likelihood of remaining abstinent (Gourlay 1990).

The first type of NRT to become widely available was chewing gum. The nicotine resin complex is presented in a buffered chewing gum base to enable the nicotine to be absorbed directly through the buccal mucosa, resulting in plasma concentrations which are approximately half that produced by smoking a cigarette (Russell 1976). Nicotine chewing gum is available either as a 2 mg or 4 mg preparation, and in many countries the lower dose is sold 'over the counter' (OTC), without a prescription from a medical practitioner. Several factors limit the usefulness of nicotine chewing gum in some smokers, including oral and gastric side effects (Henningfield 1990), impaired absorption when taken with coffee or acidic beverages (Hughes 1986), inadequate dosing, and a risk that some smokers may transfer their dependence from cigarettes to the gum (Hughes 1986).

Other forms of NRT that aim to avoid some of the problems associated with nicotine gum have been developed, including transdermal nicotine patches, intranasal nicotine spray, and nicotine inhaler devices. Transdermal patches are now widely available. Nasal spray, inhaler, lozenges and tablets of nicotine are also licensed for use in a number of countries, and other formulations are being developed (D'Orlando 2004; Park 2002).

Transdermal patches are available in several different sizes, and deliver between 7 mg and 22 mg of nicotine over a 24-hour period, resulting in plasma levels similar to the trough levels seen in heavy smokers (Fiore 1992). Some brands of patch are designed to be worn for 24 hours, whilst others are intended to be worn for 16 hours, delivering a dose of 15 mg over that period.

The introduction of transdermal patches was accompanied by strong marketing campaigns in a number of countries, targeted both at smokers and physicians, encouraging use of the patch as a "proven and effective" smoking cessation strategy (Saul 1993). This has caused much debate about the role of NRT in smoking cessation, including which group(s) of smokers should be offered NRT, which preparations should be used, in what dose regimen, and whether NRT is effective when used alone or only together with some form of additional support strategy.

More recently, the observation that nicotine patches and gum do not provide 100% nicotine replacement (Dale 1995; Hurt 1993) has led to interest in increasing the efficacy of nicotine replacement by raising patch doses (Jorenby 1995), or by combining different forms of NRT, for example, patches and gum (Kornitzer 1995; Puska 1995), or nasal spray with patches (Blondal 1999). In addition, there is growing interest in comparing NRT to newer pharmacotherapies, particularly the antidepressant bupropion.

This review assesses the effectiveness of the different forms of NRT when offered to smokers who have varying levels of dependence and motivation to quit, in a range of clinical settings, and with or without additional support programs.

## OBJECTIVES

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

A second objective, added in 2001, is to determine the effectiveness of NRT in assisting long-term reduction in the amount smoked by smokers who are unwilling or unable to quit.

We wished to test the following hypotheses:

- The use of NRT is more effective than placebo or 'no NRT' intervention in promoting smoking cessation (Comparison 1);
- 4 mg nicotine gum is more effective than 2 mg nicotine gum (Comparison 2), and fixed dose schedules are more effective than ad lib use (Comparison 13);
- The provision of high-intensity support, in addition to the use of NRT, is more effective in producing abstinence than addition of low-intensity support programs (Comparison 3);
- The effectiveness of the nicotine patch is greater with longer duration of use (Comparison 4), with weaning rather than abrupt withdrawal (Comparison 5), and with 24-hour patches rather than with 16-hour patches (Comparison 6);
- NRT is more effective when offered to smokers who are motivated to quit, and will therefore be more effective in clinical settings that selectively recruit motivated smokers (Comparison 7);
- Increasing the delivery of nicotine replacement by raising the dose of nicotine patch therapy (Comparison 8) or combining different forms of NRT (Comparison 9) is more effective than conventional dose monotherapy;
- NRT is effective in smokers who have relapsed after previous NRT use (Comparison 10);
- NRT is more effective than the antidepressant bupropion for smoking cessation (Comparison 11);
- NRT is more effective than placebo for achieving long term reduction in number of cigarettes smoked for people who cannot quit (Comparison 16).

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

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

### Types of participants

Smokers of either gender were included irrespective of the setting from which they were recruited and/or their initial level of nicotine dependence. Studies which randomized therapists, rather than smokers, to offer NRT or a control were included provided that the specific aim of the study was to examine the effect of NRT on smoking cessation. Trials that randomized physicians or other therapists to receive an educational intervention, which included encouraging their patients to use NRT, were not included but are reviewed separately (Lancaster 2000).

### Types of intervention

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

Trials of different doses of NRT were also included.

In some analyses we categorized the trials into two groups depending on the level of additional support provided (low or high). Low-intensity additional support was regarded as part of the provision of routine care. If the duration of time spent with the smoker (including assessment for the trial) exceeded 30 minutes at the initial consultation or the number of further assessment and reinforcement visits exceeded two, the level of additional support was categorized as high.

### Types of outcome measures

The review comprises a comparison of the effects of NRT versus control on smoking cessation, rather than withdrawal symptoms. Trials in which follow up was of short duration (less than six months) were excluded.

In each study the strictest available criteria to define abstinence were used. For example, in studies where biochemical validation of cessation was available, only those participants who met the criteria for biochemically confirmed abstinence were regarded as being abstinent. Wherever possible a sustained cessation rate, rather than point prevalence, was used. In trials where patients were lost to follow up they were regarded as being continuing smokers.

The review also includes trials which compared the effects of NRT versus placebo or other pharmacotherapies on achieving a sustained reduction in the number of cigarettes smoked or cessation amongst smokers not attempting to quit.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Tobacco Addiction Group methods used in reviews.

The specialized register of the Tobacco Addiction Group was searched for trials with any reference to the use of nicotine replacement therapy of any type in the title, abstract or keywords. The most recent issues of the databases included in the register as searched for the current update of this review are: the *Cochrane Central Register of Controlled Trials (CENTRAL)* (Cochrane Library) Issue 4, 2003, MEDLINE Express (SilverPlatter) 12/2003, MEDLINE (PubMed) Jan-March 2004, EMBASE 03/2004 (SilverPlatter), PsycLIT/PsycINFO (SilverPlatter) 03/2004, Science Citation Index 02/2004 (Web of Science). (Earlier versions of this review performed searches of additional databases; Cancerlit, Health Planning and Administration, Social Scisearch, Smoking & Health and Dissertation Abstracts. Since this search did not produce any additional trials these databases have not been used after December 1996. During preparation of the first version of this review letters were also sent to manufacturers of NRT preparations. Since this did not result in additional data the exercise was not repeated for subsequent updates.)

## METHODS OF THE REVIEW

Data were extracted from the published reports by two individuals independently. Disagreements were resolved by discussion or referral to a third party. No attempt was made to blind any of these individuals either to the results of the primary studies or which treatment subjects received. Reports published only in non-English language journals were examined with the assistance of translators.

Smoking cessation rates in the intervention and control groups were identified from the published reports at 6 or 12 months. Since not all studies reported cessation rates at exactly these intervals, we allowed a window period of six weeks at each follow-up point. For trials without 12-month follow up we have used six-month data in all analyses.

In trials of smoking reduction, sustained reduction was defined as a (self reported) 50% reduction in the number of cigarettes smoked per day at the evaluation point compared with the baseline.

The Fagerstrom score (0 - 11) was used to classify the level of nicotine dependence. Smokers with a Fagerstrom score of seven or more were classified as high nicotine dependence, while those with a score less than seven were classified as low nicotine dependence.

The outcome data extracted from each trial are expressed as odds ratios (ORs). Where cessation is the outcome this can be defined as (number of quitters in treatment group/number of smokers in treatment group)/(number of quitters in control group/number of smokers in control group). The OR will be greater than 1 if people have been more likely to quit in the treatment group. A pooled weighted average of ORs is estimated using a Mantel-Haenszel method, with 95% confidence intervals. This summary

statistic replaces the Peto method used in previous versions of this review, since the Mantel-Haenszel method is now recommended for Cochrane reviews (Deeks 2003). Differences in results using the two methods are small, and most likely to be apparent where numbers are unbalanced between groups, in which case the Peto method may give biased answers.

We also analyzed the odds of achieving abstinence with each type of NRT relative to control (either placebo or no intervention) in different clinical settings, and by the intensity of additional support offered. To investigate statistical heterogeneity we use the  $I^2$  statistic, given by the formula  $[(Q - df)/Q] \times 100\%$ , where  $Q$  is the chi squared statistic and  $df$  is its degrees of freedom (Higgins 2003). This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to indicate substantial heterogeneity.

In order to summarize the data from a clinical perspective we calculated the number of smokers who needed to be treated in order to produce one successful quitter at 12 months beyond that which would be achieved with the control intervention. This estimate was based on the inverse of the pooled typical event rate difference, calculated using the method described by Rothman (Rothman 1986).

## DESCRIPTION OF STUDIES

The review includes 123 studies. One hundred and three included a placebo or non-nicotine control arm, and used NRT to aid cessation to contribute to the primary analysis. In this group there were 52 trials of nicotine gum, 37 of transdermal nicotine patch, four of intranasal nicotine spray, four of inhaled nicotine, four of an oral tablet or lozenge, one offering a choice of products (Molyneux 2003) and one providing patch and inhaler, with a no placebo control (Hand 2002).

Six trials compared combinations of two forms of nicotine therapy with only one form; patch with gum to patch alone (Kornitzer 1995); patch with gum to gum alone (Puska 1995); patch with nasal spray to patch alone (Blondal 1999); patch with inhaler to inhaler alone (Bohadana 2000), patch with inhaler to either one alone (Tonnesen 2000) and patch with nasal spray to either one alone (Croghan 2003). In addition to these last two trials allowing a direct comparison between two single types, Patterson 2003 compared patch to nasal spray. A factorial trial compared nicotine and bupropion (Zyban) (Jorenby 1999).

With the exception of 12 gum trials, 15 patch trials and one lozenge trial, participants in the studies in the primary analysis were followed for at least 12 months. Sixteen of the gum trials and six of the patch trials were conducted in a primary care setting where smokers were usually recruited in response to a specific invitation from their doctor during a consultation. A further four gum tri-

als were undertaken in workplace clinics, and one in a university clinic. Since participants in these trials were recruited in a similar way to primary care, we aggregated them in analyses involving clinic setting. One patch trial conducted in a university clinic, one conducted in a worksite setting, one conducted in Veterans Affairs Medical Centers and recruiting patients with cardiac diseases (Joseph 1996) and one recruiting healthcare workers (Glavas 2003a) were also included in the primary care category. One trial in an antenatal clinic (Wisborg 2000) is kept in a separate category. Six of the gum trials, one of the nasal spray trials and one of the inhaler trials, were carried out in specialized smoking cessation clinics to which participants had usually been referred. Eight trials (three gum, four patch, one giving a choice of products and one giving a combination of products) were undertaken with hospital in- or out-patients, some of whom were recruited because they had a coexisting smoking-related illness. Recent interest has focused on use of NRT obtained 'over the counter' rather than from a medical care provider. Three trials have compared patch to placebo in this type of setting (Davidson 1998; Hays 1999; Sonderskov 1997). One of these also allowed a comparison between purchased and free patches with minimal support (Hays 1999). Two trials have compared purchased NRT without behavioural support to purchased NRT with brief physician support (using patch, Leischow 1999, using inhaler, Leischow 2003). The remaining gum, patch, inhaler and nasal spray trials were undertaken in participants from the community, most of whom had volunteered in response to media advertisements, but who were treated in clinical settings. One of the patch trials was conducted in relapsed smokers (Gourlay 1995).

Of the 52 trials comparing nicotine gum with placebo or no gum, 38 used the 2 mg dose, two used 4 mg only, and seven used a variable or mixed dosage. In the other trials the dose was not stated. Two trials compared a fixed dosage regimen with an ad lib regimen (Killen 1990; Goldstein 1989). The duration of therapy ranged from 3 weeks to 12 months. Many of the trials included a variable period of dose tapering, but most encouraged participants to be gum-free by 6 to 12 months. Five trials compared 2 mg and 4 mg gum (Garvey 2000; Herrera 1995; Hughes 1990; Kornitzer 1987; Tonnesen 1988).

Of the 37 trials comparing nicotine patch with placebo or no patch, 27 used the 24-hour preparations, nine used patches applied for 16 hours, and one trial (Daughton 1991) included comparison of groups wearing 16-hour or 24-hour patches or placebo. All but two (Cinciripini 1996; Wong 1999) of the patch trials compared active against placebo; one trial also included comparison against a no patch group (Buchkremer 1988). The minimum duration of therapy ranged from three weeks (Glavas 2003a, half the participants of Glavas 2003b) to three months, with a tapering period, if required, in 27 of the trials. Three trials directly compared two durations of therapy (Bolin 1999; CEASE 1999; Glavas 2003b). Six trials compared a higher dose to a standard dose patch (CEASE

1999; Dale 1995; Hughes 1999; Jorenby 1999; Killen 1999; Paoletti 1996).

Data are available from four completed trials of intranasal nicotine spray (Blondal 1997; Hjalmarson 1994; Schneider 1995; Sutherland 1992), and for four trials of inhaled nicotine (Hjalmarson 1997; Leischow 1996; Schneider 1996; Tonnesen 1993). One trial of a nicotine inhaler was excluded as follow up was for only three months (Glover 1992). Leischow refers to another study by different investigators which did not demonstrate any benefit of a nicotine inhaler. Four trials of nicotine sublingual tablets/lozenges are included, one of which has not yet been published in full (Dautzenberg 2001). Two used 2 mg sublingual tablets (Glover 2002, Wallstrom 2000). One used a 1 mg nicotine lozenge (Dautzenberg 2001) and one used 2 mg or 4 mg lozenges according to dependence level based on participants' time to first cigarette of the day (TTFC). The two groups are entered in the meta-analysis as separate trials; smokers whose TTFC was more than 30 minutes were randomized to 2 mg lozenges or placebo (Shiffman 2002a), whilst smokers with a TTFC less than 30 minutes had higher dose 4 mg lozenges or placebo (Shiffman 2002b).

One trial (Kornitzer 1987), conducted in a worksite setting, was confined to male smokers, and three recruited only women (Cooper 2003; Pirie 1992, Wisborg 2000). The remainder included smokers of both sexes. The range in the mean number of cigarettes smoked at entry into the trials, among the studies which provided this data, was 15.5 to 32.9.

In some analyses we categorized the trials into two groups depending on the level of additional support provided (low or high). Low-intensity additional support was regarded as part of the provision of routine care. If the duration of time spent with the smoker (including assessment for the trial) exceeded 30 minutes at the initial consultation or the number of further assessment and reinforcement visits exceeded two, the level of additional support was categorized as high. In some trials this level of support included group behaviour modification sessions.

One trial (Nebot 1992) randomized primary care physicians to offer nicotine gum or placebo to smokers. In all the other included trials the unit of randomization was the smoker.

Three trials compared NRT to placebo for helping smokers to reduce the number of cigarettes smoked (Bolliger 2000; Etter 2002; Wennike 2003). The first used an inhaler, the second a choice of products and the third gum, available for 6 to 12 months. The primary outcome was a reduction of 50% or more from baseline after six months (Etter 2002) or 24 months (Bolliger 2000; Wennike 2003). The number of quitters was also recorded.

One trial (Schuurmans 2004) tested the use of nicotine patch to placebo used for two weeks prior to the quit date. Following the quit date both study arms received active NRT.



## METHODOLOGICAL QUALITY

Thirty-five studies (28%) reported randomization procedures in sufficient detail to be rated A for their attempts to control selection bias. The majority of studies either did not report how randomization was performed or reported it in insufficient detail to determine whether a satisfactory attempt to control selection bias had been made (rated B). A small number of trials randomized to treatment according to day or week of clinic attendance (Page 1986; Richmond 1990; Russell 1983), birth date (Fagerstrom 1984), or smokers' clinic group (McGovern 1992) (rated C).

Definitions of abstinence varied considerably. Eighty-seven (71%) reported a measure of sustained abstinence, 31 (25%) reported only the point prevalence of abstinence at the longest follow up. In five studies it was unclear exactly how abstinence was defined.

All but 14 of the trials reported the use of some form of validation of self reported smoking cessation. Validation of abstinence was carried out by blinded methods (measurement of metabolites in body fluids) in 27 trials. Measurement of carbon monoxide (CO) in expired air was the most common form of validation used. However, the 'cut-off' level of CO used to define abstinence varied from less than 4 to 11 parts per million. In one trial participants who smoked up to three cigarettes per week were still classified as abstinent (Abelin 1989).

We did not assess whether trials reported an assessment of the integrity of the double-blind. A recent paper reports that few published trials report this information, but from these there is some evidence that participants are likely to assess their treatment assignment correctly (Mooney 2004). There was not enough evidence to assess whether this was associated with differences in treatment effects. If assessment of treatment assignment was influenced by success or failure in quitting it might be expected to be associated with outcome, and not necessarily be evidence of a methodological problem leading to bias (Altman 2004).

The quality of bias control did not differ significantly between trials of different forms of NRT.

Six trials are included based on data available from abstracts or conference presentations (Cooper 2003; Dautzenberg 2001; Kornitser 1999; Leischow 2003; Mori 1992; Nakamura 1990).

## RESULTS

The five forms of nicotine replacement therapy (NRT) were all significantly more effective than placebo, or no NRT, in helping smokers achieve abstinence. The benefit from using NRT was evident throughout the 6 to 12 month period of follow up despite the presence of a significant relapse rate with each type of preparation. Despite the range of variation in characteristics of trials included in this review, there was no statistical evidence of significant heterogeneity in any of the main pooled analyses. Only five

of the gum trials (Campbell 1991; Hall 1996; Harackiewicz 1988; Hughes 1990; Niaura 1999) and three of the patch trials (Joseph 1996; Killen 1997 (Video); Kornitser 1995) yielded a negative treatment effect at the end of follow up, but in a further 64 trials the 95% confidence intervals (CI) for the odds of abstinence included unity (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.

The pooled odds ratio (OR) of abstinence for any form of NRT relative to control was 1.77 (95% CI: 1.66 to 1.88). For the different forms of NRT the ORs ranged from 1.66 (95% CI: 1.52 to 1.81) with nicotine gum to 2.35 (95% CI: 1.63 to 3.38) with nicotine nasal spray. For transdermal patch, nicotine inhaler, and nicotine sublingual tablet the ORs for abstinence were 1.81 (95% CI: 1.63 to 2.02), 2.14 (95% CI: 1.44 to 3.18) and 2.05 (95% CI: 1.62 to 2.59) respectively. Since the confidence intervals around these estimates of effect overlapped there was no evidence in this indirect comparison for a significant difference in the effectiveness of the five types of NRT. For trials of nicotine gum and transdermal patch, the ORs for not smoking were not affected by whether or not the control group was placebo or no NRT (data not shown). The OR for nicotine gum was also not affected by whether or not the trial which randomized the treating physician, rather than the smoker (Nebot 1992), was included (data not shown).

The percentage of smokers who were abstinent after 12 months or more (excluding trials with shorter follow up; data not shown) was 17.4% (95% CI: 16.5% to 18.3%) amongst smokers who had been allocated to receive nicotine gum, and 13.7% (95% CI: 12.9% to 14.5%) amongst those who had been allocated to transdermal patches. For intranasal spray, nicotine inhaler and sublingual tablet, the corresponding figures were 24% (20% to 28%), 17% (14% to 21%) and 17% (15% to 20%) respectively. These figures should be interpreted cautiously because of the differences in the trial participants and in the way abstinence is defined in different trials.

When the abstinence rates for all trials were pooled (Comparison 1), using the longest duration of follow up available, 17% of smokers allocated to receive NRT had successfully quit compared with 10% in the control group. This represents a 74% increase in the odds of abstinence with the use of NRT (95% CI: 64% to 85%).

The pooled OR of abstinence in the trials which directly compared 4 mg versus 2 mg gum was 2.20 (95% CI: 1.50 to 3.25, Comparison 2.2) in highly dependent smokers (Garvey 2000; Herrera 1995; Kornitser 1987; Tonnesen 1988). In low dependence or unselected smokers there was no evidence for an effect (Garvey 2000; Hughes 1990; Kornitser 1987). Two trials compared a fixed dose regimen of 2 mg nicotine gum against use of an ad lib regimen (Goldstein 1989; Killen 1990). The fixed dose regimen had

non-significantly better quit rates (OR 1.29 95% CI: 0.90 to 1.85, Comparison 13).

There was no evidence of a difference in clinical effectiveness for 16-hour compared to 24-hour patch, although there was evidence of heterogeneity in the results of the 10 trials which used a 16-hour patch ( $I^2=57.6\%$ ) (Comparison 6). One trial directly compared the effect of only wearing the patch whilst awake (about 16 hours) with wearing it continuously for 24 hours (Daughton 1991). The study found no significant difference in the self reported OR of abstinence at six months follow up but had low power (OR: 24-hour patch versus 16-hour patch: 0.61, 95% CI: 0.26 to 1.48). In addition, use of the patch for up to eight weeks was as effective as longer courses of treatment (Comparison 4). One large trial which compared a 28- to a 12-week course of treatment found no evidence of benefit from longer treatment (CEASE 1999). Smaller trials comparing a three-week to a 12-week course (Bolin 1999) and a three-week to a six-week course (Glavas 2003b) also found no evidence for a difference. There was no difference in effect in trials where the dose was tapered, or weaned, compared to those where withdrawal was abrupt (Comparison 5). Similarly, in the two trials that directly compared weaning with abrupt withdrawal, no difference was found (Hilleman 1994; Stapleton 1995).

Six trials have compared a high patch dose to standard dose (Comparison 8). Three used 24-hour patches and compared 42/44 mg doses to standard 21/22 mg doses (Dale 1995; Hughes 1999; Jorenby 1995). Three used 16-hour patches and compared a 25 mg high dose to 15 mg standard dose (CEASE 1999; Killen 1999; Paoletti 1996). Two studies (Hughes 1999; Killen 1999) specifically recruited heavy smokers and one selected smokers with baseline cotinine levels of over 250  $\mu\text{g/ml}$  (Paoletti 1996). Pooling all six studies gives an OR of 1.21 (95% CI: 1.03 to 1.42) suggesting that there may be a small benefit from higher doses. One study in heavy smokers with a history of alcohol dependence (Kalman 2004) was excluded because follow up was only 12 weeks. This detected no significant difference, with outcomes favouring the lower dose group. Including this study would weaken the evidence of a benefit.

### Combinations of nicotine therapy:

In the two trials which compared a combination of patches and gum with gum or patch alone, early increases in abstinence rates in the more intensively treated group were not sustained at one year follow up (Kornitzer 1995; Puska 1995). A trial comparing nasal spray and patch with patch alone found a significant increase in sustained abstinence at one year with the combined therapy (Blondal 1999). One trial combining patch with inhaler also showed a non-significant increase in cessation compared to inhaler alone (Bohadana 2000). A trial combining patch and inhaler had non-significantly lower quit rates from the combination than with either of the forms alone (Tonnesen 2000). A trial comparing nasal spray and patch to either alone detected no significant benefit of the combination (Croghan 2003). A trial comparing patch and in-

haler to neither, which also contributes to comparison 1, detected no benefit of NRT (Hand 2002). Pooling all seven trials suggests a clinically modest but statistically significant benefit (Comparison 9, OR 1.42, 95% CI: 1.14 to 1.76), with only moderate heterogeneity ( $I^2=32.0\%$ ), but the trials are relatively clinically heterogeneous in the combinations and comparison therapies used.

### Clinical Settings:

The pooled OR of not smoking at 6 to 12 months when NRT is offered to smokers attending smoking cessation clinics did not differ significantly from the OR amongst those recruited from the community as volunteers, or those who were recruited opportunistically through primary care (Comparison 7). However, since the absolute abstinence rate was higher in community volunteers and smoking cessation clinics, the percentage of smokers helped to quit by using NRT was higher in these settings than in primary care or hospital patients.

Smokers recruited as hospital inpatients, or through outpatient clinics, have a lower increase in quitting using gum than smokers seen in other clinical settings, (3 trials, OR 1.12, 95% CI: 0.84 to 1.51). The results using transdermal patches in hospitals, based on four trials, are more consistent with the results seen in other settings (OR 1.75, 95% CI: 1.19 to 2.57). In a trial which offered a choice of type of NRT to hospital inpatients, in which 63% chose patch (Molyneux 2003), the use of NRT increased quit rates but the effect on continuous 12-month abstinence was not significant. In a trial providing a combination of patch and inhaler for three weeks, compared to individual counselling alone (Hand 2002) quit rates were similar at 12 months. In the single trial of a nicotine patch for women trying to quit during pregnancy no benefit of the patch was detected (OR 1.09, 95% CI: 0.54 to 2.18).

Increasingly, various forms of NRT are available without a medical prescription and can be purchased in pharmacies or other shops. Three placebo-controlled trials of nicotine patch have assessed effectiveness in an 'Over the Counter' (OTC) setting with minimum levels of support. The effectiveness of the patch was similar to that in other settings. Two trials compared patch (Leischow 1999) or inhaler (Leischow 2003) with minimal physician support and patch/inhaler with no support in a simulated OTC setting. Abstinence rates were low in both conditions but when pooled there was a marginal advantage of the physician support compared to no support (OR 0.21, 95% CI: 0.05 to 0.84) (Comparison 12).

### Intensity of additional support:

Amongst trials of nicotine gum, the odds of quitting were marginally higher in trials with low intensity support (OR 1.76, 95% CI: 1.52 to 2.05) than in those classified as high intensity (OR 1.61, 95% CI: 1.43 to 1.82), but the confidence intervals overlapped. The absolute probability of quitting was higher when gum and high intensity support was provided, but this was also based on an indirect comparison between subgroups of trials. High intensity support could include intensive group therapy, or multiple study assessment visits.

Only two small studies, both in primary care, directly compared the effect of providing high versus low intensity follow up to participants receiving nicotine gum (Fagerstrom 1984; Marshall 1985). The pooled results favour intensive follow up but the result was not statistically significant (OR intensive follow up:minimal follow up: 1.30, 95% CI: 0.75 to 2.28, data not shown). In the one patch trial which compared minimal counselling with two forms of more intensive counselling in patients receiving one of two nicotine doses, the intensive intervention did not lead to improved outcomes (Jorenby 1995).

#### **Relapsed smokers:**

Although many of the trials reported here did not specifically exclude people who had previously tried and failed to quit with NRT, only one trial has looked at the effectiveness of NRT (patch) in smokers who had relapsed after previous patch use (Gourlay 1995). Although this study did not find any difference between active treatment and placebo for continuous abstinence, they did find a small increase in quitters in the patch group using their predetermined endpoint of abstinence in the 28 days before assessment. The absolute quit rates were low (Comparison 11).

#### **Cost of therapy:**

One study comparing the effectiveness of free and purchased patch found no significant difference in quit rates between the two conditions (Hays 1999) (Comparison 12).

#### **Comparison with bupropion:**

Nicotine patch and placebo tablet were significantly less effective than bupropion and placebo patch in one study (Jorenby 1999). The combination of bupropion and nicotine patch was significantly more effective than placebo alone or patch alone, but not significantly different from bupropion alone (Comparison 11).

#### **Pretreatment with NRT prior to quit attempt:**

One trial showed a trend towards an increase in quitting for people using nicotine patch for two weeks before attempting to quit, but the difference was not significant (Schuurmans 2004) (Comparison 15).

#### **Harm reduction:**

Based on pooling three trials, there was a significant benefit from the use of NRT on the odds of reducing the number of cigarettes smoked to fewer than 50% of baseline at longest follow up, using point prevalence of reduction (OR 1.80, 95% CI: 1.41 to 1.28); a significant effect on sustained reduction was detected by pooling two trials reporting this outcome. There was also a marginally significant increase in odds of cessation (OR 1.62, 95% CI: 1.06 to 2.49).

#### **Adverse Effects:**

No attempt was made in this overview to synthesize quantitatively the incidence of the various side effects reported with the different NRT preparations. This was because of the extensive variation in reporting the nature, timing and duration of symptoms. However, the major side effects usually reported with nicotine gum,

including hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems, are not seen with transdermal patch (Fiore 1992; Palmer 1992). The only side effect which appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use (Fiore 1992). The major side effects reported with the nicotine inhaler and nasal spray are related to local irritation at the site of administration (mouth and nose respectively). For example, symptoms such as throat irritation, coughing, and oral burning were reported significantly more frequently with subjects allocated to the nicotine inhaler than to placebo control (Schneider 1996); none of the experiences, however, were reported as severe. With the nasal spray, nasal irritation and runny nose are the most commonly reported side effects. Nicotine sublingual tablets have been reported to cause hiccoughs, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers (Wallstrom 1999). A review of adverse effects based on 35 trials with over 9,000 participants did not find evidence of excess adverse cardiovascular events assigned to nicotine patch, and the total number of such events was low (Greenland 1998). There has been concern about the safety of NRT in smokers with cardiac disease (TNWG 1994). A trial of nicotine patch (Joseph 1996) which recruited smokers aged over 45 with at least one diagnosis of cardiovascular disease found no evidence that serious adverse events were more common in smokers in the nicotine patch group. Events related to cardiovascular disease such as an increase in angina severity occurred in approximately 16% of patients, but did not differ according to whether or not patients were receiving NRT. A review of safety in patients with cardiovascular disease found no evidence of an increased risk of cardiac events (Joseph 2003). This included data from two randomized trials with short-term follow up that are excluded from the present review (Tzivoni 1998; Working Group 1994) and a case-control study in a population based sample.

## **DISCUSSION**

This overview provides reliable evidence from over 35,600 participants that offering nicotine replacement therapy (NRT) to dependent smokers is more effective in helping them to stop smoking than when NRT is not offered or if placebo is used. This applies to all forms of NRT and is independent of any variations in methodology or design characteristics of trials included in the overview.

Comparisons between the relative effectiveness of the different forms of NRT can only be made indirectly. The increased odds of not smoking at 6 to 12 months follow up were greatest with the intranasal nicotine spray and nicotine inhaler; however there are still only a small number of trials involving these delivery systems and confidence intervals are wide. In making indirect comparisons it should be noted that most of the trials included in the comparison of nicotine gum versus placebo used 2 mg gum. The

pooled odds ratio (OR) of abstinence in the trials which directly compared 4 mg versus 2 mg gum in highly dependent smokers found a significant benefit in favour of 4 mg gum (OR 2.18, 95% confidence intervals (CI): 1.48 to 3.17). There have been no direct comparisons of the relative effectiveness between 4 mg gum and nicotine patch. In one study directly comparing inhaler to patch the patch was non-significantly more effective (Tonnesen 2000). One study in which smokers were randomized to nicotine gum, patch, spray or inhaler found no significant differences in abstinence rates after 12 weeks (Hajek 1999).

There is limited evidence that using combinations of NRT products is better than one product alone. Updated US clinical practice guidelines (Fiore 2000) recommend the use of nicotine patch with another form of NRT taken ad lib as a second-line therapy for patients unable to quit on a single type of NRT or bupropion. However the strength of evidence was recognized as less than optimal due to the clinical heterogeneity of the studies in the meta-analysis. Whilst two further trials have been published since then, there is still a lack of evidence that combinations produce significant additional benefits. As a recent review (Sweeney 2001) points out, it is not yet clear whether any benefit of combination therapy is due to the sensory effects provided by multiple types of delivery systems, to the higher percentage of nicotine substitution achieved, or some combination of these and other factors. The review also notes that not enough is known for NRT products to be appropriately labelled so that non-experts can be guided in the most safe and effective use of combinations of products.

All forms of NRT were associated with a high relapse rate in the first three months. Minimizing this relapse is important if long-term smoking cessation rates are to be substantially improved. There is suggestive evidence (Gourlay 1995) that repeated use of NRT in patients who have relapsed after an initial course may produce further quitters, though the absolute effect is small.

### **Clinical Setting:**

The two factors which appear to be the major determinants of the effectiveness of NRT are the setting in which it is offered, and the smoker's level of dependence on nicotine. Both of these factors have been recognized in previous reviews (Gourlay 1990; Lam 1987). The nature and flexibility of the dosage regimen appears to be a far less important determinant of the effectiveness of NRT.

Nicotine gum and transdermal patches were more effective when offered to volunteer smokers recruited from the community or those attending specialized clinics than if offered to smokers in primary care. These findings are likely to be partly explained by the high motivation to quit among many of the smokers in the community who volunteer for trials in response to media advertisements and, similarly, among those participants who are recruited as a result of their attendance at specialized smoking cessation clinics. The latter group also have access to trained therapists who specialize in assisting smokers to quit. However, given the limited

number of specialized smoking cessation clinics, access will be restricted to a small proportion of smokers wanting help to quit.

In contrast, most of the smokers recruited into trials conducted in primary care settings were unselected, and hence may be less motivated to quit. In addition, the treating physician or practice nurse had frequently received little training in smoking cessation skills. As a result, compliance with NRT among smokers treated in primary care is reported to be lower than in other settings (Lam 1987). There has been some debate about the amount of evidence for efficacy of NRT when obtained 'over the counter' (OTC) without advice or support from a healthcare professional (Hughes 2001; Walsh 2000; Walsh 2001). The small number of placebo-controlled trials in OTC settings support the conclusion that the relative effect of NRT is similar, although quit rates in both control and intervention groups have been low. A recent meta-analysis supports the conclusion of efficacy, although it differs in its inclusion criteria (Hughes 2003). In addition to the same three trials comparing nicotine patch to placebo in an OTC setting (Davidson 1998; Hays 1999; Sonderskov 1997), that review includes one study excluded here due to short follow up (Shiffman 2002c). It also pools four trials comparing NRT provided OTC to NRT provided under prescription. We exclude one paper that compared both gum and patch in these settings, but was not randomized (Shiffman 2002e), and another that has not been published and for which we have been unable to obtain reliable data for inclusion (Korberly 1999). The abstract reported that there were no significant differences in quit rates between users of nicotine patch who purchased it via a non-healthcare facility, and those receiving it on prescription. On the basis of one published and one unpublished study we find a marginally significant benefit of NRT with prescription compared to OTC, but the confidence intervals are wide.

Although some trials of NRT use in hospital inpatients have reported relatively less successful results, in the subgroup of four studies of nicotine patch amongst people recruited in inpatient and outpatient settings there was evidence of benefit.

One trial of nicotine patch in pregnant women is now included in the review. Women still smoking after their first trimester were recruited, and they were followed up until one year post partum. No significant benefit of treatment was detected, although the confidence intervals do not exclude the possibility of benefit. Quit rates one year after delivery were 15% in the patch group and 14% in the placebo group. Using quit rates at the final prenatal follow up did not alter the conclusions, with rates of 28% versus 25%. Possible explanations for the lack of relative benefit may have been low compliance with patch use, and the intensive cessation counselling offered to all participants. A second trial of the patch in pregnancy (Kapur 2001) is not included here since follow up was only to end of treatment at 12 weeks. In this trial 0/13 in the placebo group quit compared to 4/17 (24%) in the active treatment group. Enrolment was ended early in this study because

of a possible adverse event in the placebo arm. A recent study measuring nicotine metabolism in smokers during their pregnancy and postpartum has suggested that nicotine is metabolized more quickly by pregnant women and that this may affect the dose of NRT required (Dempsey 2002). More studies are needed to establish whether or not NRT does aid quitting in pregnancy and what effects there are on birth outcomes (Benowitz 2000).

Trials generally restricted recruitment to adults over the age of 18 (in a small number of trials the age range was not specified). No trials specifically recruiting adolescents have met the inclusion criteria. One trial examining the effects of the nicotine patch on craving and withdrawal symptoms, safety, and compliance among 100 adolescents was excluded because follow up was only 10 weeks. No significant difference was detected at this point (Hanson 2003).

### **Intensity Of Additional Support:**

In previous versions of this overview there seemed to be a clear trend towards a lower OR for abstinence (NRT versus control) in trials which included high intensity support programmes than in those with low intensity support. NRT had a relatively greater effect when given with minimal support even though the absolute increase in abstinence rates was larger when combined with high intensity support. The trend remains, but the overlap in the confidence intervals are such that this could have arisen by chance.

It is important that individuals do not misinterpret these results by believing that NRT offers an easy option 'medical cure' for the far more complex problem of addictive behaviour. Almost all the trials in this review included some form of additional support together with the use of NRT as part of the intervention. In the case of trials in an 'over the counter' settings the adjunctive support was limited. The absolute probability of abstinence for an individual is still low, irrespective of what support strategies are used and whether or not they include use of NRT. Many smokers will therefore need to make multiple attempts to quit using a variety of strategies before they finally succeed. Falsely raising the expectations of smokers who purchase these products 'over the counter' without at least providing minimal support and an adequate explanation of the limitations of using NRT may be counterproductive in the long term.

### **Dependence On Nicotine:**

The benefit of using nicotine gum in smokers with high levels of dependence on nicotine has been previously recognized (Gourlay 1990; Lam 1987; Tang 1994). In such patients, the 4 mg gum is significantly more effective than the lower dose.

### **Direct comparison with non-nicotine pharmacotherapies:**

There is evidence from one large study (Jorenby 1999) that bupropion is more effective than nicotine patch. A combination of NRT and bupropion was not found to be significantly more effective than bupropion alone.

### **Harm reduction:**

Offering NRT to smokers who cannot quit might help them reduce the number of cigarettes smoked and therefore decrease the harmful effects of smoking. It is not clear what reduction in consumption is needed for a clinically useful health benefit, which has led to caution about promoting reduction as an alternative to cessation. Taking as a cut-off point more than 50% self reported reduction confirmed by some reduction in carbon monoxide levels, pooled results from three trials showed a significant effect. Although quit rates were low in both active and placebo group there was also a significant increase in cessation, broadly similar to the size of effect of NRT in trials amongst people trying to quit. Although participants were recruited to these trials because they were unwilling or unable to quit smoking, the eligibility criteria for two trials included having made a serious quit attempt in the past 12 (Bolliger 2000) or 24 (Wennike 2003) months, suggesting a relatively high level of interest in cessation.

### **Methodological Limitations:**

There are two possible methodological limitations of this overview which need to be borne in mind: use of tabulated data predominantly derived from published reports (Stewart 1993) and publication bias (Simes 1986). We tried to partly address any shortcomings from having limited our analysis to tabulated data by approaching investigators, where necessary, to obtain additional unpublished data or to clarify areas of uncertainty. Although steps were taken to minimize publication bias by writing to the manufacturers of NRT products when this review was first prepared, the response was poor and we have not repeated this exercise. It is therefore possible that there are some unpublished trials, with less favourable results, that we have not identified despite our systematic efforts to do so. Indeed, a recent statistical analysis (Egger 1997; Egger personal communication) suggests that this is the case. Using a regression method to assess the symmetry of funnel plots, they showed evidence of asymmetry (and hence possible publication bias) for both nicotine gum and transdermal patches. For the nicotine inhaler we are aware of one unpublished trial with a non-significant result. The practical effect of this is that the magnitude of the effectiveness of nicotine replacement may be smaller than our estimates suggest.

## **AUTHORS' CONCLUSIONS**

### **Implications for practice**

1. All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablet) are effective as part of a strategy to promote smoking cessation. They increase the odds of long-term quitting approximately 1.5 to 2-fold regardless of setting. Use of NRT should be preferentially directed to smokers who are motivated to quit (as demonstrated by their initiative to request assistance) and who have high levels of nicotine dependence. There is little evidence about the role of NRT for individuals smoking less than 10 to 15 cigarettes a day.

2. The choice of which form to use should reflect patient needs, tolerability, and cost considerations. Patches are likely to be easier to use than gum or nasal spray in primary care settings.

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

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

5. There is some evidence of a small benefit from combining the nicotine patch with a form allowing ad lib dosing compared to use of a single form. Use of combination therapy may be considered for patients who have been unable to quit using a single type of NRT.

6. There is borderline evidence that there is a small benefit from use of the nicotine patch at doses higher than 22 mg (24 hours), or 15 mg (16 hours) compared to the standard dose patch. Use of these may be considered for heavy smokers (i.e. smoking 30 or more cigarettes a day), or for patients relapsing because of persistent craving and withdrawal symptoms on standard dose therapy (Hughes 1995).

7. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the smoker. Provision of more intensive levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT.

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

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

10. Nicotine patch was less effective than bupropion in one trial. However any decision about which pharmacotherapies to use should take into account potential adverse effects as well as benefits.

11. Finally, marketing claims by manufacturers of NRT products should reflect these points and avoid the possible misunderstanding by health professionals and members of the public that any of these products alone offers a magical 'cure' for the smoking habit.

### Implications for research

Further research is required in several areas:

1. Direct comparisons between the various forms of NRT and between different doses and durations of treatment.
2. Use of combinations of different forms of NRT.
3. Direct comparisons between NRT and other products such as bupropion.

## NOTES

Prof Chris Silagy died in December 2001. In recognition of his major contribution to the review he will remain listed as first author of this and future updates. The contact author for the review is now Lindsay Stead.

## FEEDBACK

### How should efficacy be measured?

#### Summary

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

#### Author's 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 by 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 suggests that randomised controlled trials (RCTs) alone cannot establish the effectiveness of an intervention in a population.

Author's 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

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 draws 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.

(The full text of the comment can be found at:  
[www.update-software.com/ccng/ccng.exe?SourceID=CD000146#Content1476](http://www.update-software.com/ccng/ccng.exe?SourceID=CD000146#Content1476))

Author's reply

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

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

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

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

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

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

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Criticism editor Robert West

#### Error in study description

##### Summary

In the 'Description of Studies' section, the dosing regimens for the two subgroups in a trial of the nicotine lozenge (Shiffman 2002A, Shiffman 2002B) had been transposed.

##### Author's reply

The error has been corrected; smokers whose time to first cigarette of the day was more than 30 mins were randomised to the lower dose, 2 mg (Shiffman 2000A), whilst more addicted smokers who smoked within 30 minutes of waking received the 4 mg dose. (Shiffman 2000B).

##### Contributors

Lindsay Stead

## POTENTIAL CONFLICT OF INTEREST

C. Silagy received funds for consultancy work undertaken (at various times) on behalf of Pharmacia and Upjohn, Marion Merrell Dow, Glaxo Wellcome and SmithKline Beecham. G. Fowler and D. Mant were involved in a trial of transdermal nicotine (ICRF 1994).

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\*Indicates the major publication for the study

## TABLES

### Characteristics of included studies

Study	Abelin 1989
Methods	Country: Switzerland Recruitment: Primary care clinics Randomization: not stated
Participants	199 primary care patients
Interventions	1. Nicotine patch, 24hr, 12 w; 30cm <sup>2</sup> patches (21 mg) for those smoking > 20 cigs/day, 20cm <sup>2</sup> patches (14 mg) for those smoking < 20 cigs/day 2. Placebo patch Level of support: low

## Characteristics of included studies (Continued)

Outcomes	Sustained abstinence at 12m (0-3 cigs/week) Validation: expired CO
Notes	
Allocation concealment	B – Unclear
<b>Study</b>	<b>Ahluwalia 1998</b>
Methods	Country: USA Recruitment: Hospital in- and outpatients Randomization: computer generated random number table
Participants	410 African American smokers Av. Age 47, FTQ 6
Interventions	1. Nicotine patch (21 mg with weaning, 10 weeks) 2. Placebo patch Level of support: high (1 hr initial visit and brief follow-up visits)
Outcomes	Prolonged abstinence at 6m (self report of no smoking since end of treatment) Validation: none
Notes	New trial 1998/3 update
Allocation concealment	A – Adequate
<b>Study</b>	<b>Areechon 1988</b>
Methods	Country: Thailand Recruitment: Community volunteers Randomization: not stated
Participants	200 smokers (> 15/day) recruited through advertisements
Interventions	1. Gum (2 mg) x 8 boxes 2. Placebo gum x 8 boxes Level of support: low
Outcomes	PP abstinence at 6m Validation: CO
Notes	
Allocation concealment	B – Unclear
<b>Study</b>	<b>Blondal 1989</b>
Methods	Country: Iceland Recruitment: Smoking cessation clinic Randomization method: not stated
Participants	182 patients in an Icelandic smoking cessation clinic
Interventions	1. Gum (4 mg) for at least 1m 2. Placebo gum for 1m or more Level of support: high (group therapy 5 sessions)
Outcomes	Sustained abstinence at 12m & 24m Validation: at 12m, CO. At 24m, no validation
Notes	12 m abstinence data used
Allocation concealment	B – Unclear
<b>Study</b>	<b>Blondal 1997</b>
Methods	Country: Iceland

## Characteristics of included studies (Continued)

	Recruitment: Community volunteers Randomization: computer generated code, dispensed by pharmacy. Double blind.
Participants	159 smokers
Interventions	1. Nicotine nasal spray (NNS) ad lib use. Each dose (2 squirts) delivered 1 mg nicotine. Maximum dose 5 mg/hr and 40 mg/day. Recommended duration of use 3m. 2. Placebo nasal spray containing piperine to mimic sensory effect of nicotine. Level of support: high (Group therapy 6 sessions)
Outcomes	Sustained abstinence at 1 year (continuous abstinence from quit day, follow up also at 2 years) Validation: CO < 10ppm at each of 5 follow ups
Notes	New trial 1998/3 update
Allocation concealment	A – Adequate

<b>Study</b>	<b>Blondal 1999</b>
Methods	Country: Iceland Recruitment: Community volunteers Randomization: computer generated code at pharmacy
Participants	237 smokers av.age 41-43
Interventions	1. Nicotine nasal spray (NNS) and 15 mg nicotine patches for 3m, weaning over further 2m. NNS could be continued for 1 year 2. Placebo nasal spray and 15 mg nicotine patches on same schedule Level of support: high (4 supportive group meetings)
Outcomes	Sustained abstinence at 12m (6 year data also reported) Validation: CO < 10ppm
Notes	Does not contribute to main comparisons, only combination.
Allocation concealment	A – Adequate

<b>Study</b>	<b>Bohadana 2000</b>
Methods	Country: France Recruitment: community volunteers Randomization: computer generated code
Participants	400 smokers, 18-70 years, > 10 cigs/day for > 3 years, > 1 previous quit attempt, motivated. 51% F, Av cigs/day: Group 1 26.1, Group 2 23.5 FTND > 6
Interventions	1: Nicotine inhaler, 26w, combined with nicotine patch (15 mg/16hr) for first 6w, placebo patch for next 6w 2: Nicotine inhaler, 26w, placebo patch for first 12w All received brief counselling and support from investigator at each visit
Outcomes	Sustained abstinence at 12m, (prolonged from w2, no slips allowed) Validation: CO < 10ppm at each visit (2w, 6w, 6m, 12m) (Study also reports respiratory symptoms and pulmonary function tests for completely abstinent subjects)
Notes	Does not contribute to main comparisons, only combination. Gender subgroup results reported 2003
Allocation concealment	A – Adequate

## Characteristics of included studies (Continued)

Study	Bolin 1999
Methods	Country: USA Recruitment: smoking cessation clinic Randomization: method not stated. Assignment on first day of patch use.
Participants	98 smokers
Interventions	1. Nicotine patch for 12w (21 mg/3w, 14 mg/3w, 7 mg/3w) 2. Nicotine patch for 3w (21 mg/1w, 14 mg/1w, 7 mg/1w) All received intensive group programme, 5 sessions prior to quit day.
Outcomes	Continuous abstinence at 5m (PP also recorded) Validation: expired CO
Notes	Contributes only to comparison 4 Borderline follow-up length - 20w from beginning of programme, 16w since start of NRT
Allocation concealment	B – Unclear

Study	Bolliger 2000
Methods	Country: Switzerland (2 hospital pulmonary clinics) Recruitment: Community volunteers Randomization: computer generated central list
Participants	400 smokers, aged > 18, > 15 cigs/day for 3+ years, failed at least one serious quit attempt in past 12m, wanting to reduce smoking as much as possible. 52.5% F, Av age 46, av cigs/day 29, CO 27ppm
Interventions	1. Nicotine inhalator, 6-12 cartridges over 24hrs. Encouraged to decrease after 4m but use permitted up to 18m 2. Placebo inhalator (contained menthol only) Counselling on smoking reduction provided at each clinic visit (1, 2, 3, 6w, 3, 4, 6, 12, 18, 24m)
Outcomes	Primary: > 50% self reported reduction of daily smoking, sustained from week 5 at 24m Secondary: sustained cessation from w6 at 24m, PP cessation at 24m (Paper reports outcomes after 4 and 12m, also PP rates) Validation: Reduction validated by reduced CO from baseline (at 6w, 3m, 4m), but amount of reduction not specified, cessation verified by CO < 10ppm from w6
Notes	Reduction trial, Not included in main comparisons. Smoking cessation was recommended as ultimate goal throughout study. PP rates of cessation increased through the study.
Allocation concealment	A – Adequate

Study	Br Thor Society 1983
Methods	Country: UK Recruitment: Hospital chest clinics and inpatient wards in UK Randomization: by numbered envelope
Participants	Clinic patients age 18-65 with a smoking-related illness (pulmonary or vascular) Exclusions: pregnant women, patients with cancer, terminal illness or psychiatric illness Mean number of cigarettes smoked : 24/day Therapists : physicians
Interventions	1. Brief advice 2. Brief advice plus booklet 3. Brief advice plus booklet plus placebo chewing gum 4. Brief advice plus booklet plus nicotine chewing gum (2 mg)

## Characteristics of included studies (Continued)

	Level of support: low
Outcomes	Sustained validated abstinence at 6 and 12m Validation: Venous carboxyhaemoglobin
Notes	4 vs 1+2+3 used in main comparison
Allocation concealment	B – Unclear

### Study **Buchkremer 1988**

Methods	Country: Germany Recruitment: Community volunteers Randomization: not stated
Participants	131 smokers responding to announcements in press.
Interventions	1. Nicotine Patch (24h/day, 8w, 15cm2) plus behavioural therapy 2. Placebo patch plus behavioural therapy 3. Behavioural therapy alone Level of support: high (group)
Outcomes	Abstinence (not stated how assessed) at 12m Validation: none
Notes	1 vs 2+3 used in main comparison
Allocation concealment	B – Unclear

### Study **CEASE 1999**

Methods	Country: Multicentre - 36 clinic centres in 17 European countries Recruitment: Community volunteers Randomization: Central computer generated allocation list, stratified by centre
Participants	3575 adults smoking > 14cigs/day for > 3 years Mean age 41, av cigs/day 27 (34% had previously used NRT)
Interventions	Factorial design compared two patch doses and two treatment durations. Dose was either 15 mg or 25 mg (16hr), duration of active treatment was 28w (incl 4w fading) or 12w (incl 4w fading). 1. 25 mg nicotine patch for 22w + 4w tapering (L-25) 3. 25 mg nicotine patch for 8w + 4w tapering (S-25) 4. 15 mg nicotine patch for 22w + 4w tapering (L-15) 5. 15 mg nicotine patch for 8w + 4w tapering (S-15) 6. Placebo Brief advice and self help brochure Level of support: low
Outcomes	Prolonged abstinence at 12m, sustained from w2 Authors also report PP abstinence Validation: expired CO < 10ppm at each clinic visit
Notes	Doses and durations collapsed in main analyses. Durations compared in comparison 4, dosages in comparison 8.
Allocation concealment	A – Adequate

### Study **Campbell 1987**

Methods	Country: UK Recruitment: Primary care Randomization: not stated
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**Characteristics of included studies (Continued)**

Participants	836 primary care patients agreeing to try to stop smoking after brief advice from their doctor
Interventions	1. Nicotine gum (2 mg) x 6 boxes 2. Placebo gum x 6 boxes Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

**Study Campbell 1991**

Methods	Country: UK Recruitment: Hospital inpatients Randomization: not stated
Participants	212 patients with smoking-related diseases
Interventions	1. Nicotine gum 2-4 mg (3m) 2. Placebo gum Level of support: high
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

**Study Campbell 1996**

Methods	Country: UK Recruitment: Hospital inpatients and outpatients Randomization: not stated
Participants	234 adult smokers (172 outpatients, 62 inpatients) Stratified according to level of nicotine dependency (on FTQ) (equal numbers in each category)
Interventions	1. Nicotine patch (21 mg, 24h, 12w with dose tapering) 2. Placebo patch Level of support: high (counselling at 2,4,8,12w)
Outcomes	Continuous abstinence at 12m Validation: CO
Notes	Replaces study ID Burton 1992 which was an abstract of the same trial.
Allocation concealment	B – Unclear

**Study Cinciripini 1996**

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated. Not placebo controlled
Participants	64 smokers, > 15 cigs/day for > 3 years 70% F, av cigs/day 29/22
Interventions	1. Behaviour therapy (group therapy weekly for 9w) and nicotine patch (21 mg, 12w incl weaning) 2. Behaviour therapy only (no placebo) Level of support: High
Outcomes	Sustained abstinence, 12m post treatment and all previous points (EOT, 1,3,6m)

## Characteristics of included studies (Continued)

	Validation: CO < 6ppm at each point
Notes	121 smokers recruited but only 64 followed up for 1 year. 6m quit rates were approx 53% vs 30% (personal communication 2004)
Allocation concealment	B – Unclear

### Study Clavel-Chapel 1985

Methods	Country: France Recruitment: Community volunteers Randomization: not stated
Participants	427 adults smoking at least 5 cigs/day responding to advertisement
Interventions	1. Nicotine gum (2 mg) x 1 box 2. Minimal intervention control group Level of support: low
Outcomes	Sustained abstinence at 13m Validation: Smoking cessation adjusted using exhaled CO figures from published trials
Notes	
Allocation concealment	B – Unclear

### Study Cooper 2003

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	439 women smoking at least 10 cigs/day.
Interventions	1. Nicotine gum (2 mg), 10-12 pieces/day recommended, for 9w, weaning last 3w. 2. Placebo gum Level of support: high. 13 cognitive behavioural group sessions (3rd arm tested Phenylpropanolamine gum, not included in review)
Outcomes	PP 12m Validation: CO < 10ppm (Weight change in quitters was also a primary outcome in the trial)
Notes	New for 2004 update, based on data in handout from poster presentation. Compliance stated to be poor
Allocation concealment	B – Unclear

### Study Croghan 2003

Methods	Country: USA, multicentre Recruitment: Community volunteers Randomization: central, controlling for cigs/day, yrs smoked, gender, site
Participants	1384 adults smoking at least 15 cigs/day
Interventions	1. 15 mg/16hr nicotine patch plus 0.5 mg/dose nasal spray, max 5/hr, 40/day, for 6w 2. Nicotine nasal spray only 3. Nicotine patch only Level of support: low
Outcomes	PP abstinence at 6m Validation: CO
Notes	New for 2004 update. Does not contribute to main comparison
Allocation concealment	A – Adequate

## Characteristics of included studies (Continued)

Study	Dale 1995
Methods	Country: USA Recruitment: Community volunteers and smoking clinic attenders. Randomization: not stated
Participants	71 cigarettes smokers stratified according to light, moderate and heavy smoking rates.
Interventions	1. 11 mg/24hr nicotine patch 2. 22 mg/24hr nicotine patch 3. 44 mg/24hr nicotine patch 4. Placebo patch for 1w followed by 11 or 22 mg patch for 7w. Duration of patch use 8w. Level of support: high (including 6 day inpatient stay)
Outcomes	PP abstinence at 12m Validation: Blood cotinine
Notes	Does not contribute to main comparison. Contributes to comparison 8 of high and standard dose patch.
Allocation concealment	B – Unclear
Study	Daughton 1991
Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	158 smokers aged 21-64 smoking at least 1 pack of cigarettes daily, no serious illness
Interventions	1. Nicotine patch (15 cm <sup>2</sup> , 4w) worn for 16hr/day 2. Nicotine patch (15 cm <sup>2</sup> , 4w) worn for 24hr/day 3. Placebo patch, 4w Level of support: low
Outcomes	Sustained abstinence at 6m Validation: None
Notes	1 +2 vs 3 in comparison 1. 16 vs 24 hour in comparison 6.
Allocation concealment	B – Unclear
Study	Daughton 1998
Methods	Country: USA (21 sites) Recruitment: Patients at family practices - self referred to study or recruited by physician. Randomization: centrally generated
Participants	369 smokers (> 20 cigs/day) Av age 37, av cigs/day 27-30
Interventions	1. Nicotine patch (21 mg, 16hr, 10w with weaning) 2. Placebo patch Both groups received Nicoderm Committed Quitters Programme support booklet and had a follow-up visit one week after quit day. Level of support: low
Outcomes	Sustained abstinence (continuous self-reported from quit day) at 12m Validation: CO ≤ 8ppm and saliva cotinine < 20mg/mL
Notes	There were differences in quit rates between self referred and physician selected recruits and between smokers recruited during an illness and at another visit.
Allocation concealment	A – Adequate

## Characteristics of included studies (Continued)

Study	Dautzenberg 2001
Methods	Country: France Recruitment: volunteers Randomization: not stated
Participants	433 smokers (excludes 25 from ITT population) 52% F, av age 39, av cigs/day 21
Interventions	1. Nicotine lozenge (1 mg, 8-24/day, 6w +6w weaning for quitters) 2. Placebo lozenge Level of support: not stated
Outcomes	PP abstinence at 26w Validation: CO < 10ppm
Notes	New trial 2004, based on abstract
Allocation concealment	B – Unclear

Study	Davidson 1998
Methods	Country: USA (4 centres) Recruitment: Community volunteers in shopping malls (OTC setting) Randomization: central computer generated schedule
Participants	802 smokers (> 20 cigs/day) who scored 5 or more on a questionnaire assessing motivation Av. age 39, av cigs/day 29
Interventions	1. Nicotine patch (22 mg, 24hr, for up to 6w) 2. Placebo patch Self help book provided. Participants visited the mall weekly to obtain patches. CO levels were monitored. Level of support: low
Outcomes	Prolonged abstinence at 24w (sustained from w2) Validation: Expired CO ≤ 8ppm at each weekly visit, but 24w quit based on self report
Notes	541/802 did not complete the 6 weekly visits
Allocation concealment	A – Adequate

Study	Ehrensam 1991
Methods	Country: Switzerland Recruitment: University (primary care) Randomization: not stated
Participants	112 smokers at 2 universities Av. age 26, av. cigs/day 23
Interventions	1. Nicotine patch (21 or 14 mg/24hr, 9w, tapered) 2. Placebo patch Level of support: high (no counselling)
Outcomes	Sustained abstinence at 12m Validation: urinary cotinine
Notes	
Allocation concealment	B – Unclear

Study	Etter 2002
Methods	Country: Switzerland Recruitment: community volunteers

## Characteristics of included studies (Continued)

	Randomization: computer generated list, allocation concealment not described
Participants	923 smokers (> 20 cigs/day) not intending to quit in next 6m, willing to commit to reduce consumption by half
Interventions	1. Choice of nicotine patch, 4 mg gum, inhaler or combination. 5 day supply of each provided initially, more could be ordered every 2w for 6m 2. Same choice, placebo products 3. Control, not products Minimal behavioural support: 20 page booklets after enrollment and after 3m survey, 2 page information leaflet at each mailing
Outcomes	Abstinence for 4w at 6m. Reduction $\geq$ 50% cigs/day. Validation: none
Notes	New trial 2004. Not included in main comparison Placebo & control combined. this is conservative for effect of NRT on abstinence, but increases effect on reduction.
Allocation concealment	B – Unclear

### Study **Fagerstrom 1982**

Methods	Country: Sweden Recruitment: Smoking cessation clinic Randomization: not stated
Participants	Subjects: 100 smokers (level not stated)
Interventions	1. Nicotine gum (2 mg) for at least 4w 2. Placebo gum for at least 4w Level of support: high (individual counselling)
Outcomes	PP abstinence at 6m Validation: CO
Notes	
Allocation concealment	B – Unclear

### Study **Fagerstrom 1984**

Methods	Country : Sweden Recruitment: General practices and industrial clinics (primary care) Randomization: by birthdate
Participants	145 motivated smokers av. age 40 years, av. cigs/day 19 Therapists: 10 Swedish GPs, 3 Swedish industrial physicians
Interventions	1. Short follow up (advice plus 1 appointment) 2. Long follow up (advice plus 2 appointments, phone call + letter) 3. Short follow up plus nicotine gum (2 or 4 mg) 4. Long follow up plus nicotine gum Level of support: low
Outcomes	Sustained abstinence at 12m (and at 1,6m) Validation: Results adjusted for 15% deception rate detected by expired CO measured in a random subset of claimed nonsmokers
Notes	3 & 4 vs 1 & 2 in Comparison 1
Allocation concealment	C – Inadequate

### Study **Fee 1982**

Methods	Country: UK
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## Characteristics of included studies (Continued)

	Recruitment: Smoking cessation clinic Randomization: not stated
Participants	Subjects: 352 smokers, number of cigarettes not stated
Interventions	1. Gum (2 mg) given for 5w 2. Placebo gum given for 5w Level of support: high (10 group therapy sessions)
Outcomes	PP abstinence at 12m Validation: Blood carboxyhaemoglobin
Notes	
Allocation concealment	B – Unclear

### Study **Fiore 1994a**

Methods	Country: USA Recruitment: Community volunteers Randomization: pregenerated computer sequence
Participants	88 smokers (> 15/day)
Interventions	1. Nicotine patch (22 mg/24hr, 8w plus intensive group counselling 2. Intensive group counselling and placebo patch Level of support: high
Outcomes	PP abstinence at 6m (7 days PP) Validation: CO
Notes	
Allocation concealment	A – Adequate

### Study **Fiore 1994b**

Methods	Country: USA Recruitment: Community volunteers Randomization: pregenerated computer sequence
Participants	112 heavy (> 15/day) smokers
Interventions	1. Nicotine patch (22 mg/24hr) for 4w, followed by 2w of 11 mg patches, plus weekly individual counselling for 8w 2. Placebo patches, same regimen Level of support: high
Outcomes	PP abstinence at 6m (7 days PP) Validation: CO
Notes	
Allocation concealment	A – Adequate

### Study **Fortmann 1995**

Methods	Country: USA Setting: Community volunteers (telephone recruitment) Randomization: not stated
Participants	1044 smokers aged 18-65, able to quit for 24h, and without serious illness.
Interventions	1. Nicotine gum (2 mg, 1 per hour, at least 10/day and not more than 30/day) 2. Self help materials 3. Nicotine gum plus materials 4. Incentive alone.

**Characteristics of included studies (Continued)**

	All groups offered incentive of US\$100 for quitting at 6m. Level of support: low
Outcomes	PP abstinence at 12m Validation: CO < 9 ppm/salivary cotinine < 20 ng/ml
Notes	Only groups 1 and 4 included in the main comparison
Allocation concealment	B – Unclear

<b>Study</b>	<b>Garcia 1989</b>
Methods	Country: Spain Recruitment: Primary care Randomization: not stated
Participants	106 adult smokers
Interventions	1. Gum (2 mg) for 3-4 m 2. Placebo gum for 3-4m Level of support: high (group therapy)
Outcomes	Sustained abstinence at 6m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Garvey 2000</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated, stratified by high- and low-dependence
Participants	608 smokers, aged > 20, smoking > 5 cigs/day. 51% F, av cigs/day 23
Interventions	1. 4 mg nicotine gum (recommended 9-15 pieces), weaning from 2m 2. 2 mg nicotine gum, use as 1. 3. Placebo gum All received brief counselling (5-10 mins) at each study visit (1,7,14, 30 days, 2,3,6,9,12m) Level of support: high
Outcomes	Sustained abstinence at 12m (relapse defined as 7 or more consecutive days or episodes of smoking) Validation: CO ≤ 8ppm
Notes	4 + 2 mg doses combined in main comparison. 4 mg compared to 2 mg in comparison 2 by dependence level.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Gilbert 1989</b>
Methods	Country: Canada Recruitment: Primary care Randomization: Sealed envelopes
Participants	223 patients presenting to primary care doctors and smoking at least 1 cig/day (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
Outcomes	Sustained abstinence at 12m

## Characteristics of included studies (Continued)

Validation: salivary cotinine

Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Glavas 2003a</b>
Methods	Country: Croatia Recruitment: hospital health professionals Randomization: random numbers and sealed envelopes.
Participants	112 healthcare professionals smoking at least 1 cig daily. 26% had Fagerstrom score 6 or more 66% F, av age 34, av cigs/day: 24
Interventions	1. Nicotine patch, 24hr, 25 mg/15 mg/8 mg starting dose depending on baseline cigs/day. 3w 2. Placebo patch Level of support: low
Outcomes	Sustained abstinence (3 or fewer cigs/w) at 1 year Validation: CO < 11ppm (5 year abstinence also reported, not used in MA)
Notes	New for 2004 update
Allocation concealment	A – Adequate

<b>Study</b>	<b>Glavas 2003b</b>
Methods	Country: Croatia Recruitment: community volunteers Randomization: sealed numbered envelopes independently prepared
Participants	160 smokers
Interventions	1. Nicotine patch, 24hr, 25 mg/15 mg/8 mg starting dose depending on baseline cigs/day. 6w 2. Nicotine patch, 24hr, 25 mg/15 mg starting dose depending on baseline cigs/day. 3w 3. Placebo patch. 6w 4. Placebo patch 3w Level of support: low
Outcomes	Abstinence at 6m after EOT Validation: CO < 11ppm
Notes	New for 2004 update Both durations pooled for main comparison.
Allocation concealment	A – Adequate

<b>Study</b>	<b>Glover 2002</b>
Methods	Country: USA Recruitment: Advertizing for volunteers Randomization: not stated
Participants	241 smokers (>= 10 cigs/day) 54%F, av. age 42, av cigs/day 29
Interventions	1. Nicotine sublingual tablet (2 mg). Recommended dosage 1 tab/hr for smokers with FTQ < 7, 2 tabs/hr for scores >= 7. After 3m treatment, tapering period of 3m if necessary 2. Placebo tablet Level of support: high (brief counselling at all visits 1,2,3,6w, 3,6,12m)
Outcomes	Sustained abstinence at 12m



## Characteristics of included studies (Continued)

	Validation: CO < 10ppm
Notes	First included based on abstract as Glover 1999
Allocation concealment	B – Unclear

<b>Study</b>	<b>Goldstein 1989</b>
Methods	Country: USA Recruitment: community volunteers Randomization: not stated
Participants	89 smokers (excluding 18 early treatment drop-outs not included in results)
Interventions	Factorial design of two types of group treatment, and two schedules for use of nicotine gum. Behaviour therapy arms collapsed 1. Fixed schedule nicotine gum (2 mg); 1 piece/hr for first week with tapering over 10w 2. Ad lib nicotine gum; to be used when urge to smoke, max 30/day Level of support: high (10x 1hr sessions of either intensive cognitive and behavioural skills training or non-specific education and support)
Outcomes	PP abstinence at 6m Validation: Saliva cotinine < 10ng/ml or CO < 8ppm for people still using gum
Notes	Does not contribute to main comparison. Used in comparison of fixed to ad lib schedule gum.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Gourlay 1995</b>
Methods	Country: Australia Recruitment: Community volunteers Randomization: not stated
Participants	629 smokers (> 15 cigs/day) who had relapsed after transdermal nicotine and behavioural counselling in an earlier phase of the study. Minimal additional support
Interventions	1. Nicotine patch 30 cm <sup>2</sup> (21 mg/24hr) for 4w, 20cm <sup>2</sup> (14 mg/24hr for 4w, 10cm <sup>2</sup> (7 mg/24 hrs) for 4w. 2. Placebo patch
Outcomes	Sustained abstinence at 6m Validation: expired CO < 10ppm
Notes	Does not contribute to main comparison. Used only for comparison of patches vs placebo in relapsed smokers.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Gross 1995</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated, stratified on measures of addiction, no blinding
Participants	177 smokers av. age 42 Fagerstrom score 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 All groups received intensive behavioural counselling Level of support: high
Outcomes	Continuous abstinence at 6m (up to 3 cigs allowed)

## Characteristics of included studies (Continued)

	Validation: CO $\leq$ 10ppm. Saliva thiocyanate in week 2.
Notes	Long-term abstinence rates not affected by amount of gum, so these groups collapsed for comparison with no gum condition.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hall 1985</b>
Methods	Country: USA Recruitment: Community volunteers and physician referrals Randomization: 'randomly assigned within time constraints' method not stated
Participants	120 smokers
Interventions	1. Intensive behavioural treatment (14 group sessions over an 8 week period) 2. Combined - 2mg nicotine gum 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 12m Validation: CO $<$ 10ppm and blood thiocyanate $<$ 85 mg/mL.
Notes	2 vs 1 for effect of additional gum. Treatment arm 3 not used in meta-analysis.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hall 1987</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	139 adult smokers av. cigs/day 30
Interventions	1. Nicotine gum (2mg) up to 12 months 2. Placebo gum up to 12 months Level of support: high (group therapy)
Outcomes	Point prevalence abstinence at 12m Validation: CO & cotinine & carboxyhemoglobin
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hall 1996</b>
Methods	Country: USA Recruitment: Community volunteers (US\$75 deposit) Randomization: Stratified by history of depression and no. of cigs/day. Method not stated
Participants	207 smokers of which 6 excluded from analyses because of protocol breaches.
Interventions	2x2 factorial trial of gum and psychological treatment 1. Nicotine gum (2 mg) for 8w 1 piece/hr for 12 hrs/day recommended. Health Education group 2. Nicotine gum, Mood management group 3. Placebo gum, Health Education 4. Placebo gum, Mood Management Level of support: High
Outcomes	Sustained abstinence at 12m Validation: CO $\leq$ 10ppm at 8,12,26w and urinary cotinine $\leq$ 60ng/ml at 52w

## Characteristics of included studies (Continued)

Notes	Psychological treatment arms collapsed as no evidence of a significant interaction. Both constituted high support.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hand 2002</b>
Methods	Country: UK Recruitment: Hospital inpatients or outpatients referred by hospital doctor Randomization: alternation by month of recruitment
Participants	245 patients with smoking related disease. 46%M,
Interventions	1. Nicotine patch (30 or 20 mg based on smoking rate) and inhaler for 3w including tapering. Same counselling as control 2. Individual counselling, 4 sessions in 4w. No placebo Level of support: high
Outcomes	Prolonged abstinence at 12m Validation: CO < 10ppm
Notes	New trial 2004 Used in main comparisons and comparison 9, combination
Allocation concealment	C – Inadequate

<b>Study</b>	<b>Harackiewicz 1988</b>
Methods	Country: USA Recruitment: Primary care (University Health Centre) Randomization: not stated
Participants	Subjects: 197 men and women smoking average 26/day
Interventions	1. Nicotine gum (2 mg) for 6w plus self help manual 2. Self help manual 3. Control Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO in all subjects, cotinine and carboxyhemoglobin in a sub-sample of subjects
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hays 1999</b>
Methods	Country: USA (3 sites) Recruitment: Community volunteers Randomization: not described, but 2 stages - randomization to open label or double blind study then to active or placebo patch
Participants	958 smokers, > 15/day Av age 44
Interventions	1. Nicotine patches (22 mg, 24hr for 6w) purchased by participants, open label 2. Nicotine patches (22 mg 24hr for 6w) provided, double blind 3. Placebo patches provided The intervention replicated an over the counter (OTC) environment, with no counselling intervention and minimal study recording. Level of support: low

**Characteristics of included studies (Continued)**

Outcomes	Abstinence at 6m Validation: CO $\leq$ 8ppm
Notes	1 & 2 vs 3 in patch vs placebo comparisons 2 vs 1 in free versus paid comparison (Comparison 12.1)
Allocation concealment	B – Unclear

<b>Study</b>	<b>Herrera 1995</b>
Methods	Country: Venezuela Recruitment: Community volunteers Randomization: not stated Stratified into high and low dependence groups, who were randomized to different treatments
Participants	smoking >10 cigarettes/day, age > 20, scoring $\geq$ 4 on FTQ, no serious illness. Only those who were ready to quit after 6w of behavioural treatment were randomized.
Interventions	Low dependence smokers (FTQ 4-6): 1. 2 mg nicotine gum 2. Placebo gum Level of support: high (12 group sessions) High dependence smokers (FTQ 7-11): 1. 4 mg nicotine gum plus 2. 2 mg nicotine gum Level of support: high All randomized patients had undergone an intensive 6w behavioural treatment programme.
Outcomes	Sustained abstinence at 12m (and at 2 years). Validation: expired CO < 6ppm
Notes	Low dependence smokers included in comparison 1. High dependence smokers in comparison 2, 4 mg vs 2 mg gum
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hilleman 1994</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated, open label
Participants	140 smokers (excluding a buspirone treatment group), smoking > 20/day, Fagerstom $\geq$ 8 55%F, av cigs/day 25-26
Interventions	1. Nicotine patch (21 mg/24hr) for 6w, no weaning 2. Nicotine patch, 21 mg 4w, weaning to 14 mg 4w, 7 mg 4w Level of support: high (12 weekly behaviour therapy sessions)
Outcomes	Abstinence at 6m Validation: Plasma thiocyanate
Notes	Does not contribute to main comparison
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hjalmarsen 1984</b>
Methods	Country: Sweden Recruitment: Smoking cessation clinic Randomization: not stated
Participants	Subjects: 206 adult smokers

## Characteristics of included studies (Continued)

	Av. cigs/day 23-4
Interventions	1. Nicotine gum (2 mg) (no restrictions on amount or duration of use) 2. Placebo gum Level of support: high (group)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hjalmarson 1994</b>
Methods	Country: Sweden Recruitment: cessation clinic/ community volunteers Randomization: not stated
Participants	248 daily smokers Av. cigs/day 24
Interventions	1. Nicotine nasal spray 2. Placebo spray Spray (0.5 mg/spray) used as required up to 40 mg/day for up to 1 year. Level of support: high (group sessions with clinical psychologist)
Outcomes	Sustained abstinence at 12 months Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Hjalmarson 1997</b>
Methods	Country: Sweden Recruitment: Smoking cessation clinic Randomization: Participants assigned a number on attending first group session. Numbers on a list randomizing to medication. Participants from the same household randomized to same treatment.
Participants	247 smokers (> 10 cigs/day) who had previously made a serious attempt to stop using nicotine gum
Interventions	1. Nicotine Inhaler 2. Placebo inhaler Level of support: high (8 group meetings over 6w)
Outcomes	Sustained abstinence at 12m Validation: CO < 10ppm at 2 and 6w and 3,6,12m.
Notes	New trial 1998/3 update
Allocation concealment	A – Adequate

<b>Study</b>	<b>Huber 1988</b>
Methods	Country: Germany Recruitment: Community volunteers Randomization: method not stated
Participants	225 smokers
Interventions	1. Nicotine gum alone 2. Behaviour therapy, 5 weekly group meetings 3. Nicotine gum and behaviour therapy Level of support: high

## Characteristics of included studies (Continued)

	4. 6m waiting list control
Outcomes	Abstinence at 12m Validation: none
Notes	3 vs 2 in comparison 1.
Allocation concealment	B – Unclear

### Study Hughes 1989

Methods	Country: USA Recruitment: Primary care Randomization: by entering random digit to their subject number
Participants	315 daily cig smokers Av. cigs/day 29
Interventions	1. Nicotine gum (2 mg 3-4m) 2. Placebo gum Level of support: low
Outcomes	Sustained abstinence at 12m Validation: salivary cotinine
Notes	
Allocation concealment	A – Adequate

### Study Hughes 1990

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	78 adult smokers Av. cigs/day 24-30
Interventions	1. Placebo gum 2. 1 mg nicotine gum 3. 2 mg nicotine gum 4. 4 mg nicotine gum Level of support: low
Outcomes	Sustained abstinence at 6m Validation: Independent observer report
Notes	2+3+4 vs 1 in Comparison 1. 4 vs 3 in Comparison 2, low dependence smokers
Allocation concealment	B – Unclear

### Study Hughes 1999

Methods	Country: USA (12 sites), Australia (1 site) Recruitment: Advertisement, referrals and word of mouth. Randomization: not stated
Participants	1039 smokers ( ≥ 30 cigs/day) who had made a prior quit attempt, motivated to try again Av cigs/day 38 50% male Av age 43
Interventions	1. 42 mg nicotine patch (24 hr, 6w + 10w tapering) 2. 35 mg nicotine patch 3. 21 mg nicotine patch

## Characteristics of included studies (Continued)

	4. Placebo patch Group behaviour therapy for 7w, brief individual counselling at 5 dose tapering meetings. Self help booklet Level of support: high
Outcomes	Prolonged abstinence at 6m (from 2w post-quit) verified at each follow-up visit. (12m follow up only completed for 11 of 13 sites) Validation: CO = < 10ppm
Notes	All doses pooled in comparison with placebo. 44 vs 22 in dose response comparison 6m abstinence rates used in analyses since not all centres completed 12m follow up due to sponsor termination of study. Denominators confirmed by author.
Allocation concealment	B – Unclear

### Study **Hughes 2003**

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	115 smokers with a history of alcohol dependence, >= 30 cigs/day 68%M, av cigs/day 30
Interventions	1. 21 mg Nicotine patch (24hr, 6w + 4w tapering + 2w placebo 2. Placebo patch 12w Group behaviour therapy x6, brief individual counselling x3 Level of support: high
Outcomes	Sustained abstinence at 6m (from 2w postquit) Validation: CO=< 10ppm at each follow-up visit
Notes	New trial 2004 Unadjusted ORs not significant, significant when adjusted for smoking variables.
Allocation concealment	B – Unclear

### Study **Hurt 1990**

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	62 adult smokers Av. cigs/day 30
Interventions	1. Nicotine patch (24 hrs, 6w with weaning) 2. Placebo patch Level of support: high (brief advice at study visits)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

### Study **Hurt 1994**

Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	240 adult smokers (mean cigs/day 30)

## Characteristics of included studies (Continued)

Interventions	1. Nicotine patch (22 mg/24hr, 8w, no weaning) 2. Placebo patch Level of support: high (nurse counselling)
Outcomes	Point prevalence abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>ICRF 1994</b>
Methods	Country: UK Setting: Primary Care Randomization: random allocation of study numbers to treatment group and sequential allocation of study numbers.
Participants	1686 heavy (> 15/day smokers)
Interventions	1. Nicotine patch (24hr, 12w with weaning) 2. Placebo Level of support: high (brief advice at study visits)
Outcomes	Sustained abstinence at 12m Validation: Salivary cotinine or CO
Notes	8 year follow up published 2003, not used in MA
Allocation concealment	A – Adequate

<b>Study</b>	<b>Jamrozik 1984</b>
Methods	Country: UK Recruitment: Primary care Randomization: alphabetical code list
Participants	200 adult smokers who had failed to stop smoking during a previous study of the effect of physician advice. Mean cigs/day not stated
Interventions	1. Nicotine gum (2 mg) for 3m or more 2. Placebo gum Level of support: low
Outcomes	PP abstinence at 6m Validation: expired CO
Notes	
Allocation concealment	A – Adequate

<b>Study</b>	<b>Jarvik 1984</b>
Methods	Country: USA Recruitment: Community Volunteers Randomization: method not stated
Participants	Subjects: 48 heavy smokers (> 1 pack/day)
Interventions	1. Nicotine gum (2 mg) given for unstated period 2. Placebo gum Level of support: low
Outcomes	Follow up for 12m. Definition of abstinence endpoint not given Validation: CO



## Characteristics of included studies (Continued)

Notes

Allocation concealment B – Unclear

### Study Jarvis 1982

Methods	Country: UK Recruitment: Smoking cessation clinic Randomization: method not stated
Participants	116 attenders at clinic Av. cigs/day, 26-30
Interventions	1. Nicotine gum (2 mg) unrestricted amount for at least 3m 2. Placebo gum Level of support: high (group therapy)
Outcomes	Sustained abstinence at 12m Validation: CO

Notes

Allocation concealment B – Unclear

### Study Jensen 1991

Methods	Country: Denmark Recruitment: Smoking cessation clinic Randomization: method not stated
Participants	255 adult smokers Av. cigs/day 21-22
Interventions	1. Nicotine gum (2 mg for 3m) 2. Silver acetate chewing gum 3. Placebo gum Level of support: high (9 group meetings over a year)
Outcomes	Sustained abstinence at 6m Validation: CO

Notes

Allocation concealment B – Unclear

### Study Jorenby 1995

Methods	Country: USA Recruitment: Community volunteers Randomization: double blind, no further details
Participants	504 adult smokers $\geq 15$ cigs/day for at least 1 yr
Interventions	1. Nicotine patch 22 mg for 6w then 2w 11 mg with minimal counselling 2. same patch, individual counselling 3. same patch, group counselling. 4. 44 mg patch for 4w then 2w 22 mg then 2w 11 mg with minimal counselling 5. same patch, individual counselling 6. same patch, group counselling.
Outcomes	Abstinence ( $> 1w$ ) at 6m Validation: CO $< 10ppm$
Notes	Does not contribute to comparison 1. Support levels collapsed in comparison 8 between high and standard dose

## Characteristics of included studies (Continued)

Allocation concealment B – Unclear

Study	Jorenby 1999
Methods	Country: USA (4 sites) Recruitment: Advertisements for community volunteers Randomization: method not stated. Unequal cell design, not balanced within sites
Participants	893 smokers, > 15 cigs/day. Av. age 42-44, av cigs/day 25-28
Interventions	1. Nicotine patch (21 mg/24hr for 6w, tapered for 2w) and sustained release bupropion 300 mg for 9w from 1w before quit day 2. Bupropion 300 mg and placebo patch 3. Nicotine patch and placebo tablets 4. Placebo patch and placebo tablets Brief (< 15 min) individual counselling session at each weekly assessment. One telephone call 3 days after quit day Level of support: high
Outcomes	Abstinence at 12m (primary outcome for study was PP abstinence; this analysis uses continuous abstinence since quit day) Validation: Expired CO < 10ppm at each clinic visit
Notes	3 vs 4 in main comparisons. Combinations compared in Comparison 9
Allocation concealment	B – Unclear

Study	Joseph 1996
Methods	Country: USA, multicentre trial Recruitment: 10 Veterans Affairs Medical Centers Randomization: Co-ordinating centre used computer-generated schedule to randomly assign in blocks of 10
Participants	584 smokers (> 15 cigs/day) with a history of cardiac disease. Patients with cardiac events within the last 2w were excluded.
Interventions	1. Nicotine patch, (21 mg/24hr for 6w, 14 mg for 2w, 7 mg for 2w) 2. Placebo patch Level of support: High (self help pamphlets and brief behavioural counselling on 3 occasions)
Outcomes	PP abstinence at 6m (Joseph 1996), 12m (Joseph 1999) Validation: CO ≤ 10ppm
Notes	New trial 1998/3 update using 6 month outcomes. 12 month outcomes reported 1999, used from 2000/3 update.
Allocation concealment	A – Adequate

Study	Killen 1984
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	64 adult smokers. Mean cigs/day 31.7.
Interventions	1. Nicotine gum (2 mg) for 7w 2. Skills training 3. Skills training plus nicotine gum Level of support: high (group therapy)
Outcomes	Sustained abstinence at 10.5 months Validation: CO

## Characteristics of included studies (Continued)

Notes	1+3 vs 2
Allocation concealment	B – Unclear

<b>Study</b>	<b>Killen 1990</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	1218 adult smokers. Mean cigs/day 25.
Interventions	1. Nicotine gum (2 mg, 8w) ad lib dosing 2. Nicotine gum on a fixed dose 3. Placebo gum 4. No gum Each group was also factorially randomized to one of three psychological interventions (all high support).
Outcomes	Sustained abstinence at 12m Validation: CO

Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Killen 1997</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	424 smokers
Interventions	2x2 factorial design 1. Nicotine patch (21 mg/24hr) for 8w, 14 mg for 4w, 7 mg for 4w 2. Placebo patch 3. Nicotine patch and video (The video was shown at initial visit and a copy supplied for home use) 4. Placebo patch and video Level of support: low (All treatment groups received a self help treatment manual designed to develop self regulatory skills.
Outcomes	Sustained abstinence at 12m (7 day PP at 6 and 12m) Validation: saliva cotinine < 20ng/ml with the exception of participants living outside the area
Notes	Since there was evidence of an interaction between nicotine and video conditions, arms entered separately.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Killen 1997 (Video)</b>
Methods	Dummy study for Killen 1997 to enter treatment conditions using a video in addition to self help manual
Participants	
Interventions	
Outcomes	
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Killen 1999</b>
Methods	Country: USA Recruitment: Community volunteers responding to advertisements - heavy smokers selected from responders Randomization: method not stated

**Characteristics of included studies (Continued)**

Participants	408 heavy smokers (> 25/day) 59% M Av cigs/day 36 Modified Fagerstrom score 18 Av age 47
Interventions	1. 25 mg nicotine patch for 6w (16 hr, no tapering) 2. 15 mg nicotine patch for 6w Self help treatment manual, short video showing patch use and placement
Outcomes	Sustained abstinence at 12m (7 day PP abstinence at both 6 and 12m) (Follow up at 2m in person, 6 and 12m by telephone Validation: Saliva cotinine < 20 ng/ml (not required for 3 individuals not in area)
Notes	Does not contribute to comparison 1. 85% of self reported quitters provided samples for validation at 12m
Allocation concealment	B – Unclear

**Study Kornitzer 1987**

Methods	Country: Belgium Recruitment: Worksite primary care clinic Randomization: method not stated
Participants	199 adult smokers (mean cigs/day 24-5)
Interventions	1. Nicotine gum (4 mg) for at least 3m 2. Nicotine gum (2 mg) for same time period Level of support: low
Outcomes	PP abstinence at 12m Validation: cotinine and carboxyhemoglobin in a sub-sample of subjects
Notes	Contributes data only to 4 mg vs 2 mg Comparison 2
Allocation concealment	B – Unclear

**Study Kornitzer 1995**

Methods	Country: Belgium Recruitment: Worksite Randomization: Computer generated list.
Participants	374 healthy volunteers, male and female, age >20 years Number of cigarettes: >10 day for > 3 years.
Interventions	1. Nicotine patch (12w 15mg/16hr, 6w 10mg, 6w 5mg) and nicotine gum (2mg, as required) 2. Nicotine patch and placebo gum 3. Placebo patch and placebo gum. Level of support: high (nurse counselling)
Outcomes	Sustained abstinence at 12m Validation: CO <10 ppm
Notes	Contributes data to main comparisons and to patch plus gum vs patch alone comparison.
Allocation concealment	A – Adequate

**Study Leischow 1996**

Methods	Country: USA Recruitment: Community volunteers Randomization: computer generated code
Participants	222 smokers > 20 cigs/day. (2 excluded from analysis having received incorrect prescription)

## Characteristics of included studies (Continued)

Interventions	1. Nicotine Inhaler. Advised to use 4-20 cartridges/day for 3m. After this tapering was encouraged until 6m. 2. Placebo inhaler Participants received advice and watched a video showing proper use of the inhaler. Level of support: high (brief individual smoking cessation support at each study visit, 10 in all)
Outcomes	Sustained abstinence at 12m Validation: CO < 10ppm at each follow up
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Leischow 1999</b>
Methods	Country: USA Recruitment: media advertisements Randomization: method not stated
Participants	300 smokers prepared to purchase patch and make a quit attempt
Interventions	1. Nicotine patch (15 mg/16hr) which could be purchased (1w supply for US\$15) for up to 26w. No behavioural support apart from patch package insert. 2. Nicotine patch for purchase as 1. Prescription for 12w provided after physician visit. Prescription renewed on request up to 26w. Behavioural support based on NCI guidelines, 5-10 mins. Study staff also allowed to give behavioural support.
Outcomes	Continuous abstinence from date of first patch purchase at 12m (non-purchasers counted as failures) (PP rates also reported) Validation: CO < 9ppm
Notes	Does not contribute to main comparison. Compared different ways of buying patch - simulating OTC, or with physician prescription and support.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Leischow 2003</b>
Methods	Country: USA Recruitment: media advertisements Randomization: method not stated
Participants	520 smokers prepared to purchase inhaler and make a quit attempt
Interventions	1. Nicotine inhaler could be purchased ad lib. Standard package information, no further behavioural support 2. Nicotine inhaler could be purchased ad lib via health care provider. Support materials and brief behavioural intervention given at first clinic visit and week 2
Outcomes	Continuous abstinence at 12m Validation: CO
Notes	New trial based on abstract 2004. Does not contribute to comparison 1. See Leischow 1999
Allocation concealment	B – Unclear

<b>Study</b>	<b>Lewis 1998</b>
Methods	Country: USA Recruitment: Hospitalized patients willing to make a quit attempt Randomization: predetermined computer generated code
Participants	185 smokers, av. age 43-44, cigs/day 23-24
Interventions	1. Minimal intervention, 2-3 mins motivational message and self help pamphlet 2. As 1. plus placebo patch. Nurse provided brief telephone counselling at 1,3,6 and 24w

## Characteristics of included studies (Continued)

	3. As 2. plus nicotine patch (22 mg/ 24hs for 3w, tapered to 11 mg for 3w) Level of support: low
Outcomes	PP abstinence at 6m Validation: CO $\leq$ 10ppm
Notes	3 vs 1+2
Allocation concealment	A – Adequate

<b>Study</b>	<b>Llivina 1988</b>
Methods	Country: Spain Recruitment: Smoking cessation clinic Randomization: method not stated
Participants	216 adult smokers. Mean cigs/day 28-30
Interventions	1. Nicotine gum (dose not stated) for 1m 2. Placebo gum Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Malcolm 1980</b>
Methods	Country: UK Recruitment: Community volunteers Randomization: method not stated
Participants	194 adult smokers (mean cigs/day 25-26)
Interventions	1. Nicotine gum (2 mg) for at least 3m 2. Placebo gum 3. Control Level of support: high (individual counselling)
Outcomes	Sustained abstinence at 6m Validation: venous carboxyhaemoglobin
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Marshall 1985</b>
Methods	Country: UK Setting: Primary care - patients responding to a postcard from a GP (ie selected by motivation) Randomization: method not stated, married couples allocated to same group
Participants	200 smokers, 21% had a smoking-related disease Av. age 41, av.cigs/day 22
Interventions	1. Physician advice plus nicotine gum 2. As 1. and offer of 4 follow-up visits over 3m
Outcomes	Sustained abstinence at 12m (and 6m) Validation: expired CO.
Notes	Does not contribute to comparison 1. Test of different intensity of support.
Allocation concealment	B – Unclear

## Characteristics of included studies (Continued)

Study	McGovern 1992
Methods	Country: USA Recruitment: Community volunteers Randomization: by clinic group
Participants	293 adult smokers. Mean cigs/day not stated. 58% smoked > 25/day
Interventions	1. ALA Freedom from Smoking clinic program plus nicotine gum (2 mg for 3m) 2. ALA Freedom from Smoking clinic program alone (no placebo gum) Level of support: high
Outcomes	PP abstinence at 12m Validation: salivary thiocyanate
Notes	
Allocation concealment	C – Inadequate

Study	Molyneux 2003
Methods	Country: UK Recruitment: hospital Randomization: in blocks of 9, concealment not described
Participants	274 smokers (182 in relevant arms) admitted to medical and surgical wards, smoked in last 28 days 60% M, av age 60, median cigs/day 17, 81% had previous quit attempt
Interventions	1. Choice of NRT products (15 mg 16hr 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 meta-analysis) Level of support: low
Outcomes	Continuous abstinence at 12m Validation: CO < 10ppm
Notes	New 2004 update. 63% chose patch, 13% inhalator, 11% gum, 8% tablets and 1% nasal spray, 4% declined use
Allocation concealment	B – Unclear

Study	Mori 1992
Methods	Country: Japan Recruitment: hospital Randomization: method not stated
Participants	264 smokers with smoking-related illness. Number of cigs/day not stated.
Interventions	1. Nicotine gum 2 mg for 3m 2. Placebo gum Level of support: low
Outcomes	Abstinence (not defined) at 6m Validation: serum thiocyanate
Notes	
Allocation concealment	B – Unclear

Study	Nakamura 1990
Methods	Country: Japan Recruitment: Community volunteers

## Characteristics of included studies (Continued)

	Randomization: by number in screening programme, and by worksite
Participants	60 adult smokers. Mean cigs/day 31
Interventions	1. Nicotine gum (2 mg, 2m or longer) 2. Non-placebo control group received counselling Level of support: high
Outcomes	Sustained abstinence at 6m Validation: CO
Notes	
Allocation concealment	B – Unclear

### Study Nebot 1992

Methods	Country: Spain Recruitment: Primary care Randomization: physicians randomized to treatment, method not stated
Participants	425 unselected smokers. 60-70% smoking > 15 cigs/day
Interventions	1. Brief counselling from physician 2. Physician counselling plus nicotine gum 3. Health education from nurse Level of support: low
Outcomes	PP abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

### Study Niaura 1994

Methods	Country: USA Recruitment: Outpatient settings and physician referrals. (volunteers) Randomization: method not stated. Stratified by nicotine dependence.
Participants	77 low dependence and 96 high dependence smokers
Interventions	1. Nicotine gum 2 mg, ad lib for up to 4m (participants given prescription for gum, not free) 2. No gum Level of support: high (4 individual counselling sessions and ALA self help treatment manuals)
Outcomes	Continuous abstinence at 12m Validation: saliva cotinine, or CO for gum users
Notes	Data collapsed across dependence levels.
Allocation concealment	B – Unclear

### Study Niaura 1999

Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated, no placebo
Participants	120 smokers 50% F, av cigs/day 28, av age 43.5
Interventions	1. Brief cognitive behavioral relapse prevention (CBRP) , 15 min sessions 2. Intensive CBRP with nicotine gum (2 mg) 3. Intensive CBRP with cue exposure



**Characteristics of included studies (Continued)**

	4. Intensive CBRP with cue exposure + nicotine gum Level of support: high (group)
Outcomes	Sustained abstinence, 12m and all previous follow ups (1, 3, 6m) Validation: CO < 8ppm
Notes	4 vs 3, behavioural support not identical in others
Allocation concealment	B – Unclear

**Study Ockene 1991**

Methods	Country: USA Recruitment: Primary care Randomization: Each physician delivered one of the three interventions according to instructions in a packet for each patient.
Participants	1223 unselected smokers, mean cigs/day 22-23
Interventions	1. Advice only 2. Patient-centred counselling 3. Patient-centred counselling and nicotine gum (2 mg) plus minimal or intensive follow up by telephone. Level of support: mixed
Outcomes	PP abstinence at 6m Validation: none
Notes	
Allocation concealment	A – Adequate

**Study Page 1986**

Methods	Country: Canada Recruitment: Primary care (5 family practices in Ontario) Randomization: by day of attendance
Participants	275 unselected smokers. Primary care attenders aged 18 - 65 years Number of cigs smoked not stated
Interventions	1. No advice 2. Advice to quit 3. Advice to quit plus offer of nicotine chewing gum prescription (2 mg) Level of support: low
Outcomes	Sustained abstinence at 6m Validation: none
Notes	3 vs 1+2
Allocation concealment	C – Inadequate

**Study Paoletti 1996**

Methods	Country: Italy Recruitment: Community volunteers Randomization: method not stated, parallel group design
Participants	297 adult smokers (at least 10 cigs/day for at least 3 years) Stratified according to baseline cotinine levels
Interventions	Stratum A (Baseline cotinine < 250 ng/ml) 1. Nicotine patch (15 mg/16hr) 2. Placebo patch Stratum B (Baseline cotinine > 250 ng/ml)

## Characteristics of included studies (Continued)

	3. Nicotine patch 15 mg 4. Nicotine patch 25 mg Level of support: low
Outcomes	PP abstinence at 12m Validation: CO and plasma cotinine
Notes	Stratum A in Comparison 1 Stratum B in Comparison 8 (high versus standard dose patch)
Allocation concealment	B – Unclear

<b>Study</b>	<b>Patterson 2003</b>
Methods	Country: USA Recruitment: Community volunteers and referrals Randomization: method not stated
Participants	353 adult smokers (at least 10 cigs/day for last year) 54% F, av cigs/day 22
Interventions	1. Nicotine patch (21 mg/24hr) for 8w incl weaning 2. Nicotine nasal spray (8-40 doses/day, max 5/hr) for 8w, weaning over final 4 Both arms received 7x90 min behavioural group counselling. TQD in week 3.
Outcomes	Continuous (no lapses to smoking on 7 consecutive days since TQD) abstinence at 6m Validation: CO < 10ppm
Notes	New for 2004 Does not contribute to main comparison 1, only head to head comparison
Allocation concealment	B – Unclear

<b>Study</b>	<b>Perng 1998</b>
Methods	Country: Taiwan Recruitment: Outpatient chest clinics Randomization: performed by an independent facility
Participants	62 volunteers smokers (> 20 cigs/day)
Interventions	1. Nicotine patch (24 mg/24 hr for 6w, no weaning) 2. Placebo patch Weekly visit to Outpatient department for assessment, unclear if counselling was provided Level of support: low
Outcomes	Abstinence at 12m Validation: CO < 10ppm during patch use, but no validation at 12m
Notes	
Allocation concealment	A – Adequate

<b>Study</b>	<b>Pirie 1992</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: not stated
Participants	417 women smokers. Mean cigs/day 25-27.
Interventions	1. Group therapy 2. Group therapy plus weight control programme 3. Group therapy plus nicotine gum 4. Group therapy plus weight control programme and nicotine gum.

## Characteristics of included studies (Continued)

	Gum type: 2 mg ad lib Level of support: high
Outcomes	Sustained abstinence at 12m Validation: expired CO
Notes	3 & 4 compared to 1 & 2
Allocation concealment	B – Unclear

### Study **Puska 1979**

Methods	Country: Finland Recruitment: Community volunteers Randomization: method not stated
Participants	229 adult smokers, 80% smoking > 15 cigs/day
Interventions	1. Nicotine gum (4 mg) for 3w 2. Placebo gum for 3w Level of support: high (group therapy)
Outcomes	PP abstinence at 6m. Validation: none
Notes	
Allocation concealment	B – Unclear

### Study **Puska 1995**

Methods	Country: Finland Recruitment: Community volunteers Randomization: not stated
Participants	300 volunteers aged 20-65, smoking >10 ciges/day for >3 years, no serious illness
Interventions	1. Nicotine patch for 16hrs daily for 12w, tapered for further 6w plus 2 mg nicotine gum at least 4 daily 2. Placebo patch plus nicotine gum (same regimen) Patch type: 15 mg worn for 16hrs (Nicorette) Gum type: 2 mg (Nicorette) Level of support: low (advice from study nurses)
Outcomes	Sustained abstinence at 12m Validation: expired CO < 10 ppm
Notes	Does not contribute to main comparison, only combinations comparison
Allocation concealment	B – Unclear

### Study **Richmond 1990**

Methods	Country: Australia Recruitment: Primary Care Randomization: by week
Participants	450 adult smokers. Mean cigs/day 15-21.
Interventions	1. Smokescreen programme plus nicotine gum, dose and duration not stated 2. Smokescreen programme alone 3. Brief advice. Level of support: mixed
Outcomes	PP abstinence at 12m Validation: expired CO

**Characteristics of included studies (Continued)**

Notes

Allocation concealment C – Inadequate

**Study Richmond 1994**

Methods Country: Australia  
Recruitment: Community volunteers  
Randomization: central pharmacy generation

Participants 315 smokers, mean cigs/day 29.

Interventions 1. Nicotine patch (24hr, 22 mg for 6w, 14 mg 2w, 7 mg 2w)  
2. Placebo patch  
Level of support: high (group therapy)

Outcomes Sustained abstinence at 12m  
Validation: expired CO

Notes 12m data from 1997 paper

Allocation concealment A – Adequate

**Study Roto 1987**

Methods Country: Finland  
Recruitment: Primary care (occupational health centres)  
Randomization: method not stated

Participants 121 smokers (> 10 cigs/day, > 1 year)  
43%F

Interventions 1. Nicotine gum (2 mg and 4 mg), + advice  
2. Advice only (no placebo)  
Level of support: low

Outcomes Abstinence at 6m (not defined)  
Validation: not described

Notes

Allocation concealment B – Unclear

**Study Russell 1983**

Methods Country: UK  
Recruitment: Consecutive attenders admitting to being cigarette smokers and consenting to participate at 6 general practices (primary care)  
Randomization: according to week of attendance

Participants 2106 adult smokers. Mean cigs/day 17.5

Interventions 1. No intervention  
2. Advised to stop smoking plus provided with a “give up smoking” booklet  
3. As group 2, plus offer of nicotine gum prescription, Individual therapy, Single visit, One minimal content, one more intensive content, intervention, untrained therapist  
Level of support: low

Outcomes Sustained abstinence at 4 and 12m  
Validation: 66% of those claiming to have quit validated with CO

Notes 3 vs 2+1

Allocation concealment C – Inadequate

## Characteristics of included studies (Continued)

Study	Sachs 1993
Methods	Country: USA Recruitment: Community volunteers Randomization method: not stated
Participants	220 adult smokers. Mean cigs/day 28-9.
Interventions	1. Nicotine patch (16hr, 3m + tapering) 2. Placebo patch Level of support: high (physician advice)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear
Study	Schneider 1985
Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	Study A: 60 heavy smokers (mean cigs/day 30-35) treated in clinic setting. Study B: 36 heavy smokers (mean cigs/day 30-35) treated by dispensing only.
Interventions	Study A: 1. 2 mg nicotine gum, duration not stated 2. Placebo gum Level of support: high (individual support at multiple assessment visits) Study B: 1. Nicotine gum, 2 mg duration not stated 2. Placebo gum Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear
Study	Schneider 1995
Methods	Country: USA Recruitment: Community volunteers (radio and newspaper ads) Randomization: method not stated
Participants	255 adults with no serious illness, smoking > 15 cigs/day for > 2 years with baseline CO level > 20 ppm. Mean cigs/day 28-29.
Interventions	1. Nicotine nasal spray 2. Placebo spray Nicotine dosage: 0.5 mg of nicotine per spray. Not less than 8 doses/day and not more than 32 doses/day for 6w, with free use for further 6m Level of support: high (repeated clinic visits for assessment)
Outcomes	Sustained abstinence at 12m Validation: CO < 8 ppm
Notes	
Allocation concealment	B – Unclear

## Characteristics of included studies (Continued)

<b>Study</b>	<b>Schneider 1996</b>
Methods	Country: USA Recruitment: Community volunteers Randomization: Centralized computer generated by a third party
Participants	223 adult smokers (at least 10 cigs/day for 3 years)
Interventions	1. Nicotine inhaler (4-20 inhalers per day) for up to 6m, with weaning from 3m 2. Placebo inhaler Level of support: high (repeated clinic visits for assessment)
Outcomes	Sustained abstinence at 12m Validation: CO and salivary cotinine
Notes	
Allocation concealment	A – Adequate
<b>Study</b>	<b>Schuermans 2004</b>
Methods	Country: South Africa Recruitment: Community volunteers Randomization: computer generated, independent, blinding maintained
Participants	200 smokers 45% F, av. age 46, av cigs/day 25
Interventions	1. Pretreatment with nicotine patch for 2w prior to quit date. Then active patch (15 mg) patch for 12w including weaning. 4 sessions of counselling over 10w. 2. Pretreatment with placebo patch. The active patch as 1.
Outcomes	Sustained abstinence at 6m Validation: CO < 10ppm
Notes	New 2004. Does not contribute to main comparison
Allocation concealment	A – Adequate
<b>Study</b>	<b>Segnan 1991</b>
Methods	Country: Italy Recruitment: Consecutive patients attending 44 general practices in Italy Randomization: Sequential, sealed envelopes
Participants	Subjects: General practice attenders aged 20-60. Mean cigs/day not stated. Therapists: GPs who had undergone a 3hr training session
Interventions	1. Advice and leaflet 2. Repeated counselling (followup at 1,3,6,9 months) 3. Repeated counselling plus nicotine gum, dose not stated up to 3 months 4. Repeated counselling plus spirometry Level of support: high
Outcomes	Sustained abstinence at 12m Validation: urinary cotinine
Notes	3 vs 1+2+4
Allocation concealment	A – Adequate
<b>Study</b>	<b>Shiffman 2002a</b>
Methods	Country: USA & UK (15 sites) Recruitment: community volunteers

## Characteristics of included studies (Continued)

	Randomization: method not stated
Participants	917 smokers, time to first cigarette over 30 mins. 58% F, Av age 41, cigs/day 17
Interventions	1. Nicotine lozenge, 2 mg. Recommended dose 1 every 1-2 hrs, min 9, max 20/day for 6w, decreasing 7-12w, available as needed 13-24w 2. Placebo lozenge, same schedule Level of support: high (brief advice at 4 visits)
Outcomes	Continuous abstinence at 12m (Sustained from 2w, no slips allowed). Validation: CO $\leq$ 10ppm at all follow ups. (only abstainers continued in study)
Notes	Dose based on dependence level. Low dependence group here. High dependence group in Shiffman 2002B
Allocation concealment	B – Unclear

### Study Shiffman 2002b

Methods	Country: USA & UK (15 sites) Recruitment: Community volunteers Randomization: method not stated
Participants	901 smokers, time to first cigarette < 30 mins 55% F, Av age 44, cigs/day 26
Interventions	1. Nicotine lozenge, 4 mg. Recommended dose 1 every 1-2 hrs, min 9, max 20/day for 6w, decreasing 7-12w, available as needed 13-24w. 2. Placebo lozenge, same schedule
Outcomes	Continuous abstinence at 12m. (Sustained from 2w, no slips allowed). Validation: CO $\leq$ 10ppm at all follow ups. (only abstainers continued in study)
Notes	Dose based on dependence level. high dependence group here. Low dependence group in Shiffman 2002A
Allocation concealment	D – Not used

### Study Sonderskov 1997

Methods	Country: Denmark Recruitment: Customers seeking to buy nicotine patches over the counter at 42 pharmacies Randomization: Sequential treatment packages, stratified by smoking level
Participants	522 smokers of > 10 cigs/day. Smokers of > 20 cigs/day used a higher dose patch than lower rate smokers.
Interventions	1. Nicotine patch (24hr). > 20/day smokers used 21 mg for 4w, 14 mg for 4w, 7 mg for 4w. Smokers of < 20/day used 14 mg for first 8w, 7 mg for 4w 2. Placebo patches Level of support: low
Outcomes	Abstinence at 6m - no reported smoking in the last 4w, by telephone interview with neutral independent assessor Validation: none
Notes	
Allocation concealment	A – Adequate

### Study Stapleton 1995

Methods	Country: UK Setting: Primary care Randomization: computer generated list
Participants	1200 smokers considered by GP to be highly dependent and motivated to give up. Mean cigs/day 23-4
Interventions	1. 16hr (18w) nicotine patch at standard dose 2. 16hr (18w) nicotine patch with dose increase as required

## Characteristics of included studies (Continued)

	3. Placebo patch group The nicotine patch groups were further randomized to gradual or abrupt withdrawal at week 12. Level of support: high (physician advice)
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	A – Adequate

<b>Study</b>	<b>Sutherland 1992</b>
Methods	Country: UK Recruitment: Smoking cessation clinic Randomization: Drew card with A or P for active or placebo allocation
Participants	227 adult smokers. Mean cigs/day: 25-27
Interventions	1. Nicotine nasal spray, maximum 40 mg/day 2. Placebo spray Level of support: high
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	Follow up beyond 1 year reported in Stapleton 1998. Data not used in review.
Allocation concealment	B – Unclear

<b>Study</b>	<b>Sutton 1987</b>
Methods	Country: UK Recruitment: Worksite primary care clinic Randomization: method not stated.
Participants	334 adult smokers. Mean cigs/day 15.5.
Interventions	1. Nicotine gum (2 mg) x at least 4 boxes, duration not stated 2. No intervention control group (no placebo) Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Sutton 1988</b>
Methods	Country: UK Recruitment: Worksite primary care clinic in UK Randomization: not stated
Participants	161 adult smokers who were still smoking after three months of a videotape smoking cessation programme. Mean cigs/day 15-19.
Interventions	1. Nicotine gum (2 mg) up to 12w 2. Non-intervention control group (no placebo) Level of support: low
Outcomes	Sustained abstinence at 12m Validation: CO
Notes	
Allocation concealment	B – Unclear



## Characteristics of included studies (Continued)

Study	TNSG 1991
Methods	Country: USA (9 sites) Recruitment: Community volunteers (treated at smoking cessation clinics) Randomization: not stated
Participants	808 adult smokers Mean cigs/day 30-31
Interventions	1. Nicotine patch 21 mg (24hr, 6w+) 2. Nicotine patch 14 mg 3. Placebo patch Level of support: high (group therapy)
Outcomes	Sustained abstinence at 6m Validation: CO
Notes	Two trials pooled and data relating to a 7 mg patch group used in only one trial omitted. Long-term (4-5 year) follow-up data reported for 7/9 sites (Daughton 1999). Data not used in review
Allocation concealment	B – Unclear
Study	Tonnesen 1988
Methods	Country: Denmark Recruitment: primary care Randomization: by numbered envelope
Participants	Subjects: Study A: 113 smokers with medium dependence randomized to gum or placebo Study B: 60 highly dependent smokers randomized to 4 mg or 2 mg gum
Interventions	Study A: 1. Nicotine Gum (2 mg) for 16w 2. Placebo Level of support: high (group therapy) Study B: 1. Nicotine gum 4 mg 2. Nicotine gum 2 mg
Outcomes	Sustained abstinence at 24m Validation: expired CO
Notes	Study A in Comparison 1, Study B in Comparison 2, high dependence smokers.
Allocation concealment	A – Adequate
Study	Tonnesen 1991
Methods	Country: Denmark Recruitment: Community volunteers Randomization: Packages labelled with consecutive numbers generated by computer generated random code
Participants	289 adult smokers of at least 10 cigs/day. (mean 21-22)
Interventions	1. 16hr (12w) nicotine patch (15+/-3,5 mg) with tapering 2. Placebo patch Level of support: low
Outcomes	Sustained abstinence at 24m Validation: expired CO
Notes	
Allocation concealment	A – Adequate

## Characteristics of included studies (Continued)

Study	Tonnesen 1993
Methods	Country: Denmark Recruitment: Community volunteers Randomization: Computer generated randomization code
Participants	286 smokers, mean cigs/day 20.
Interventions	1. Nicotine inhaler (2-10/day) up to 6m 2. Placebo inhaler Level of support: high (brief advice at clinic visits)
Outcomes	Sustained abstinence at 12m Validation: expired CO
Notes	
Allocation concealment	A – Adequate

Study	Tonnesen 2000
Methods	Country: Denmark Recruitment: Referrals to lung clinic Randomization: computer generated list of random numbers, (open label)
Participants	446 smokers > 10 cigs/day willing to quit and use NRT 52% F, av age 49, av cigs/day 18
Interventions	1. 5 mg nicotine patch (placebo) 2. 15 mg (16hr) nicotine patch for 12w (up to 9m on request) 3. Nicotine inhaler (4-12/day ad lib) 4. Combination, 15 mg patch and inhaler All received physician advice + brief nurse counselling at each follow up visit Level of support: high
Outcomes	Abstinence at 12m, sustained from week 2 (paper also reports PP and with slips rates) Validation: CO < 10ppm at all visits
Notes	In main comparison, combination, and head to head comparisons.
Allocation concealment	A – Adequate

Study	Villa 1999
Methods	Country: Spain Recruitment: Volunteers working in a university health and safety department Randomization: method not described
Participants	47 smokers av age 36, cigs/day 24-26
Interventions	1. Nicotine gum (2 mg) 2. No gum Level of support: high (8 weekly group sessions)
Outcomes	Abstinence at 12m (not defined) Validation: none
Notes	
Allocation concealment	B – Unclear

Study	Wallstrom 2000
Methods	Country: Sweden

## Characteristics of included studies (Continued)

	Recruitment: community volunteers Randomization: computer assignment
Participants	247 smokers aged $\geq 20$ , smoking $\geq 10$ cigs/day for $\geq 3$ years 59% F, av age 45, av cigs/day 18-20
Interventions	1. Nicotine sublingual tablet. Recommended dosage 1 tabt/hr for smokers with FTQ $< 7$ , 2 tabs/hr for scores $\geq 7$ . After 3m treatment, tapering period of 3m if necessary 2. Placebo tablet Level of support: high (brief 5mins counselling at all study visits)
Outcomes	Abstinence (sustained from week 2) at 12m Validation: CO $< 10$ ppm
Notes	
Allocation concealment	A – Adequate

<b>Study</b>	<b>Wennike 2003</b>
Methods	Country: Denmark Recruitment: community volunteers for smoking reduction Randomization: method not stated
Participants	411 smokers interested in reducing but unwilling/unable to give up, smoking $\geq 15$ cigs/day 62% F, av age 45, av cigs/day 24
Interventions	1. Nicotine gum, 2 mg if FTND = 5, 4 mg if = 6-10, for up to 12m 2. Placebo gum Brief individual information on smoking reduction, effects on health, suggestions on ways to reduce number of cigs, cessation recommended as ultimate goal
Outcomes	PP abstinence at 24m Sustained (4, 12, 24m) and PP reduction of $> 50\%$ at 24m Validation: CO $< 10$ ppm
Notes	New for 2004 update Reduction study. Does not contribute to main comparisons. PP reduction gives a more conservative treatment effect so used in MA
Allocation concealment	B – Unclear

<b>Study</b>	<b>Westman 1993</b>
Methods	Country: USA Recruitment: community volunteers Randomization: not stated
Participants	159 volunteers smoking at least 1 pack cigs daily
Interventions	1. 2x 24hr nicotine patches (25 mg) per day for 4w, then 1 patch per day for 2w 2. Placebo patches Level of support: high (telephone counselling and self help materials)
Outcomes	Sustained abstinence at 6m Validation: CO
Notes	
Allocation concealment	B – Unclear

<b>Study</b>	<b>Wisborg 2000</b>
Methods	Country: Denmark Recruitment: volunteers, antenatal clinic

## Characteristics of included studies (Continued)

	Randomization: centrally held list
Participants	250 pregnant women who continued to smoke after 1st trimester Av age 28, av cigs/day 14 43% primiparous
Interventions	1. Nicotine patch, 15 mg/16hr, tapering to 10 mg. 11w total 2. Placebo patch Level of support: high. 4x 15-20 min sessions of midwife counselling at 0,4,11w from enrolment, and 4w before expected delivery
Outcomes	Abstinence at 1 year post partum (telephone interview). (Rates at 3m post partum and 4w prior to delivery also reported) Validation: Cotinine < 26 ng/ml at 4w 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. Quit rate high in both groups.
Allocation concealment	A – Adequate

### Study Wong 1999

Methods	Country: USA Recruitment: Community volunteers Randomization: Computer generated schedules, stratified by gender
Participants	100 smokers (> 10 cigs/day for > 1 year) Av age 42, 53%F, cigs/day 28
Interventions	Factorial study of nicotine patch and naltrexone, No placebo patch Nicotine patch: 21 mg (24hr) for 8w, tapering to 14 mg for 4w Naltrexone: 50 mg/day for 12w Level of support: High (individual counselling, 15-20 mins at 8 study visits)
Outcomes	Continuous abstinence at 6m Validation: CO ≤ 8ppm
Notes	One site from a multicentre trial. No significant main effects of naltrexone, so arms collapsed.
Allocation concealment	A – Adequate

### Study Zelman 1992

Methods	Country: USA Recruitment: Community volunteers Randomization: method not stated
Participants	126 smokers, (mean cigs/day 24-27)
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 (group format)
Outcomes	Sustained abstinence at 12m Validation: Independent observer report
Notes	
Allocation concealment	B – Unclear

CO = carbon monoxide in exhaled air. hr=hour. w=week. m=month. EOT=end of treatment. MA=meta-analysis. FTND=Fagerstrom Test for Nicotine Dependence. FTQ=Fagerstrom Tolerance Questionnaire. PP=point prevalence. ITT=intention-to-treat. OR=Odds Ratio. OTC=over the counter. ALA=American Lung Association. TQD=target quit date

## Characteristics of excluded studies

Study	Reason for exclusion
Brantmark 1973	Double blind gum/placebo only for 1st week of clinic, then both groups offered active gum during 6 month follow-up period
Carpenter 2003	Control group also offered NRT if a quit attempt planned.
Chou 2004	Only 3 month follow up
Christen 1984	Only 15 week follow up
Cohen 1989a	Primarily a trial of training dentists. Included in review of training of health professionals (Lancaster 1996)
Cohen 1989b	Primarily a trial of training doctors. Included in review of training of health professionals (Lancaster 1996)
Dey 1999	Compared free and paid prescription for nicotine patch. Only 14 week follow up
Elan Pharm 88-02	No long-term follow up. Long-term follow up for 1 site included as Hurt 1990
Elan Pharm 90-03	No long-term follow up. Long-term follow up for 1 site included as Fiore 1994 (Study 1)
Fagerstrom 1993	Endpoint withdrawal symptoms not cessation
Fagerstrom 1997	Short-term crossover 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.
Fagerstrom 2000	Short-term crossover trial comparing 2 nicotine delivery devices
Foulds 1993	Follow up less than 6 months
Glover 1992	Follow up less than 6 months
Hajek 1999	Follow up less than 6 months. There were no significant differences in 12 week abstinence rates between gum, patch, spray or inhaler groups.
Hanson 2003	Follow up only 10 weeks; primary outcomes were withdrawal, craving, safety and compliance among adolescents
Hughes 1989b	No long-term follow up, primarily a trial of the effect of instructions.
Hurt 1994b	Not randomized
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
Kalman 2004	Follow up only 12 weeks. No significant difference between high and standard dose patch.
Kapur 2001	Only 12 weeks follow up. Trial of nicotine patch in pregnant smokers. 30 participants.
Korberly 1999	Insufficient data in unpublished abstracts to include.
Kozak 1995	Open label study in which smokers with higher nicotine dependence scores were given higher patch doses
Krumpe 1989	Only 10 week follow up
Kupecz 1996	Participants were randomized by month of treatment to group therapy with nicotine patch (n=21) or gum (n=17).
Leischow 1996b	Only 10 weeks follow up
Levin 1994	Only 9 weeks follow up
Lin 1996	Only 8 weeks follow up
Meier 1990	Short-term follow up. Compared dependence individualized to standard dose patch.

**Characteristics of excluded studies (Continued)**

Merz 1993	Only 3 months follow up
Minneker 1989	Only 9 weeks follow up
Molander 2000	Crossover study with 2 day smoke-free periods
Mulligan 1990	Only 6 weeks follow up
Pomerleau 2003	Compared extended treatment (18 weeks) to 10 week treatment with nicotine patch. No follow up beyond 18 weeks
Rose 1990	Only 3 weeks follow up
Sachs 1995	Only 6 weeks follow up
Shiffman 2000d	Comparison between 24 and 16 hour patches. Assessment of craving and abstinence over 2 weeks.
Shiffman 2002c	Only 10 weeks follow up
Shiffman 2002e	Not a randomized trial. Compared prescription and OTC patch in different populations using different methods.
Sutherland 1999	No long-term follow up reported
Thorsteinsson 2001	No long-term follow up reported
Tzivoni 1998	Follow up less than 6 months
Vial 2002	Treatment groups differed from control in amount of counselling as well as use of NRT
Working Group 1994	Follow up less than 6 months
OTC=over the counter	

**ANALYSES****Comparison 01. Effect of nicotine replacement therapy versus control**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation at maximum follow-up (6-12 months)	105	39503	Odds Ratio (Fixed) 95% CI	1.77 [1.66, 1.88]

**Comparison 02. Effect of 4 mg vs 2 mg Nicotine Gum**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking Cessation	7	856	Odds Ratio (Fixed) 95% CI	1.59 [1.15, 2.19]

**Comparison 03. Effect of NRT with different levels of additional support**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Low intensity support	35	16551	Odds Ratio (Fixed) 95% CI	1.81 [1.61, 2.02]
02 High intensity support	66	20391	Odds Ratio (Fixed) 95% CI	1.78 [1.64, 1.93]

**Comparison 04. Effect of duration of nicotine patch therapy**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking Cessation			Odds Ratio (Fixed) 95% CI	Subtotals only

**Comparison 05. Effect of tapering/weaning off nicotine patches**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking Cessation	38	14796	Odds Ratio (Fixed) 95% CI	1.73 [1.55, 1.93]

**Comparison 06. Effect of nicotine patch type (16 or 24 hr)**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking Cessation			Odds Ratio (Fixed) 95% CI	Subtotals only

**Comparison 07. Effect of clinical/recruitment setting on NRT therapy (indirect comparison)**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Nicotine Gum	52	17819	Odds Ratio (Fixed) 95% CI	1.66 [1.51, 1.81]
02 Nicotine Patch	37	16228	Odds Ratio (Fixed) 95% CI	1.84 [1.65, 2.06]
03 Nicotine Intranasal spray	4	887	Odds Ratio (Fixed) 95% CI	2.35 [1.63, 3.38]
04 Nicotine Inhaler/inhalator	4	976	Odds Ratio (Fixed) 95% CI	2.14 [1.44, 3.18]
05 Nicotine tablet/lozenge	5	2739	Odds Ratio (Fixed) 95% CI	2.05 [1.62, 2.59]
06 Combination of NRT	1	245	Odds Ratio (Fixed) 95% CI	1.08 [0.52, 2.23]
07 Choice of NRT	1	182	Odds Ratio (Fixed) 95% CI	2.69 [0.81, 8.90]

**Comparison 08. Effect of higher dose patches**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation at maximum follow-up	6	4504	Odds Ratio (Fixed) 95% CI	1.21 [1.03, 1.42]

**Comparison 09. Effect of combinations of different types of NRT**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Long term smoking cessation	7	3202	Odds Ratio (Fixed) 95% CI	1.42 [1.14, 1.76]

**Comparison 10. Effect of nicotine patches in relapsed smokers**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation at six months	1	629	Odds Ratio (Fixed) 95% CI	1.25 [0.33, 4.70]
02 Not smoking in 28 days before maximal followup	1	629	Odds Ratio (Fixed) 95% CI	2.59 [1.12, 5.98]

**Comparison 11. Effect of combinations of nicotine patch and bupropion**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation at 12 months (continuous abstinence)			Odds Ratio (Fixed) 95% CI	Totals not selected

**Comparison 12. Effect of Over the Counter setting**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Free nicotine patch versus paid patch (no support)			Odds Ratio (Fixed) 95% CI	Totals not selected
02 Smoking cessation using NRT without support versus physician prescribed NRT (all NRT purchased)	2	820	Odds Ratio (Fixed) 95% CI	0.21 [0.05, 0.84]

**Comparison 13. Fixed versus ad lib schedule of gum**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation	2	689	Odds Ratio (Fixed) 95% CI	1.29 [0.90, 1.85]

**Comparison 14. Direct comparisons between NRT types**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation	3	1497	Odds Ratio (Fixed) 95% CI	0.74 [0.54, 1.03]

**Comparison 15. Effect of pretreatment with nicotine patch**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Smoking cessation	1	200	Odds Ratio (Fixed) 95% CI	2.07 [0.96, 4.45]

**Comparison 16. NRT for smoking reduction.**

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Sustained reduction to <50% of baseline cigarette consumption at longest follow-up	2	811	Odds Ratio (Fixed) 95% CI	4.93 [2.14, 11.36]
02 Point prevalence reduction to <50% of baseline cigarette consumption at longest follow-up	3	1734	Odds Ratio (Fixed) 95% CI	1.80 [1.41, 2.28]
03 Sustained abstinence at longest follow-up	1	400	Odds Ratio (Fixed) 95% CI	4.06 [0.45, 36.66]
04 Point prevalence abstinence at longest follow-up	3	1734	Odds Ratio (Fixed) 95% CI	1.62 [1.06, 2.49]



## INDEX TERMS

### Medical Subject Headings (MeSH)

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

### MeSH check words

Humans

## COVER SHEET

<b>Title</b>	Nicotine replacement therapy for smoking cessation
<b>Authors</b>	Silagy C, Lancaster T, Stead L, Mant D, Fowler G
<b>Contribution of author(s)</b>	The review was initiated by CS. CS, LS & TL have extracted data and contributed to the text. DM and GF commented on the text of the original review and one or more updates.
<b>Issue protocol first published</b>	1996/2
<b>Review first published</b>	1996/2
<b>Date of most recent amendment</b>	23 August 2006
<b>Date of most recent SUBSTANTIVE amendment</b>	07 April 2004
<b>What's New</b>	Twelve new studies included for issue 3, 2004. There were no changes to main conclusions. A response to a comment was added for issue 4, 2004. Two corrections were made in issue 1, 2005; one on the description of stratification in Shiffman 2002A & Shiffman 2002B one in comparison 1 graph to include Shiffman 2002B in the tablet subgroup. Data in the text already included this study and remain unchanged.
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	07 April 2004
<b>Date authors' conclusions section amended</b>	22 May 2001
<b>Contact address</b>	Mrs Lindsay Stead Review Group Co-ordinator Department of Primary Health Care Oxford University Old Road Campus Headington Oxford OX3 7LF UK E-mail: lindsay.stead@dphpc.ox.ac.uk Tel: +44 1865 289285 Fax: +44 1865 289287
<b>DOI</b>	10.1002/14651858.CD000146.pub2

**Cochrane Library number** CD000146

**Editorial group** Cochrane Tobacco Addiction Group

**Editorial group code** HM-TOBACCO

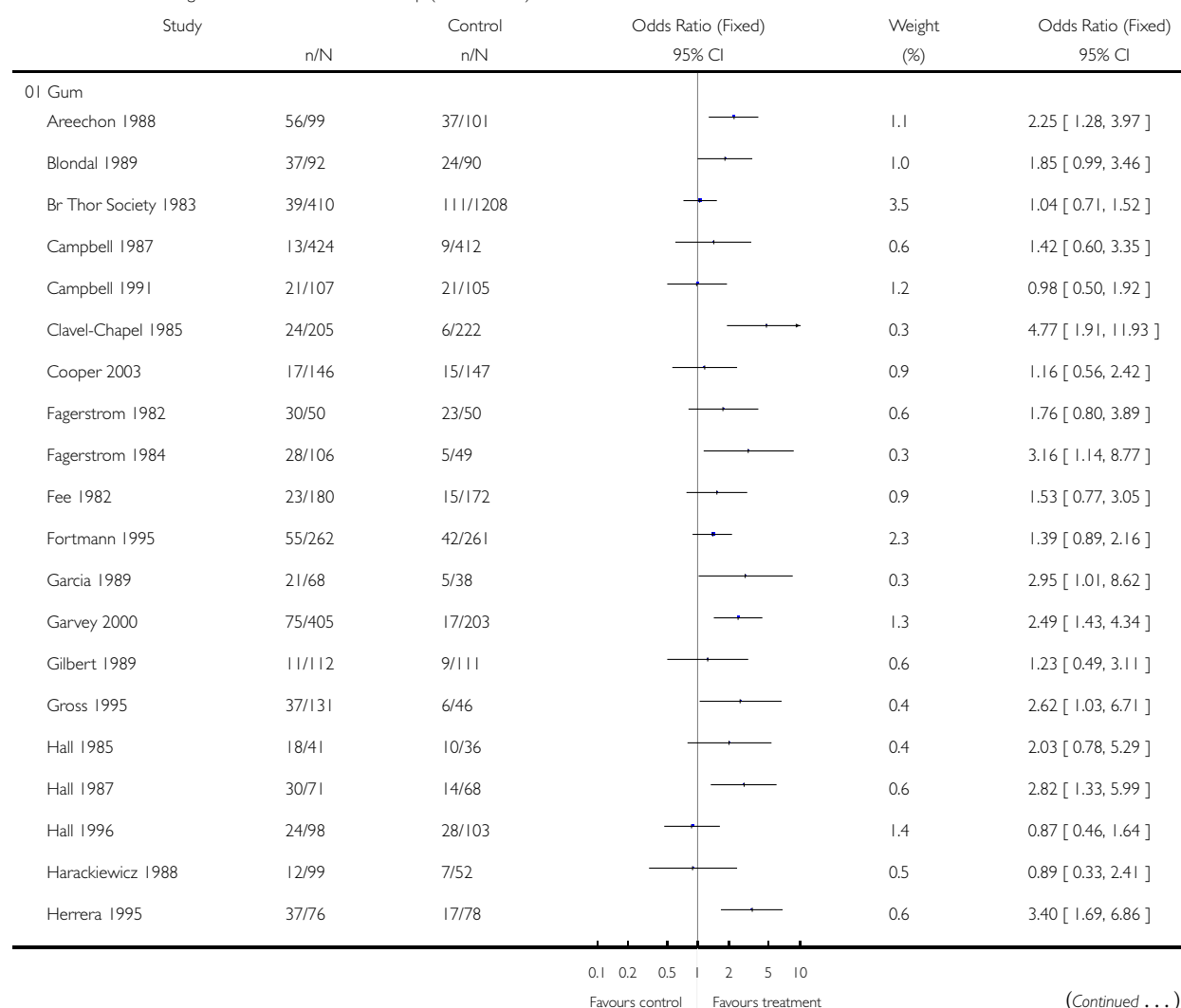
## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Effect of nicotine replacement therapy versus control, Outcome 01 Smoking cessation at maximum follow-up (6-12 months)

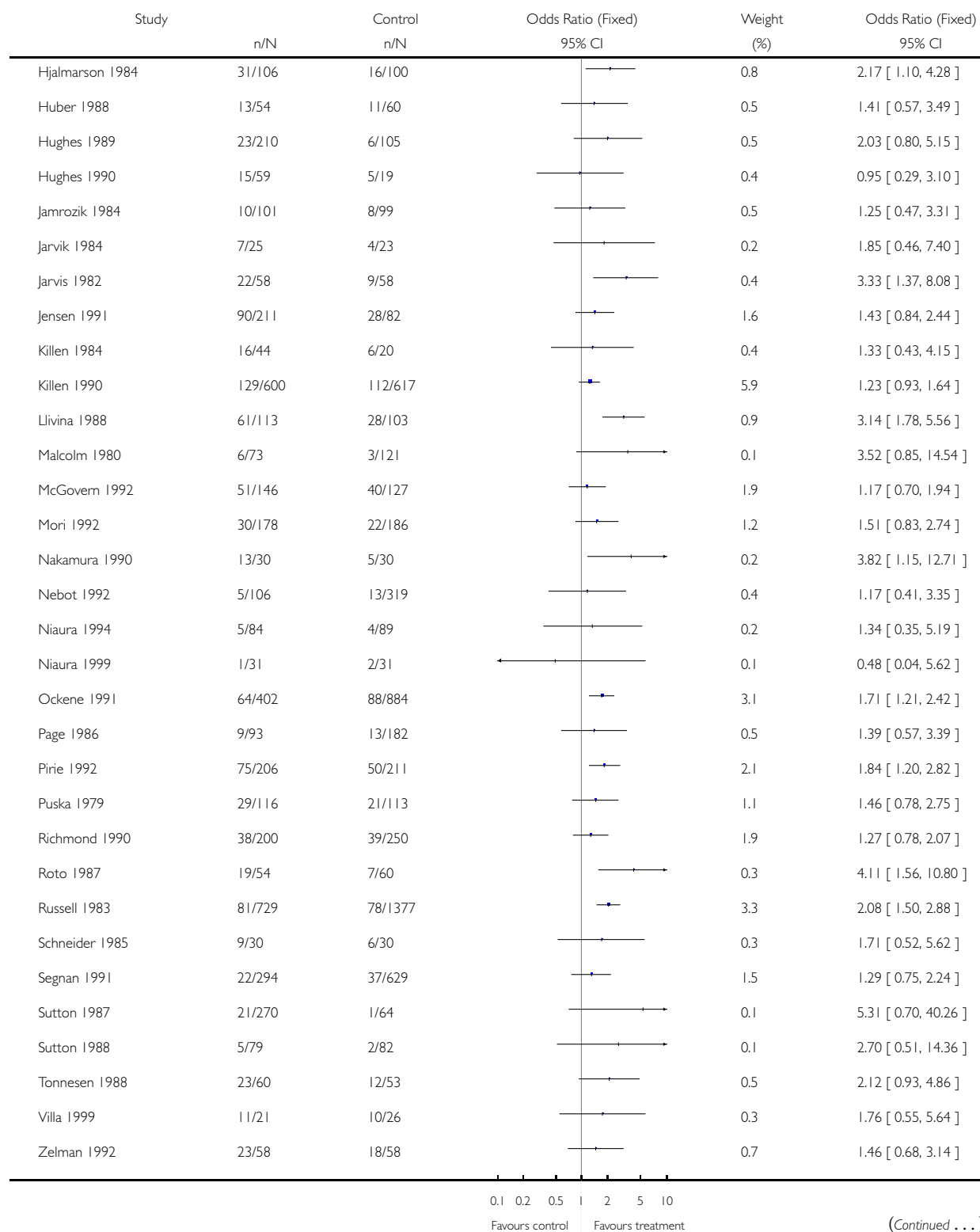
Review: Nicotine replacement therapy for smoking cessation

Comparison: 01 Effect of nicotine replacement therapy versus control

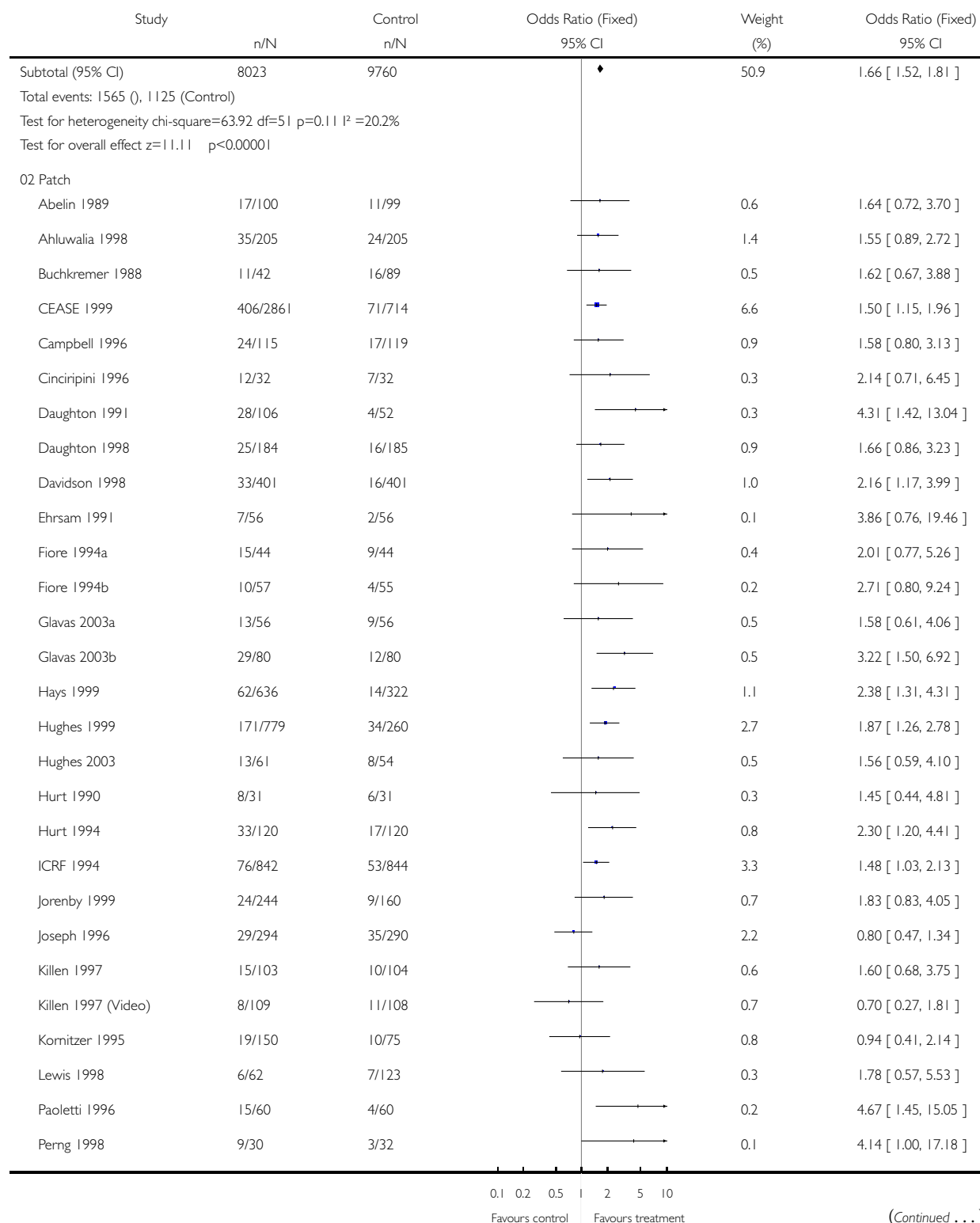
Outcome: 01 Smoking cessation at maximum follow-up (6-12 months)



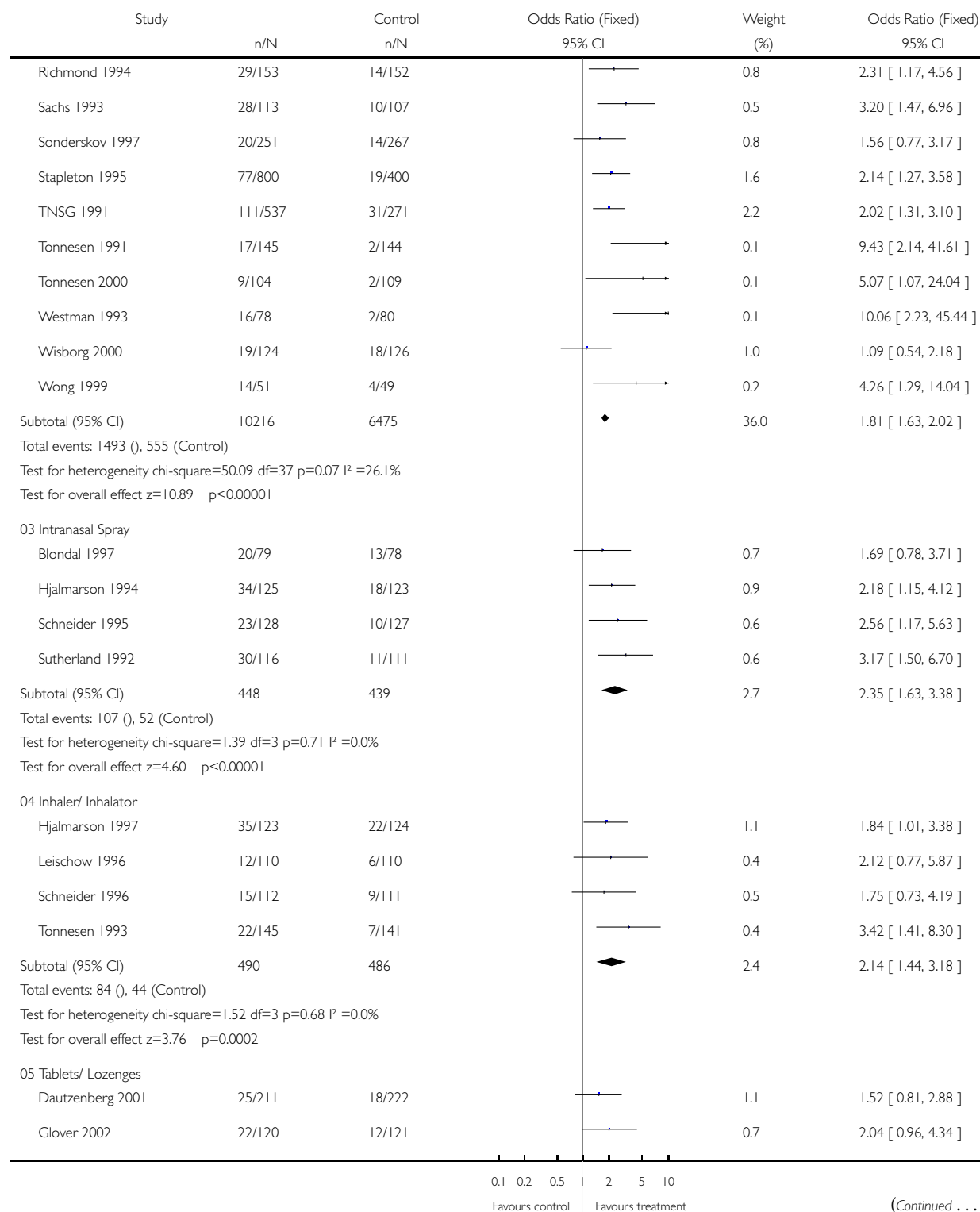
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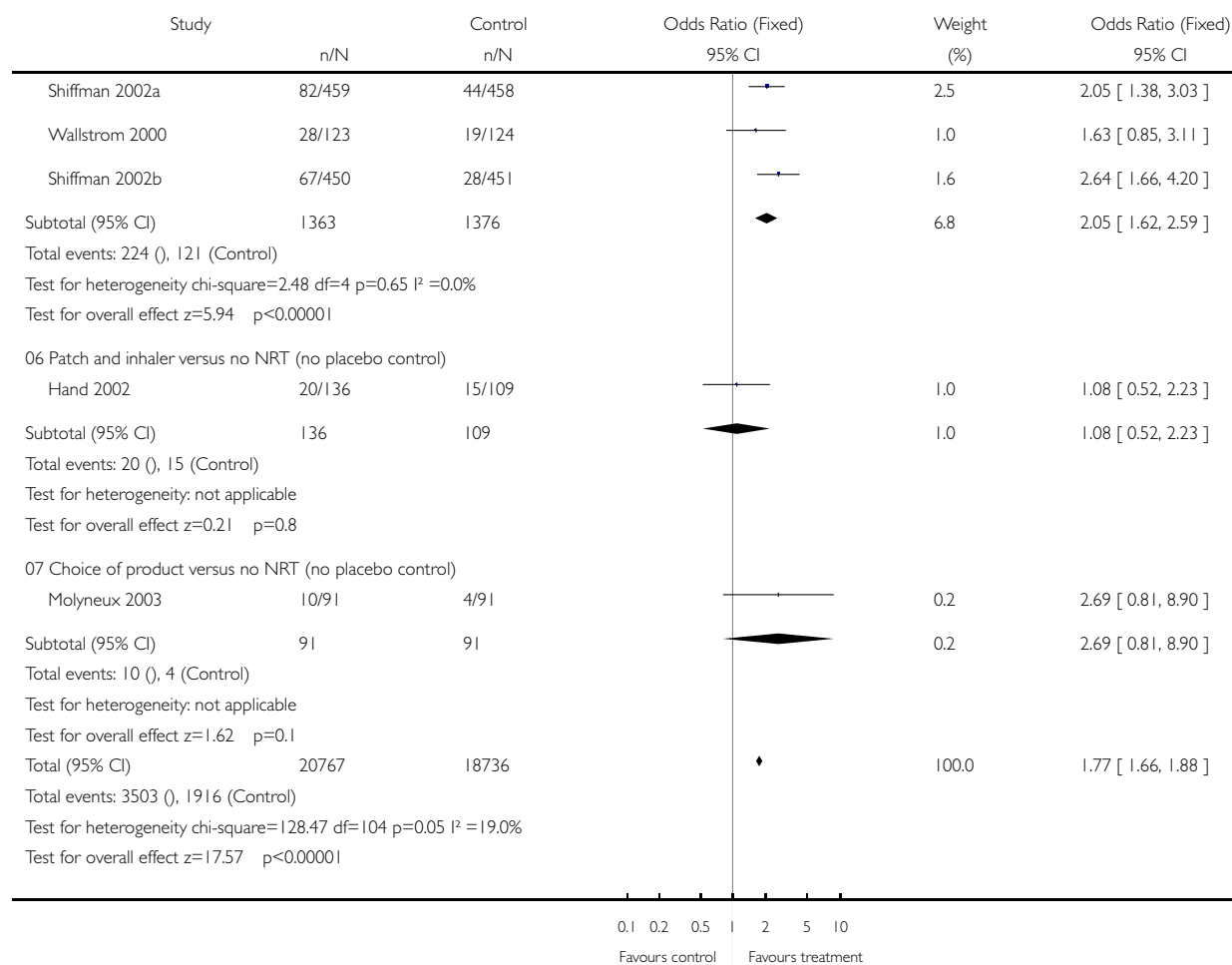
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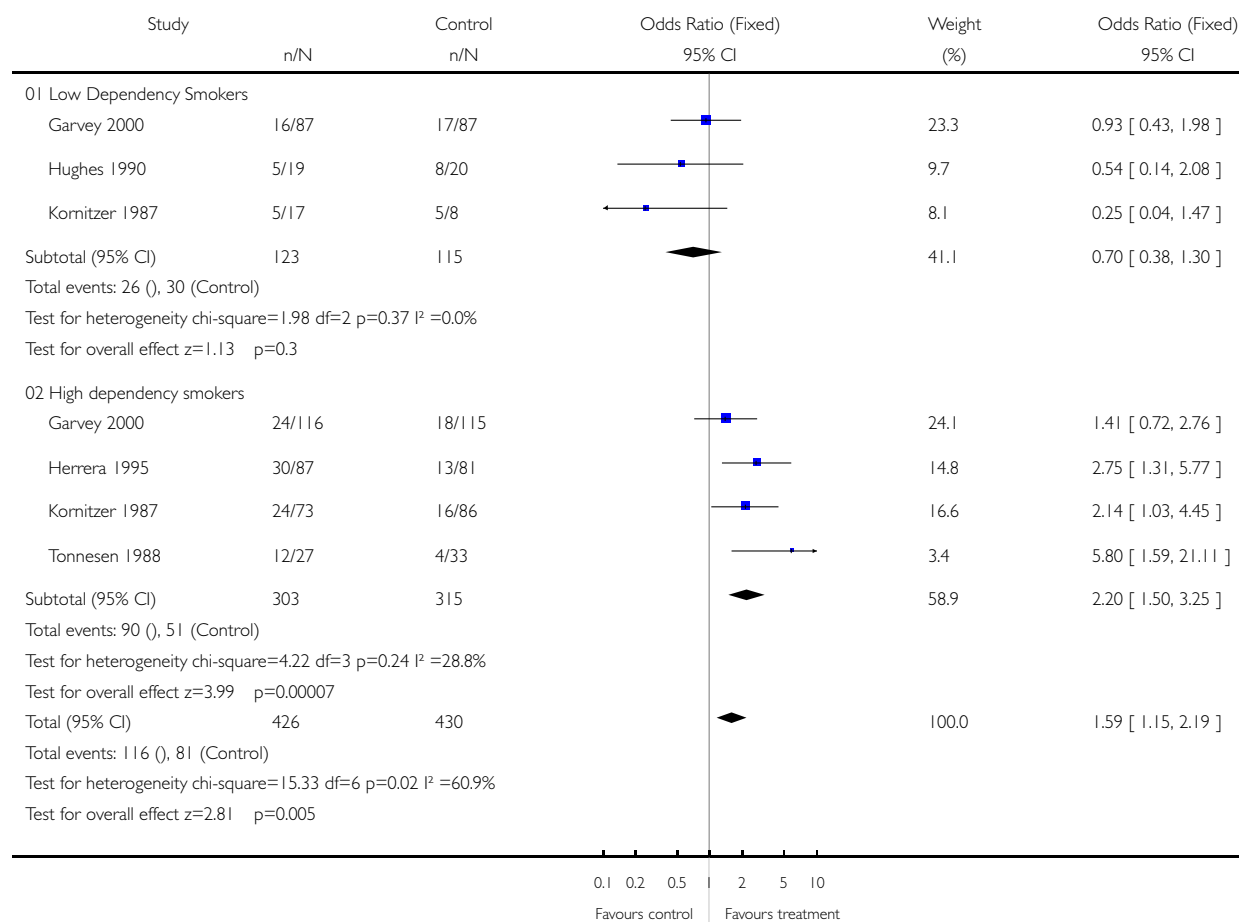


## Analysis 02.01. Comparison 02 Effect of 4 mg vs 2 mg Nicotine Gum, Outcome 01 Smoking Cessation

Review: Nicotine replacement therapy for smoking cessation

Comparison: 02 Effect of 4 mg vs 2 mg Nicotine Gum

Outcome: 01 Smoking Cessation

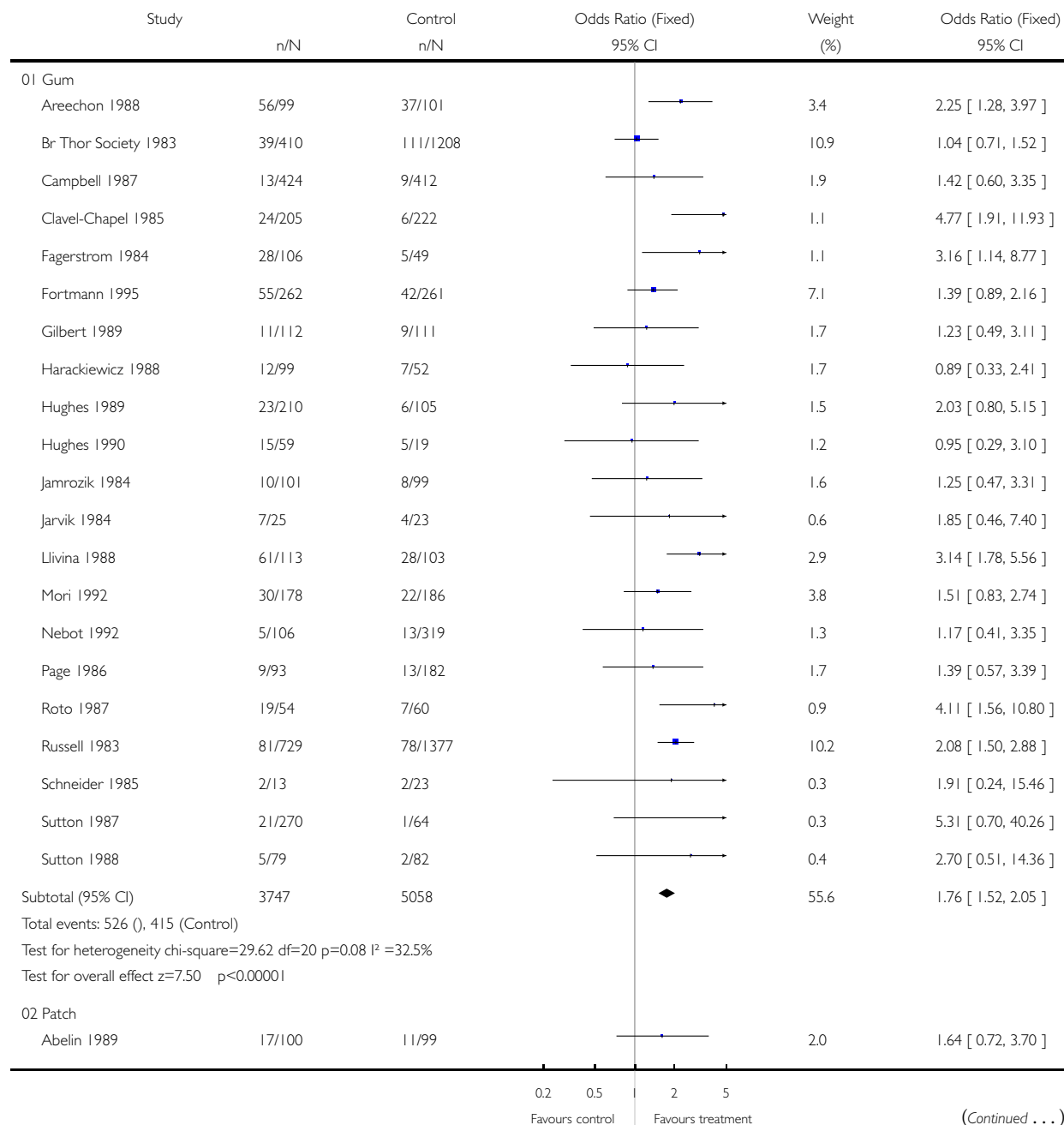


### Analysis 03.01. Comparison 03 Effect of NRT with different levels of additional support, Outcome 01 Low intensity support

Review: Nicotine replacement therapy for smoking cessation

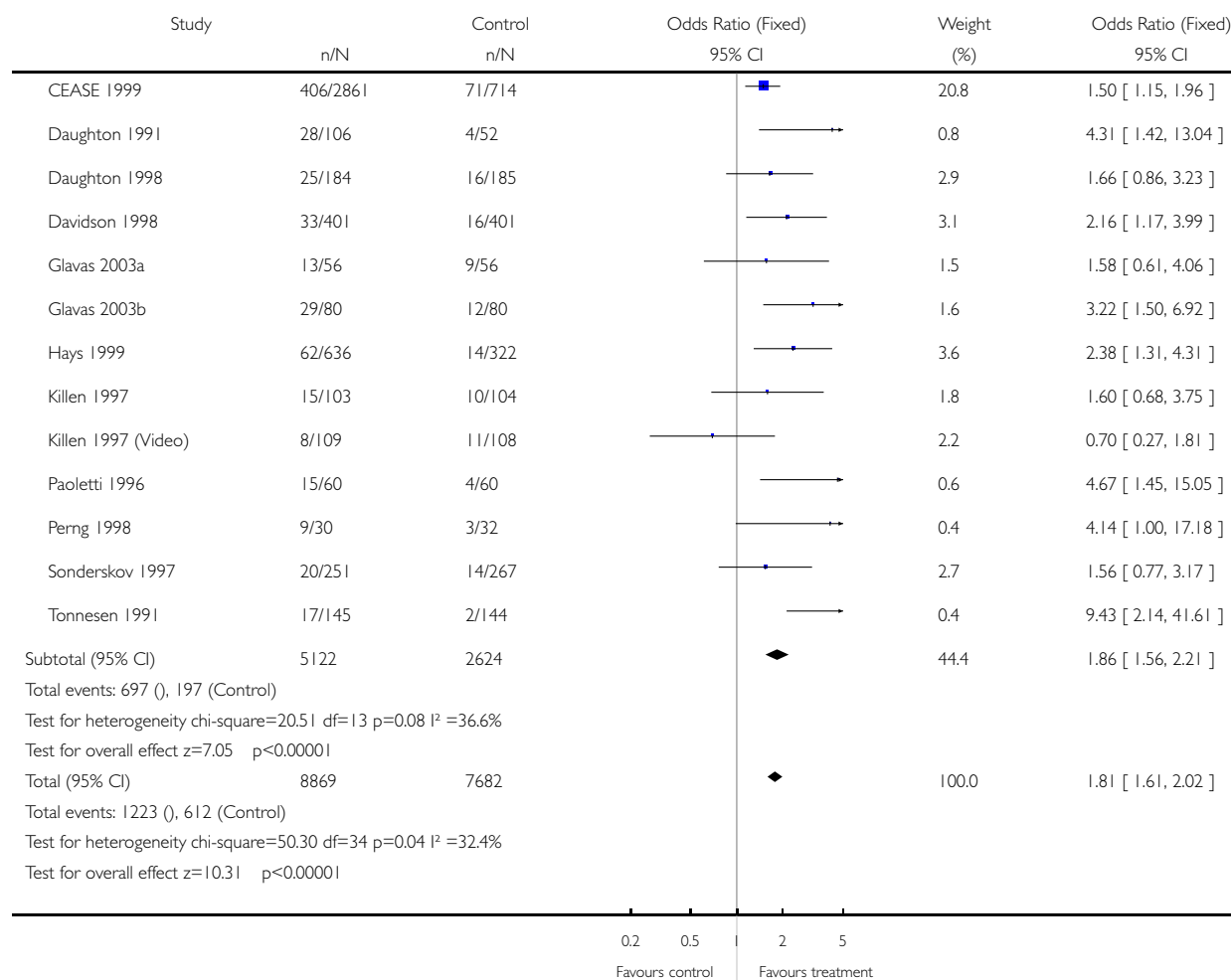
Comparison: 03 Effect of NRT with different levels of additional support

Outcome: 01 Low intensity support





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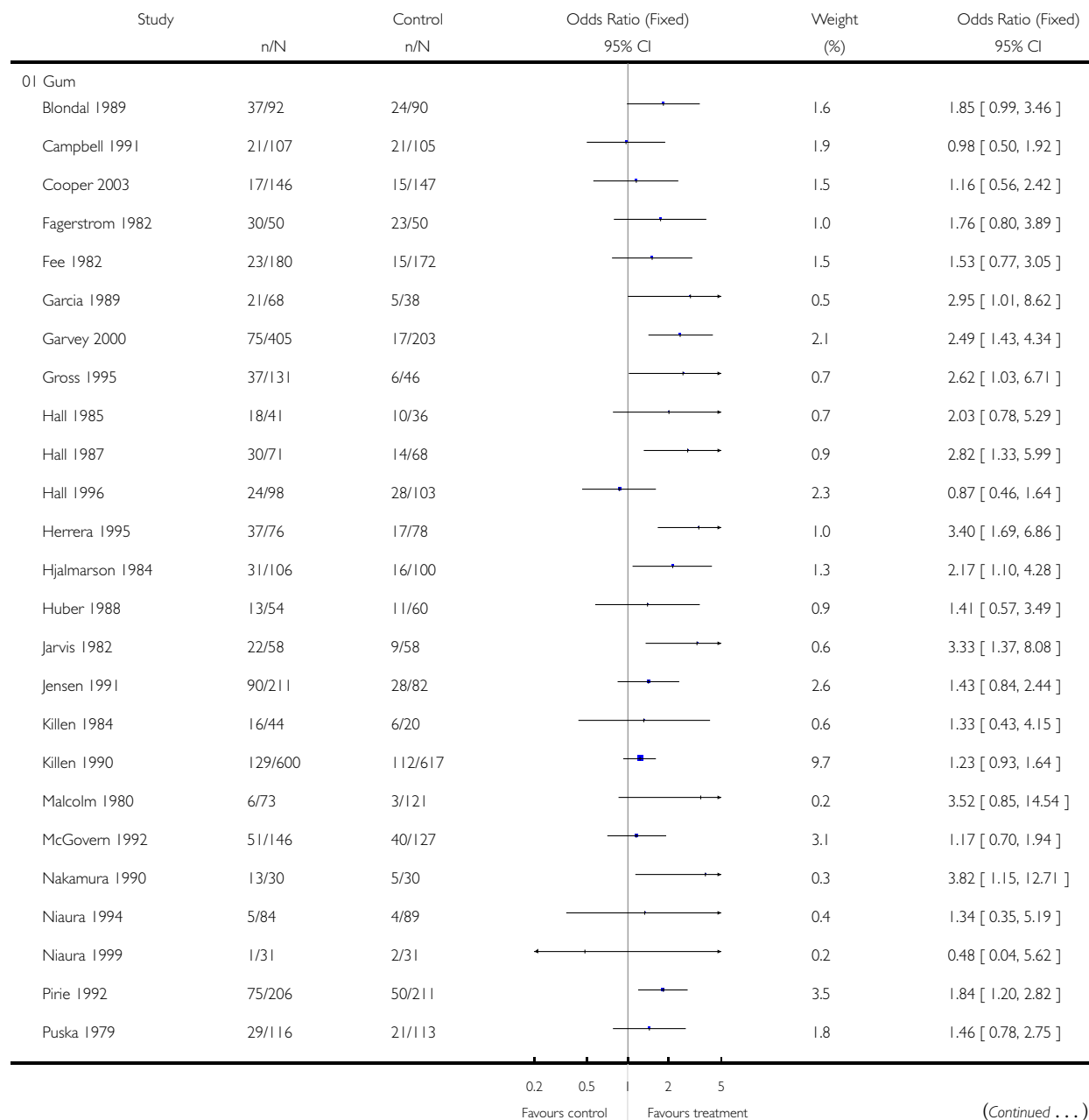


### Analysis 03.02. Comparison 03 Effect of NRT with different levels of additional support, Outcome 02 High intensity support

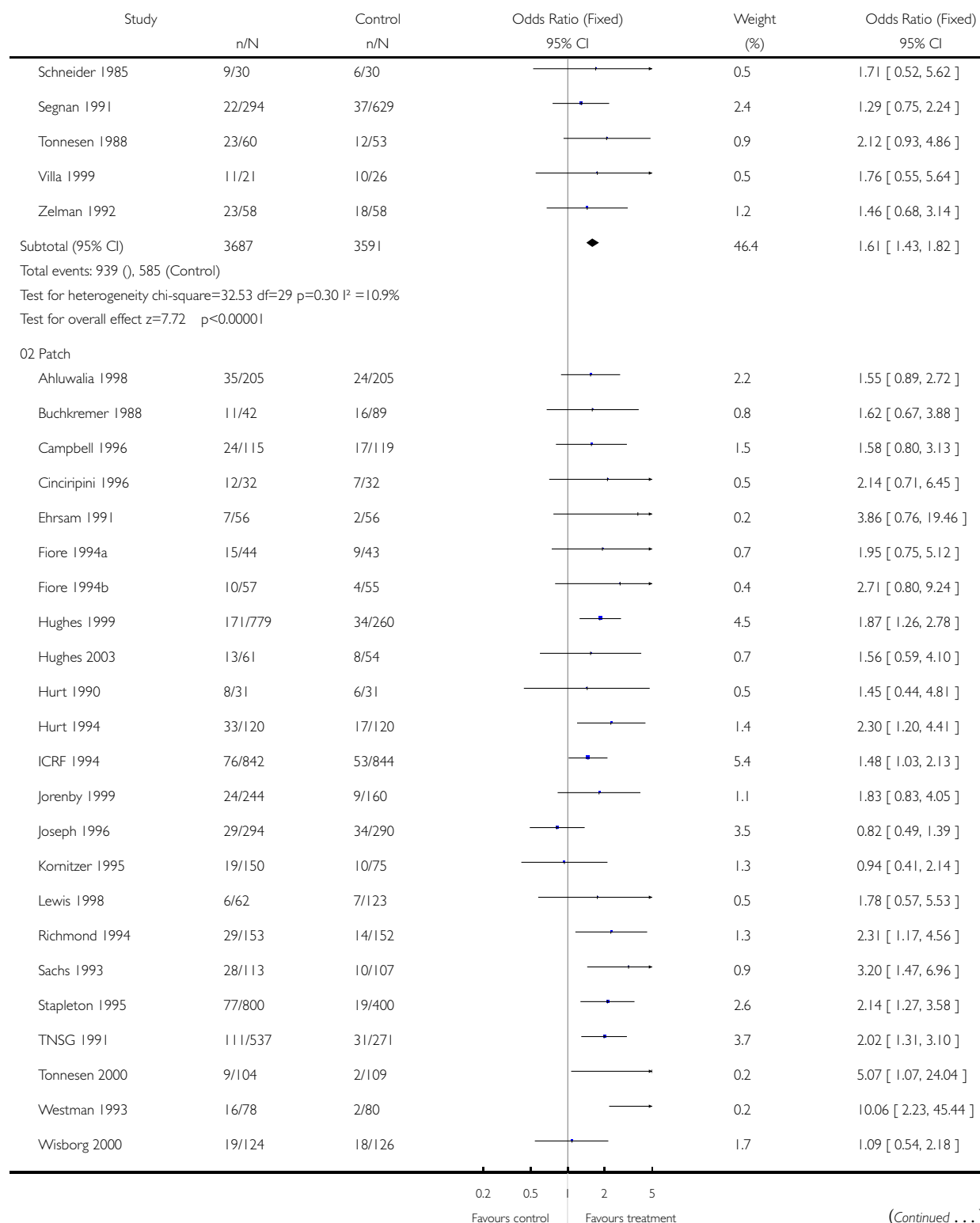
Review: Nicotine replacement therapy for smoking cessation

Comparison: 03 Effect of NRT with different levels of additional support

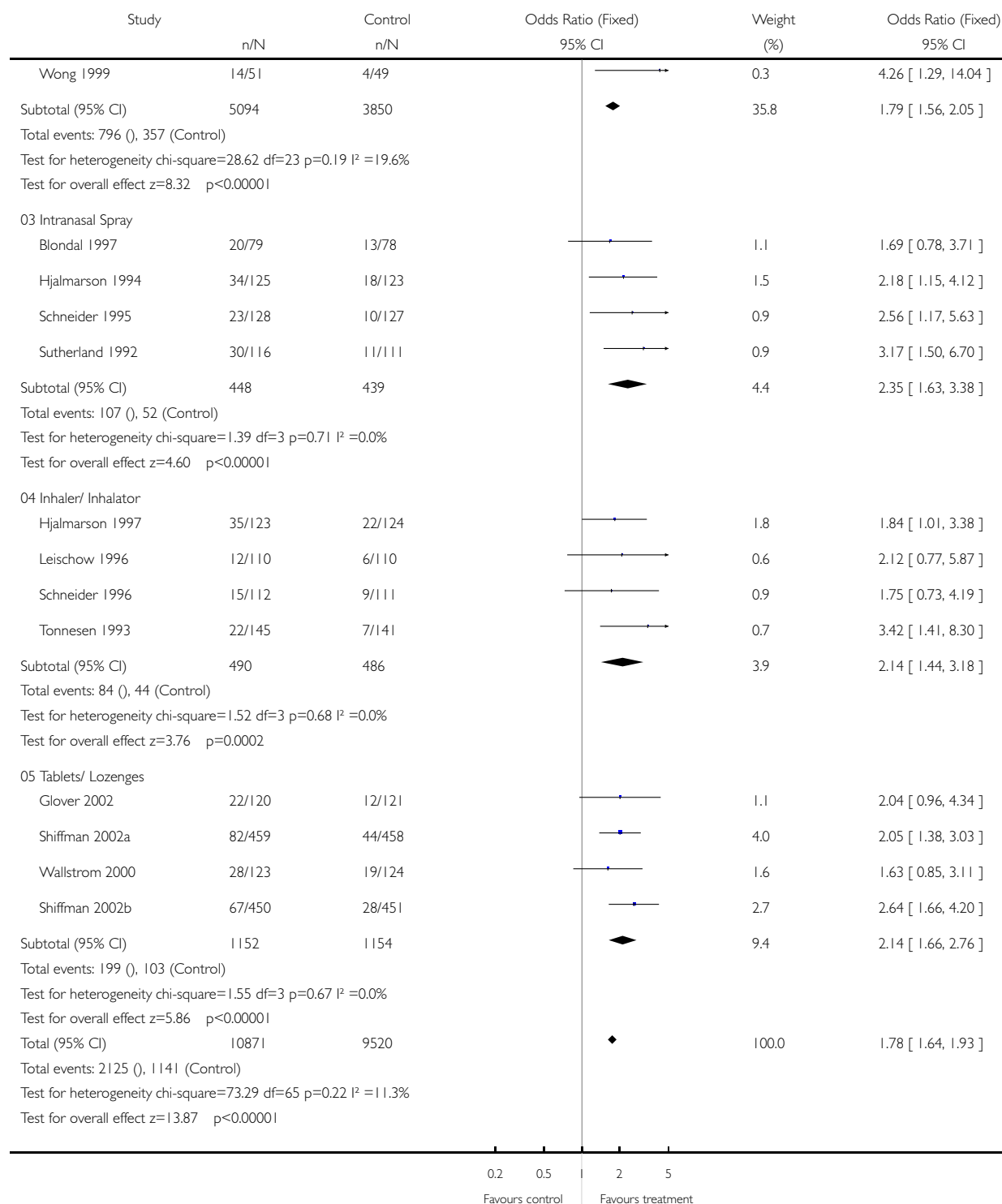
Outcome: 02 High intensity support



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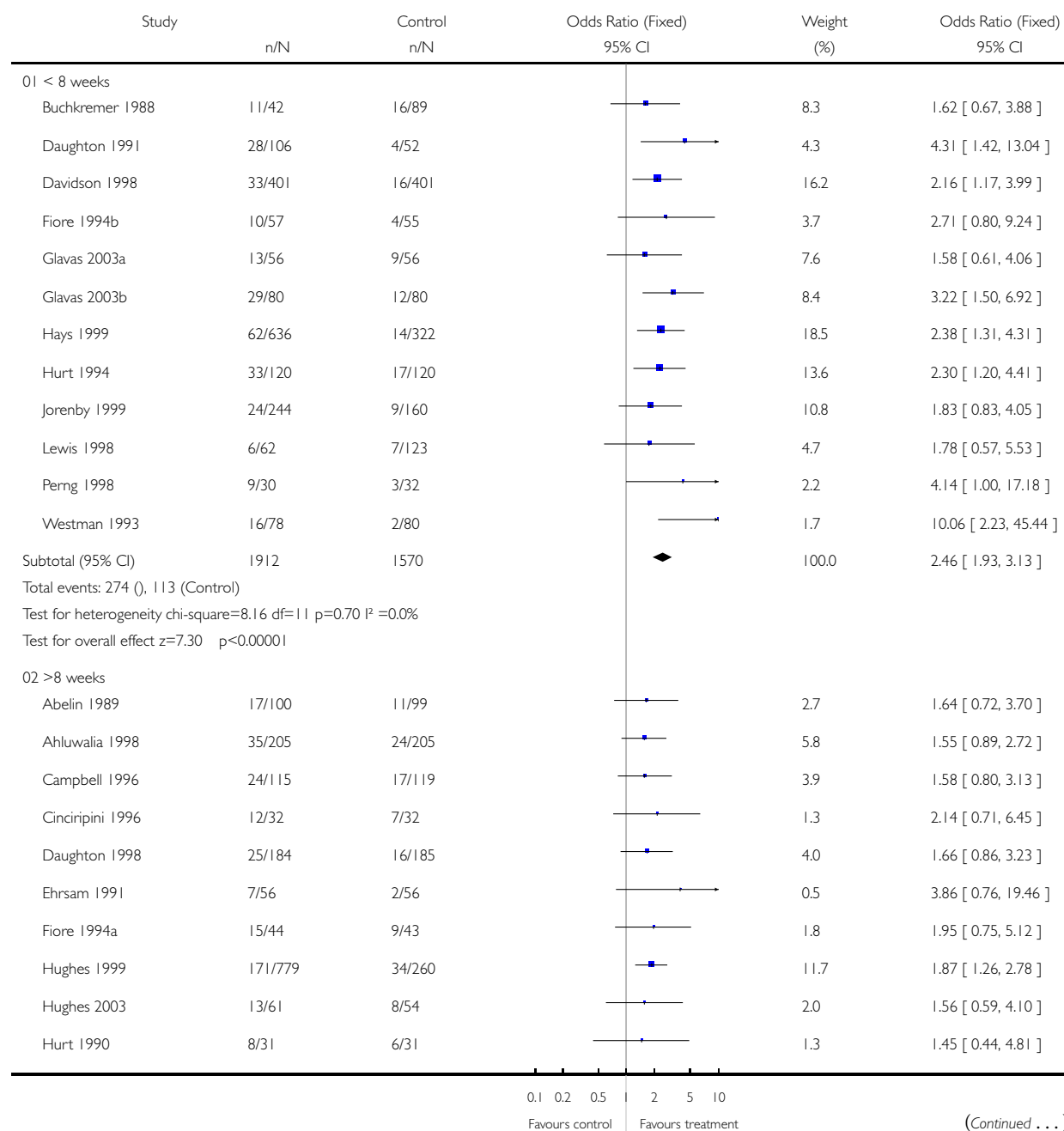


# **Analysis 04.01. Comparison 04 Effect of duration of nicotine patch therapy, Outcome 01 Smoking Cessation**

Review: Nicotine replacement therapy for smoking cessation

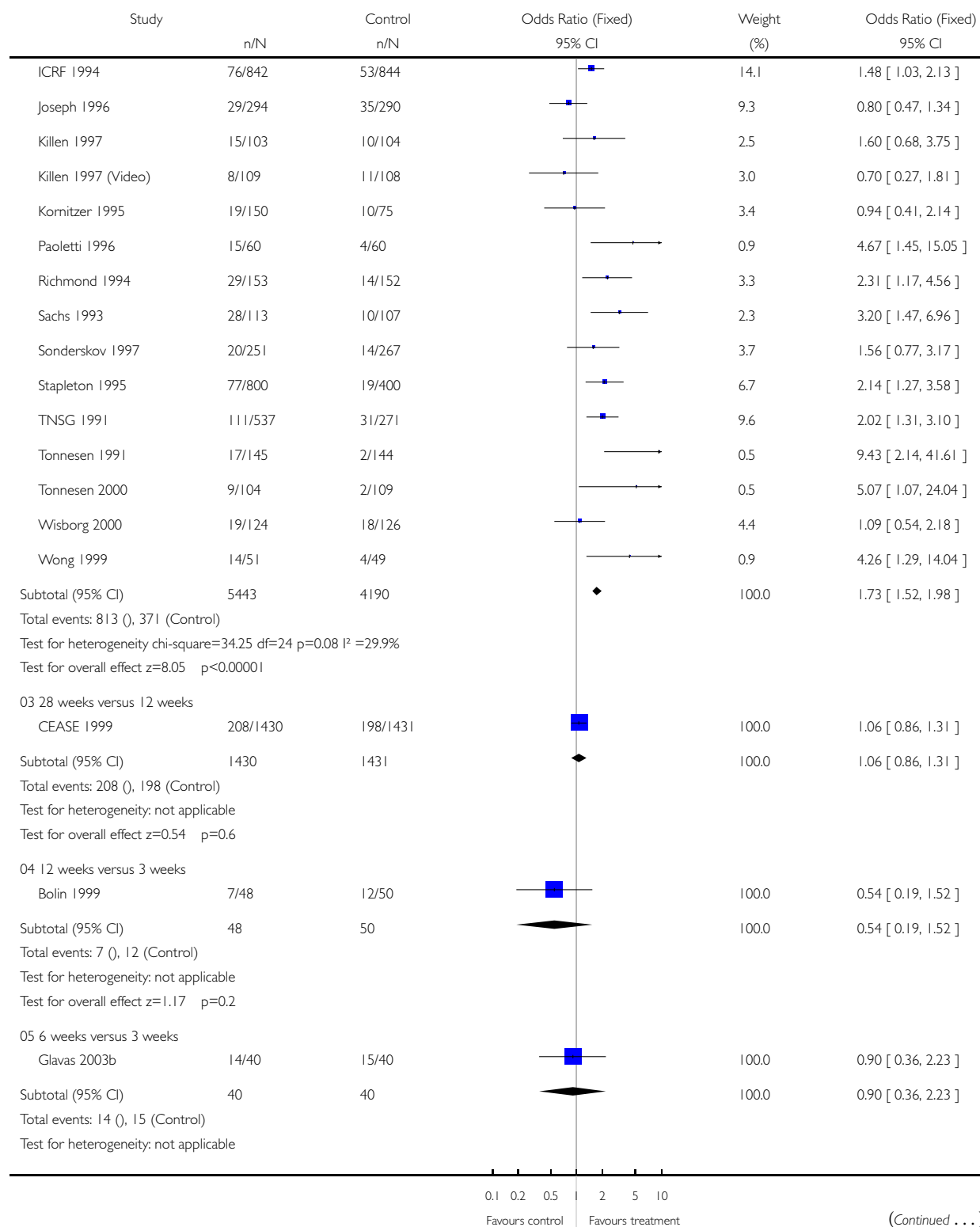
Comparison: 04 Effect of duration of nicotine patch therapy

Outcome: 01 Smoking Cessation

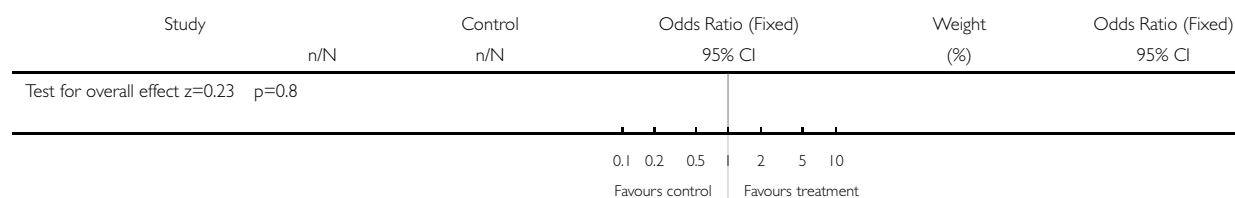


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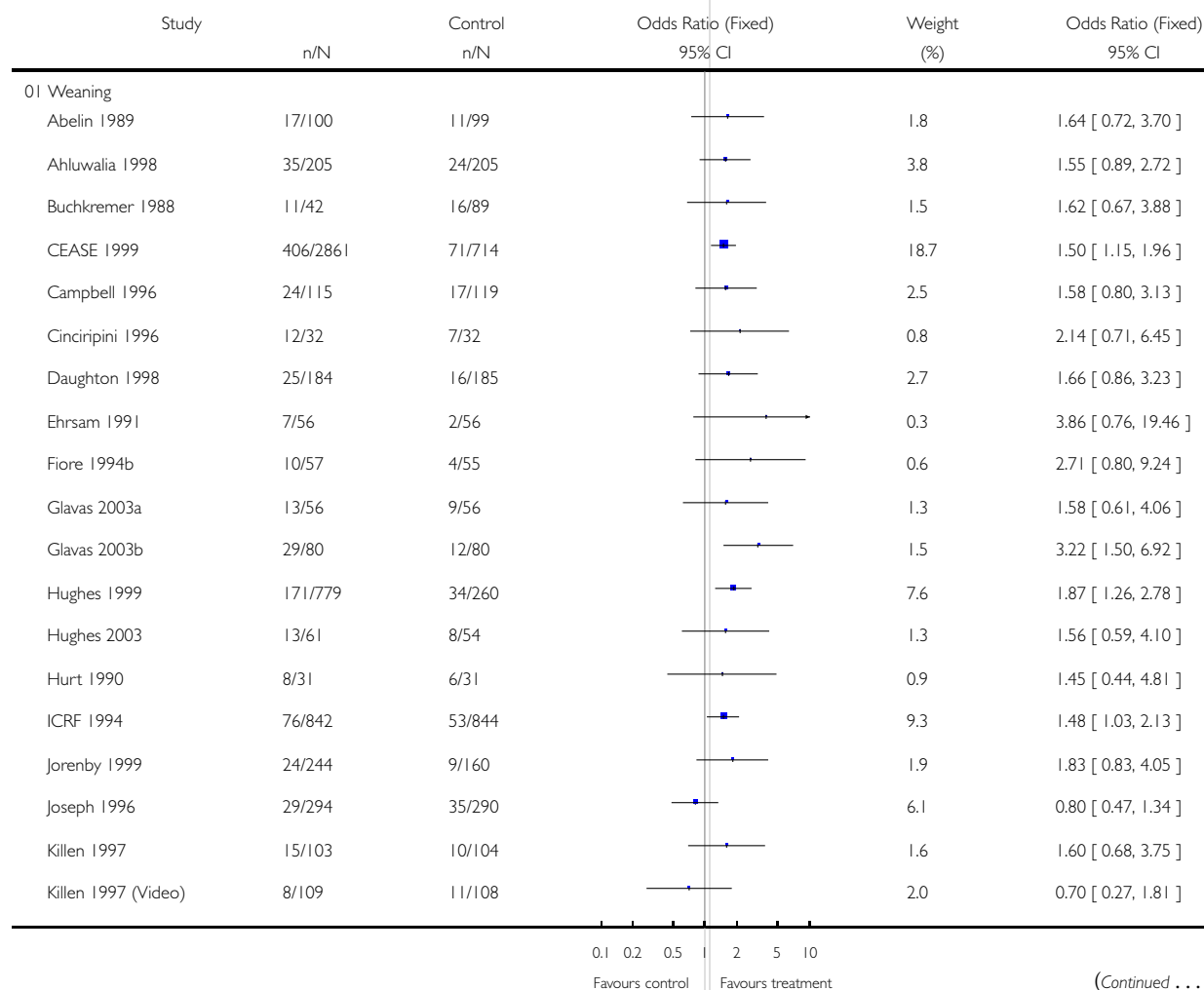


### Analysis 05.01. Comparison 05 Effect of tapering/weaning off nicotine patches, Outcome 01 Smoking Cessation

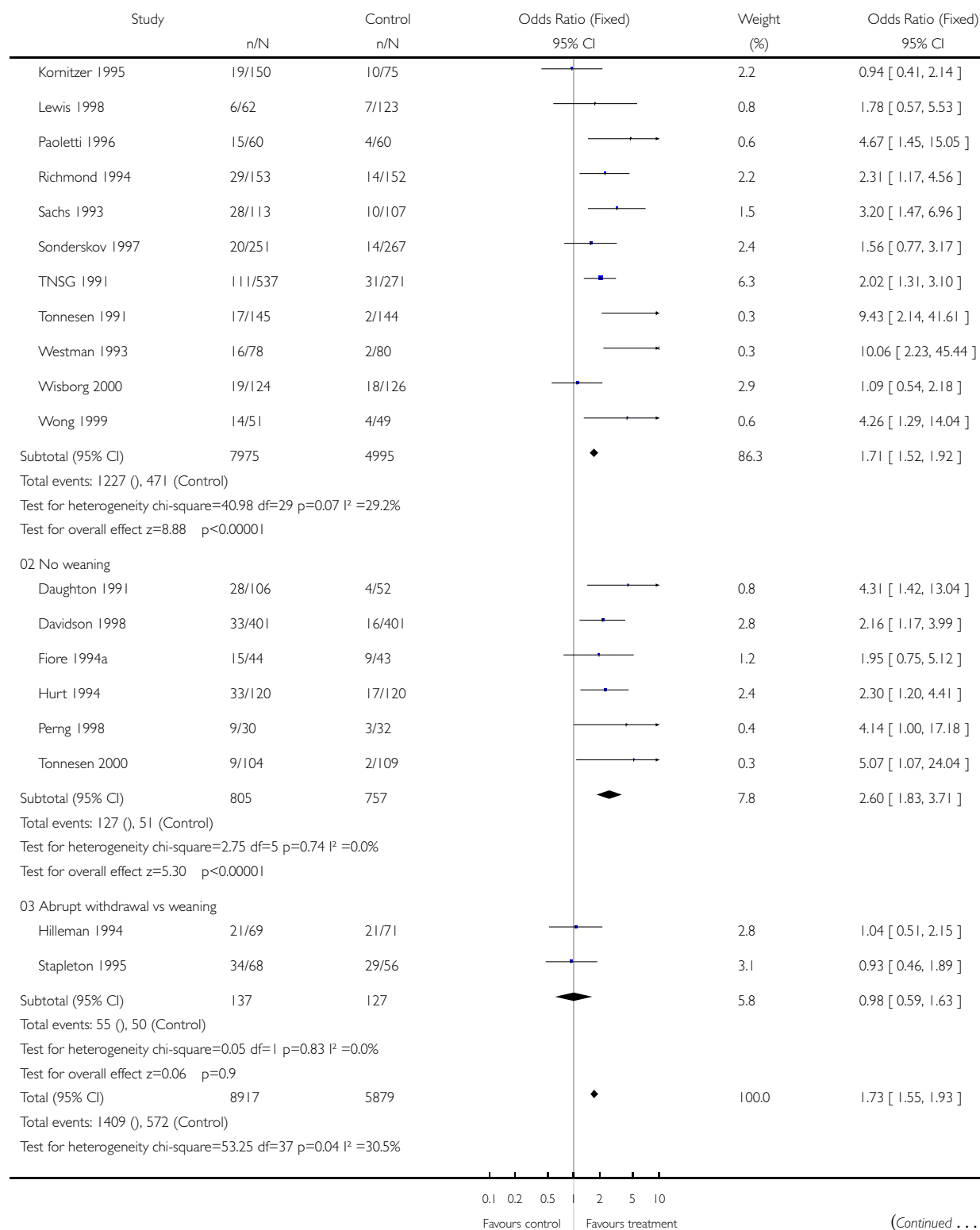
Review: Nicotine replacement therapy for smoking cessation

Comparison: 05 Effect of tapering/weaning off nicotine patches

Outcome: 01 Smoking Cessation

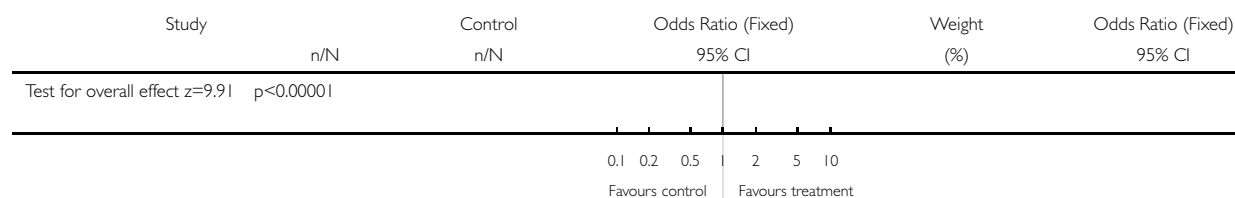


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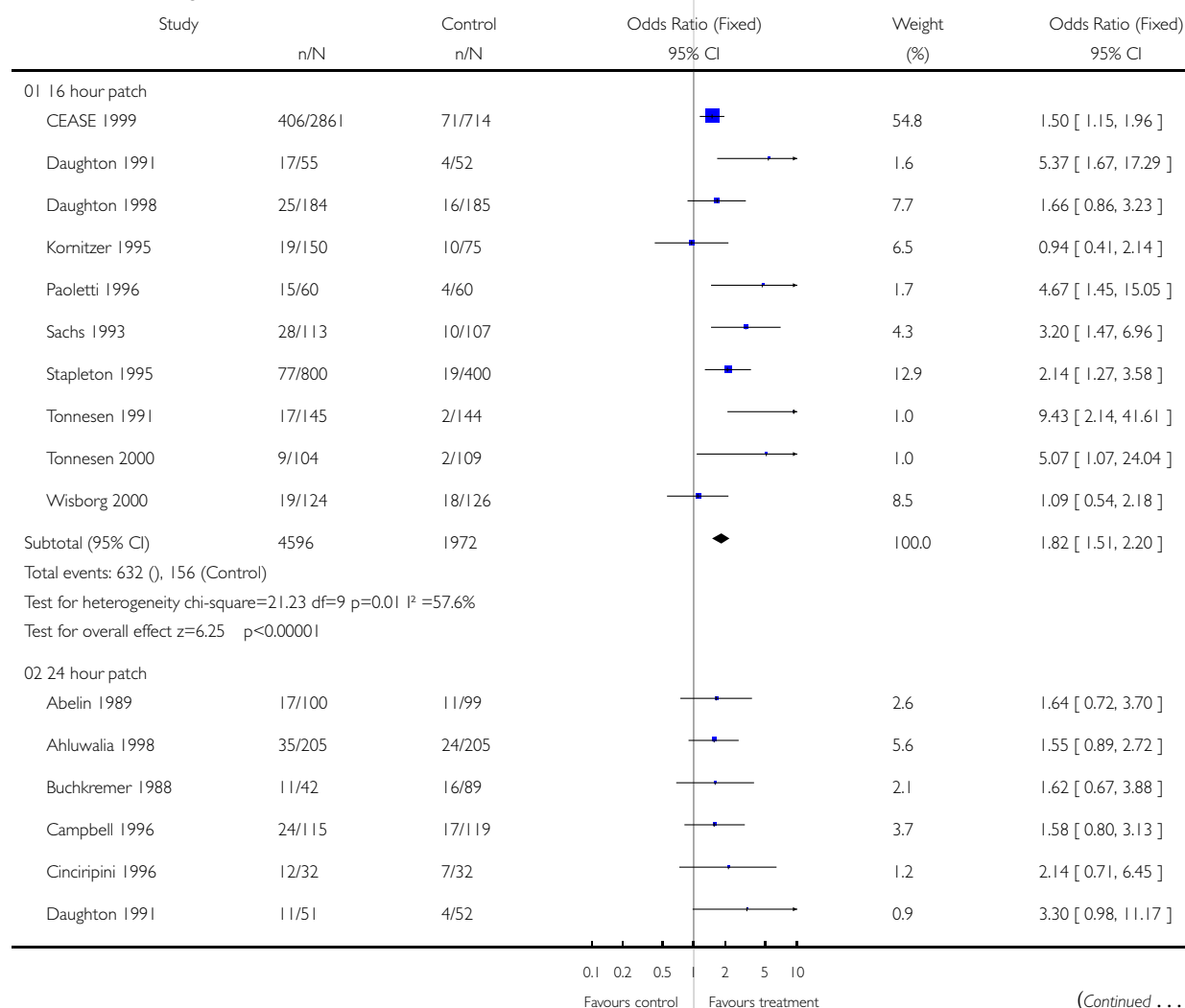


### Analysis 06.01. Comparison 06 Effect of nicotine patch type (16 or 24 hr), Outcome 01 Smoking Cessation

Review: Nicotine replacement therapy for smoking cessation

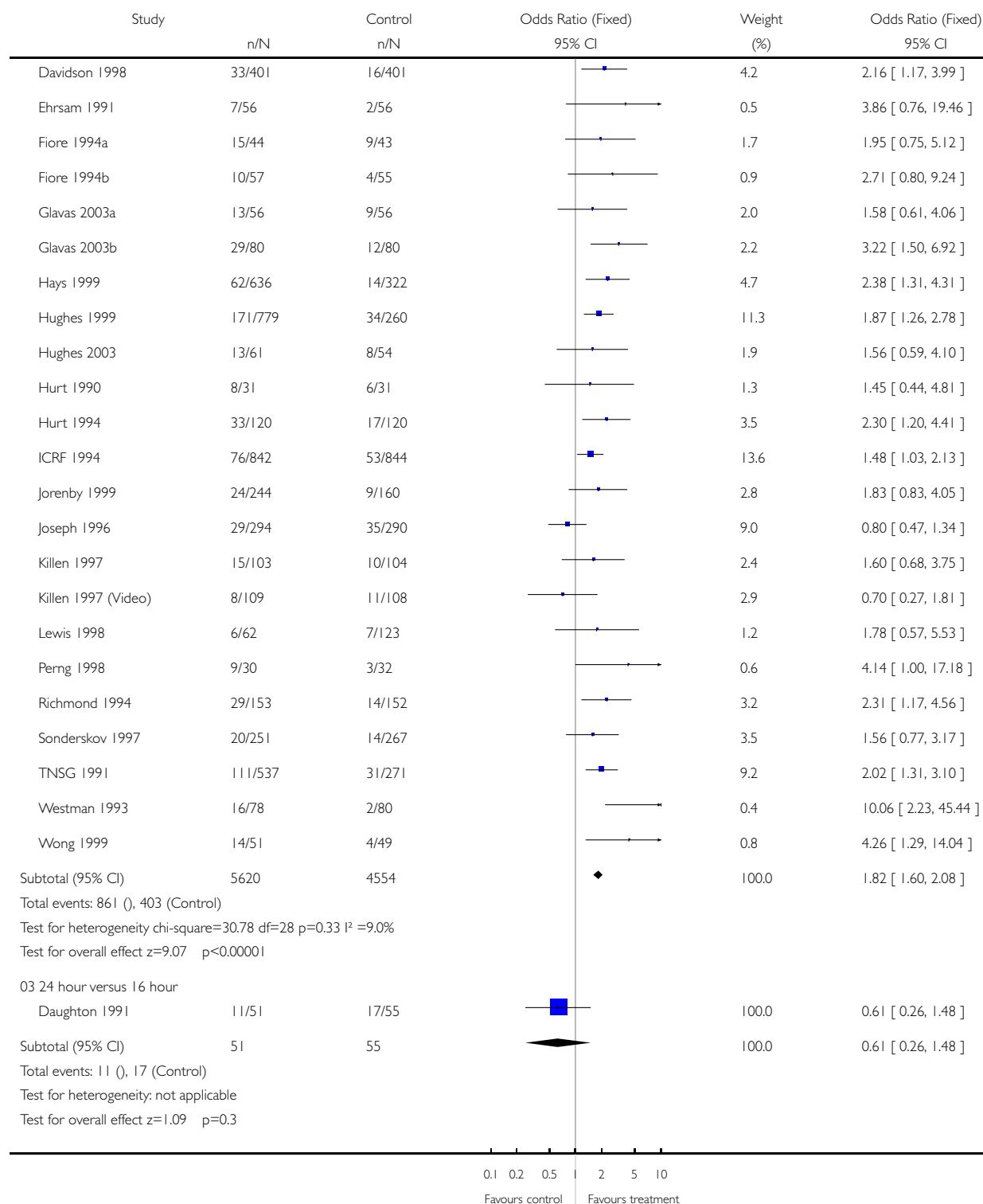
Comparison: 06 Effect of nicotine patch type (16 or 24 hr)

Outcome: 01 Smoking Cessation



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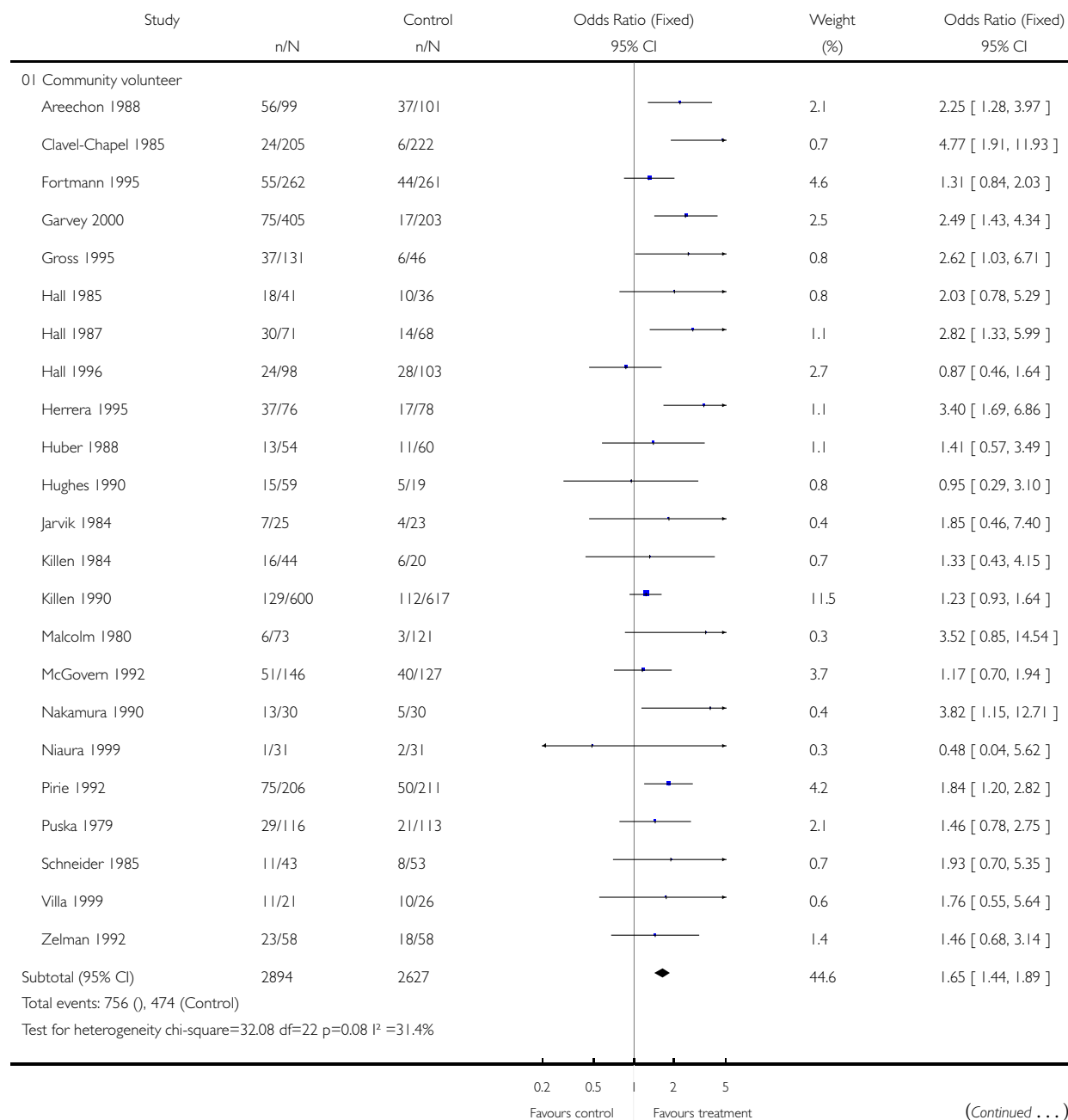


# **Analysis 07.01. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 01 Nicotine Gum**

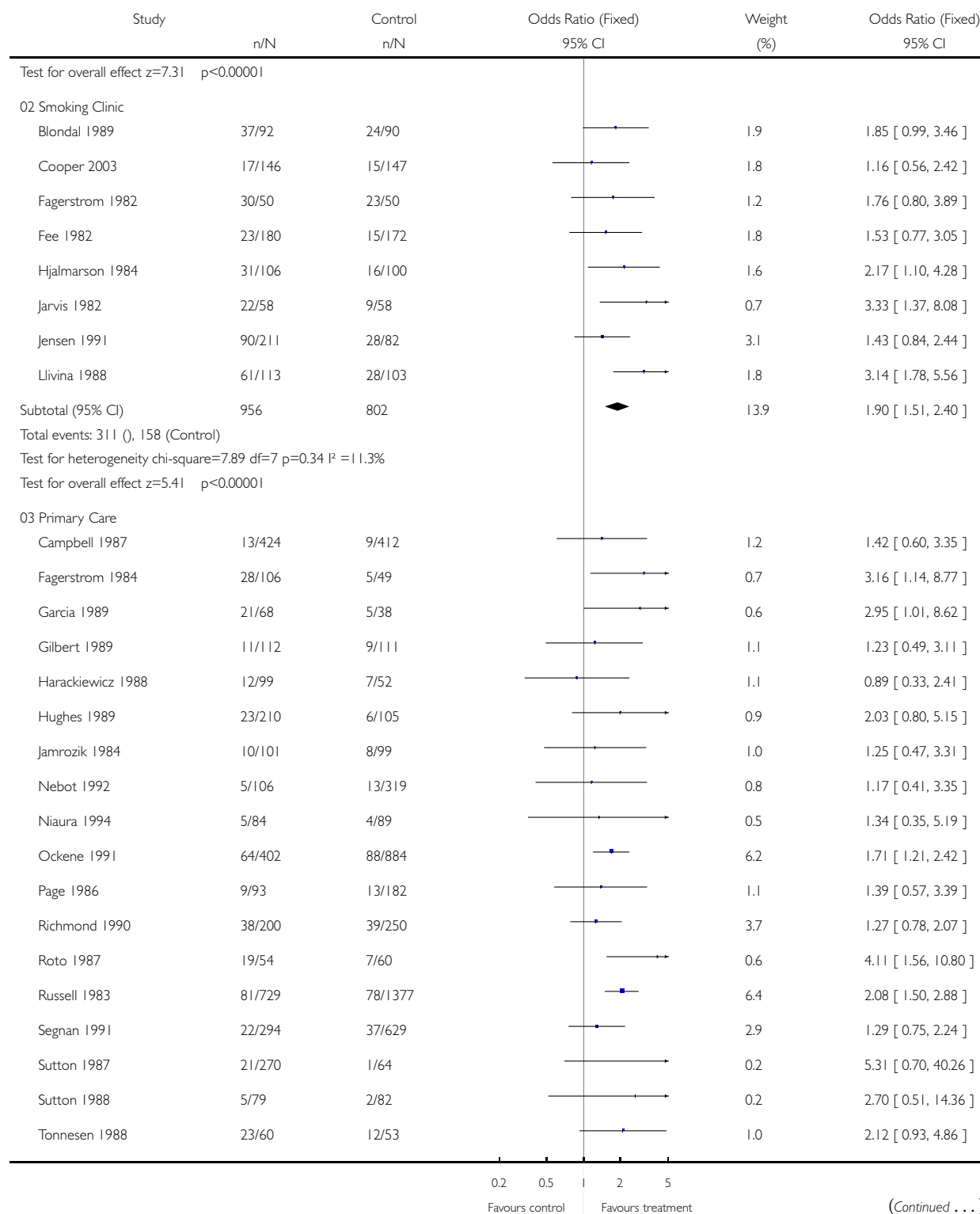
Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

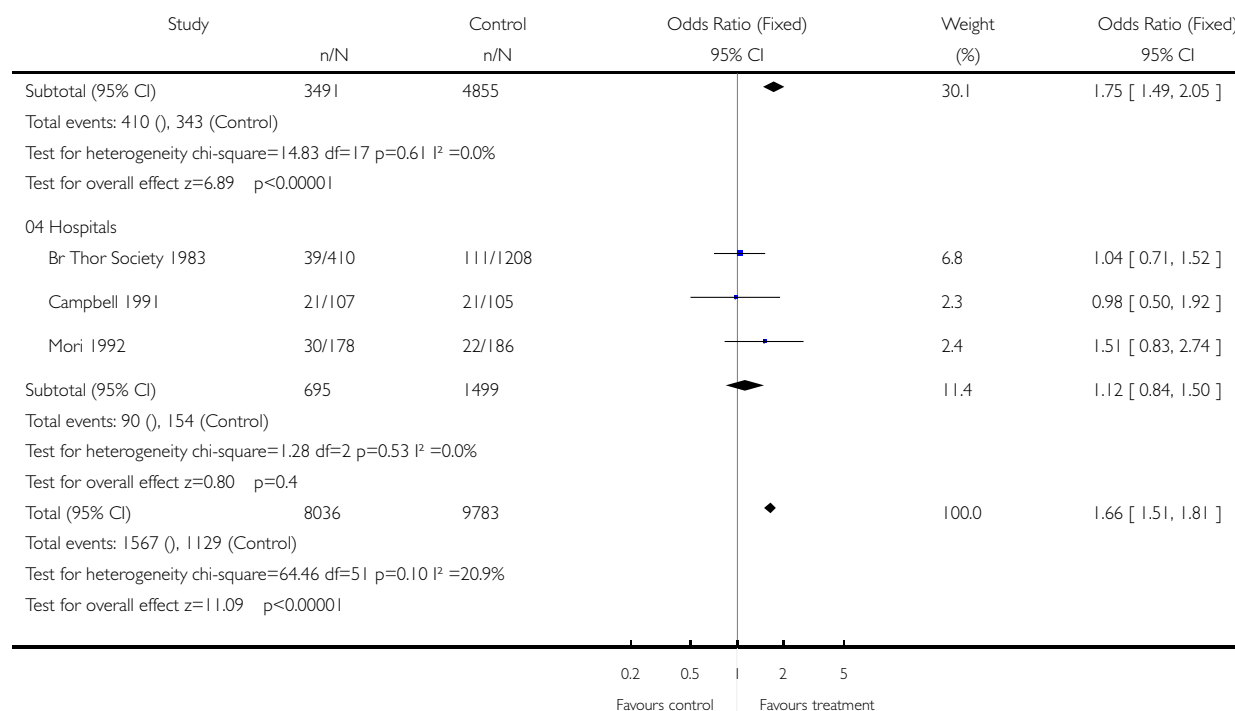
Outcome: 01 Nicotine Gum



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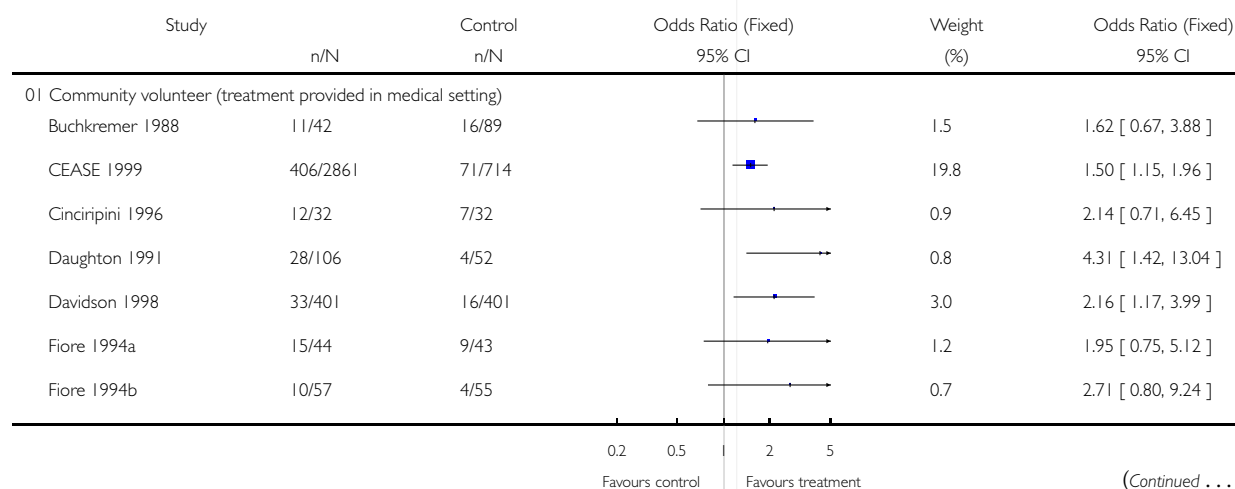


## Analysis 07.02. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 02 Nicotine Patch

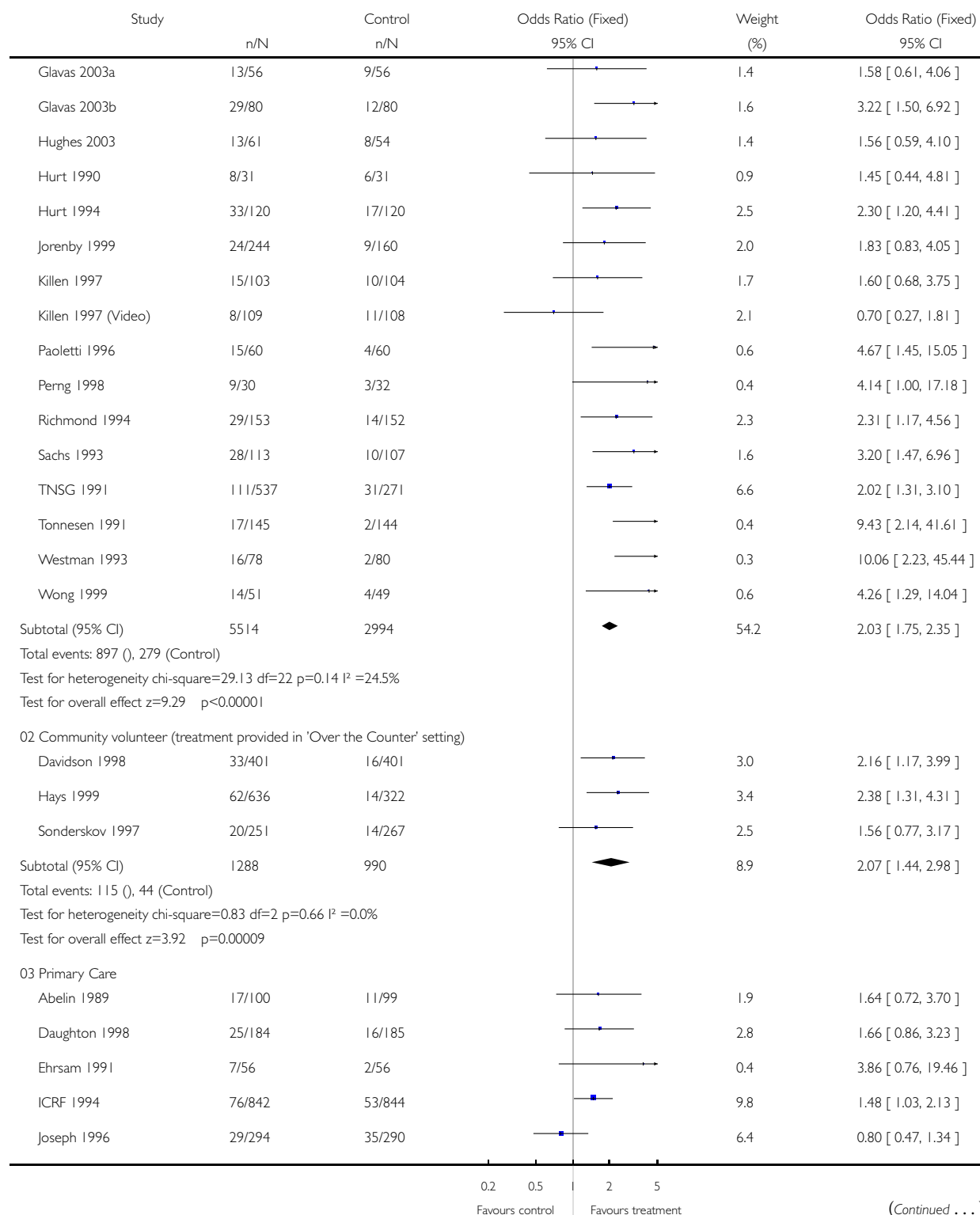
Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

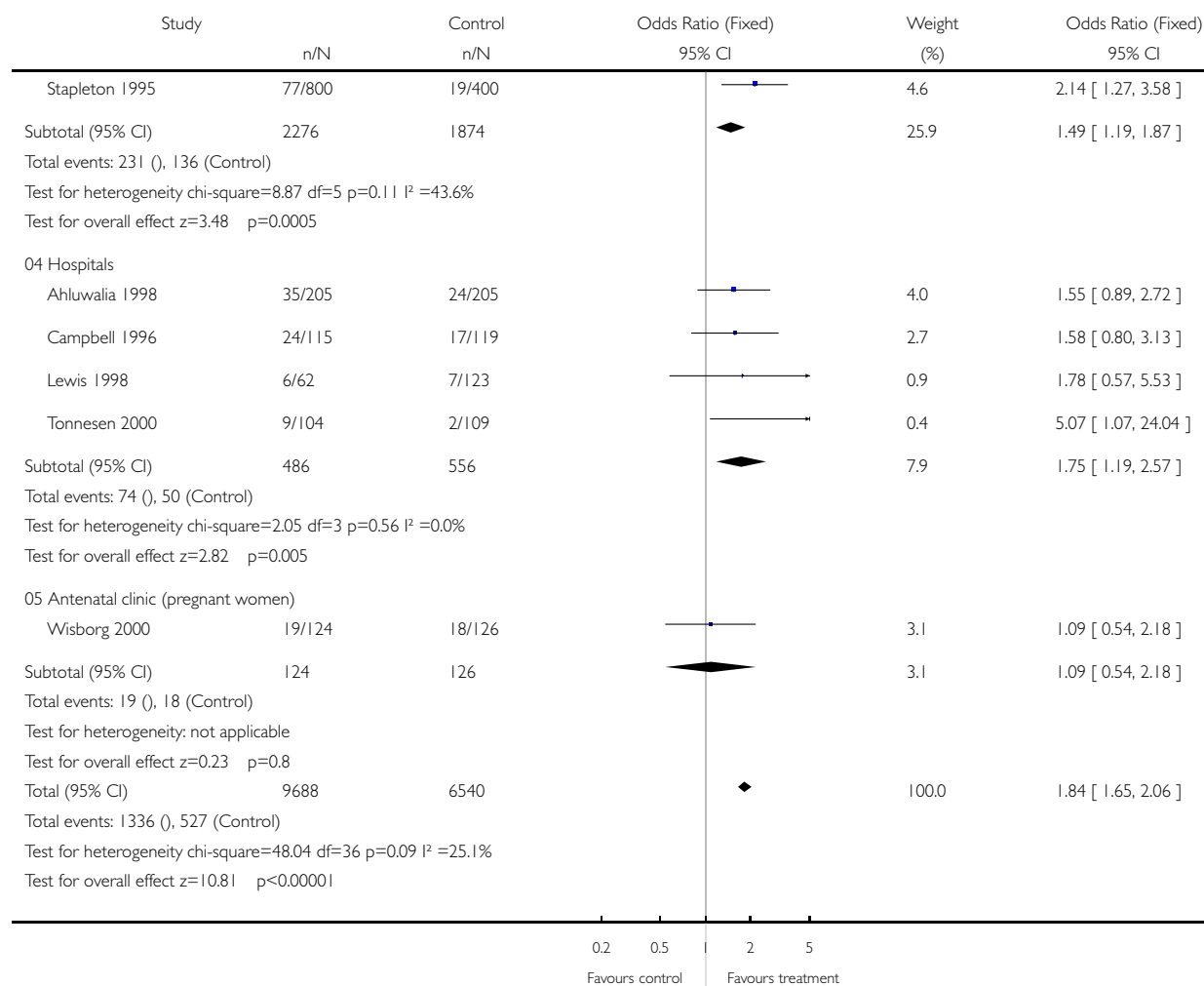
Outcome: 02 Nicotine Patch



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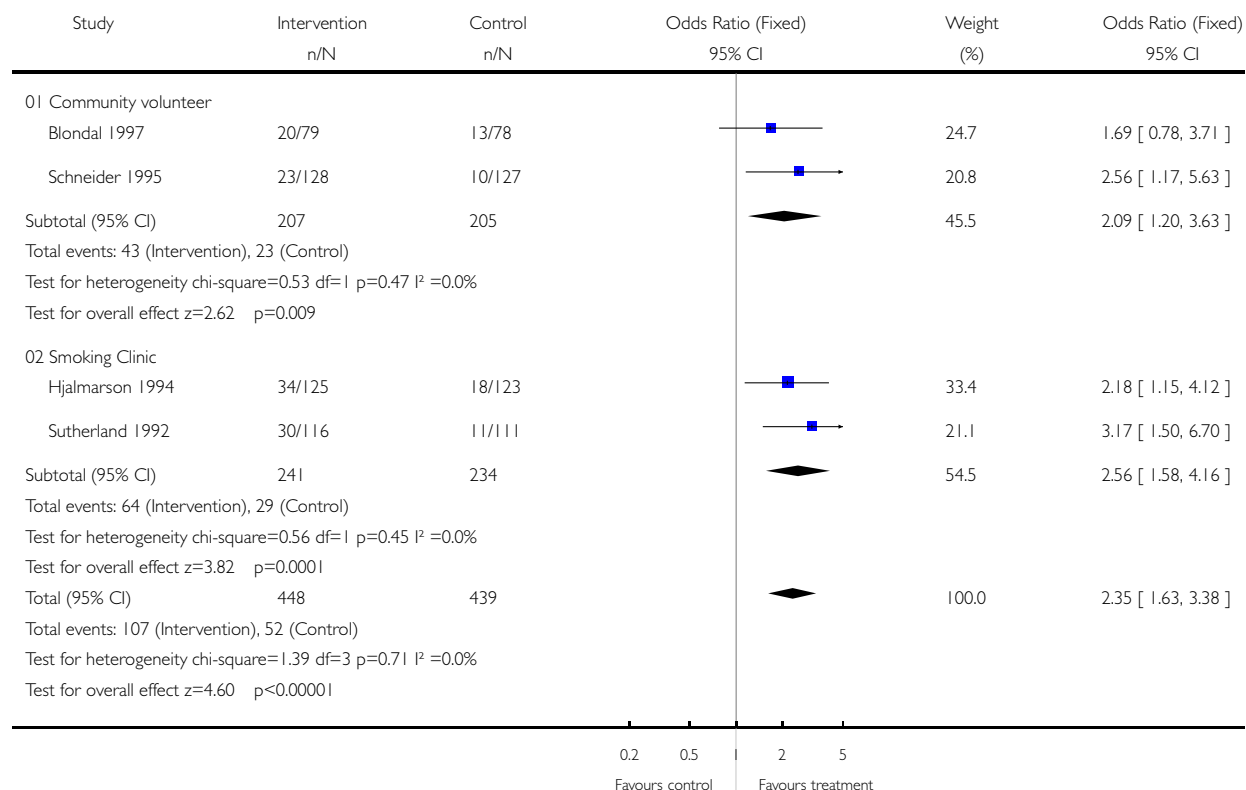


**Analysis 07.03. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 03 Nicotine Intranasal spray**

Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

Outcome: 03 Nicotine Intranasal spray



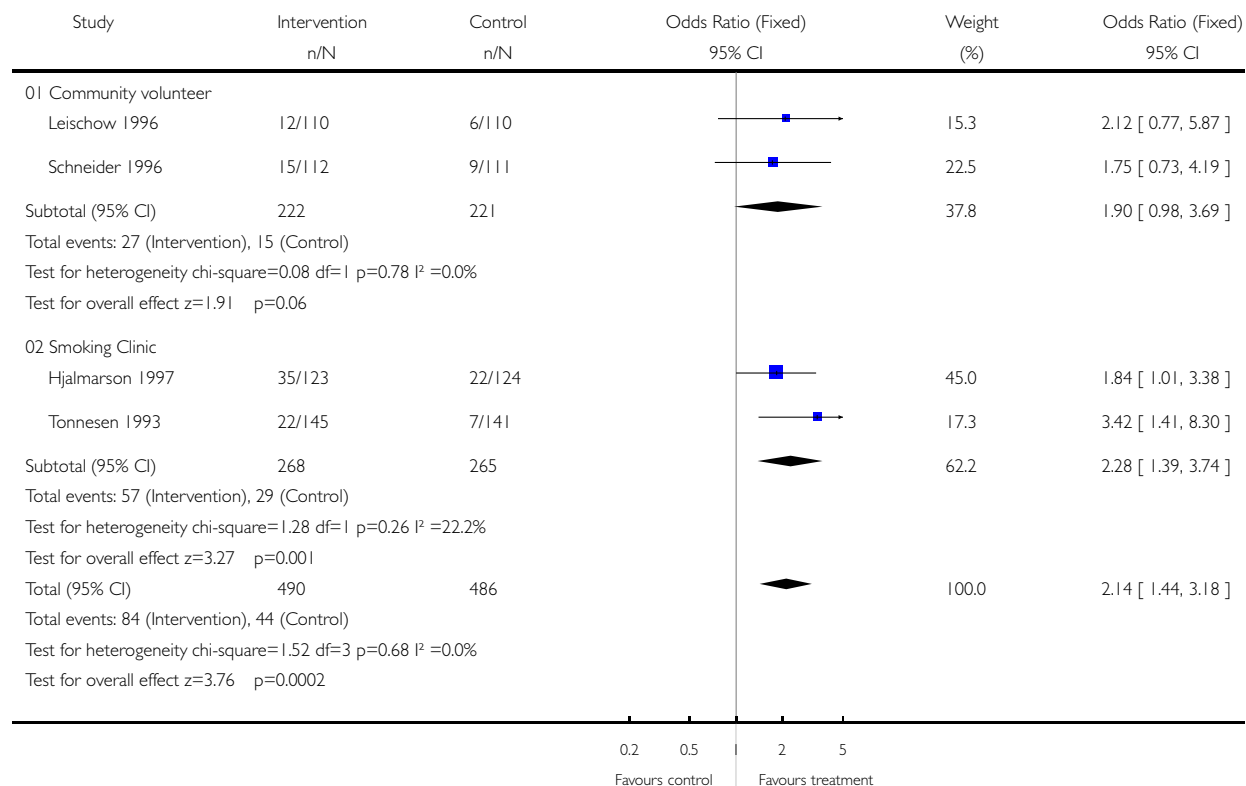


**Analysis 07.04. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 04 Nicotine Inhaler/inhalator**

Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

Outcome: 04 Nicotine Inhaler/inhalator

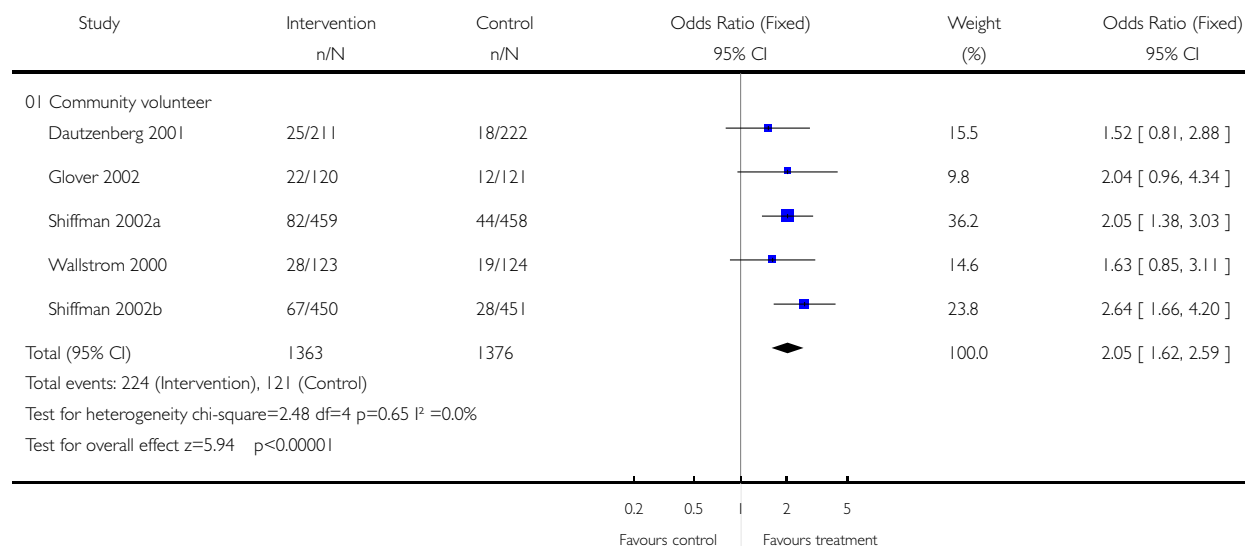


**Analysis 07.05. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 05 Nicotine tablet/lozenge**

Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

Outcome: 05 Nicotine tablet/lozenge

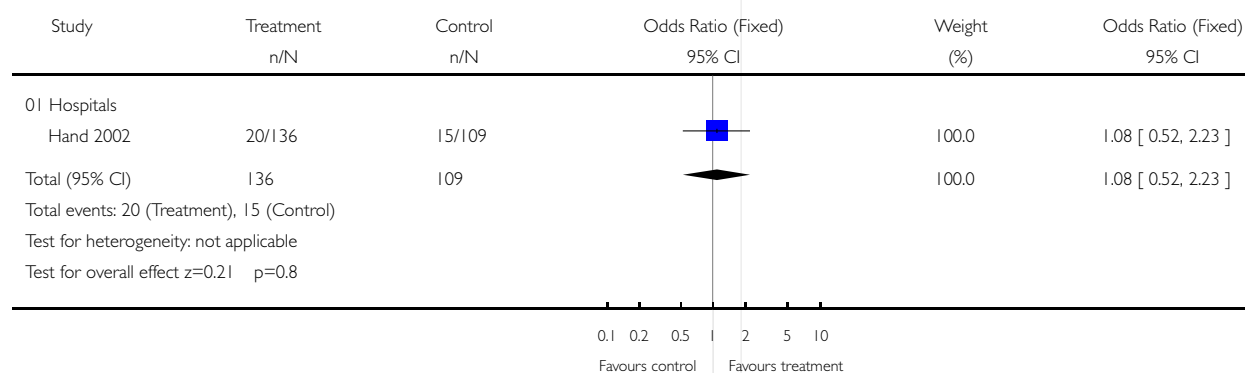


**Analysis 07.06. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 06 Combination of NRT**

Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

Outcome: 06 Combination of NRT

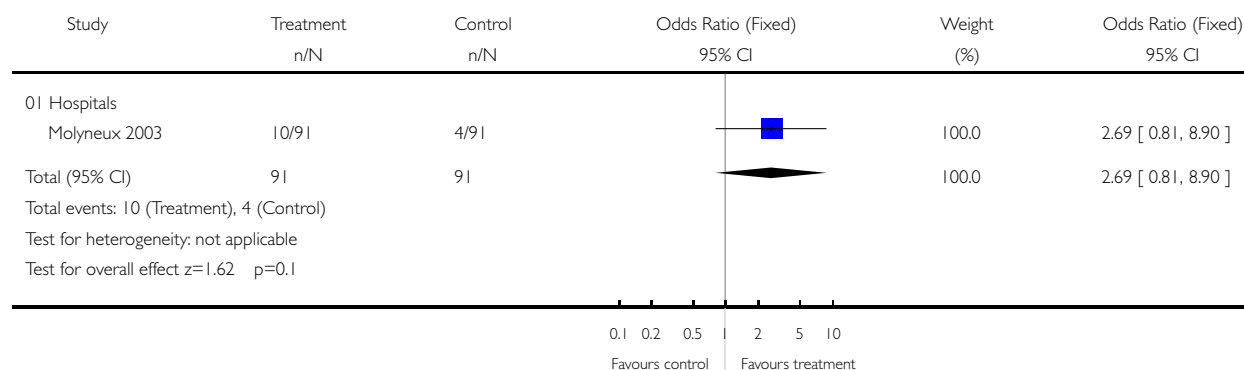


### Analysis 07.07. Comparison 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison), Outcome 07 Choice of NRT

Review: Nicotine replacement therapy for smoking cessation

Comparison: 07 Effect of clinical/recruitment setting on NRT therapy (indirect comparison)

Outcome: 07 Choice of NRT

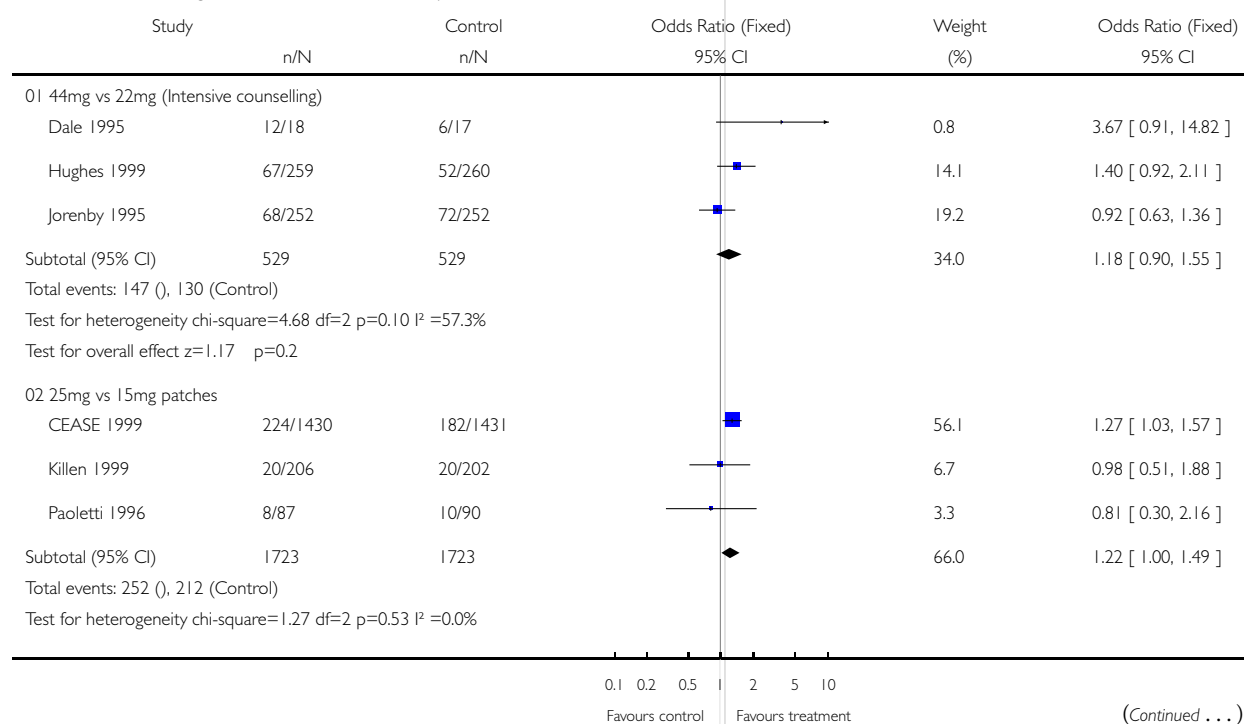


### Analysis 08.01. Comparison 08 Effect of higher dose patches, Outcome 01 Smoking cessation at maximum follow-up

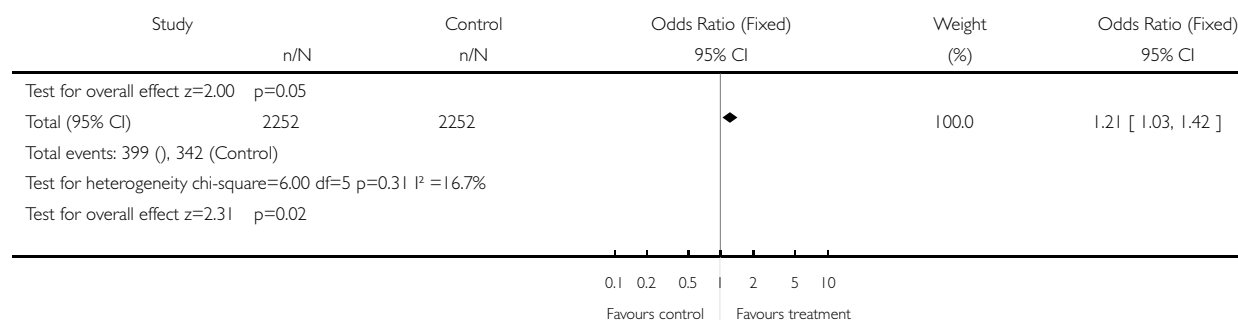
Review: Nicotine replacement therapy for smoking cessation

Comparison: 08 Effect of higher dose patches

Outcome: 01 Smoking cessation at maximum follow-up



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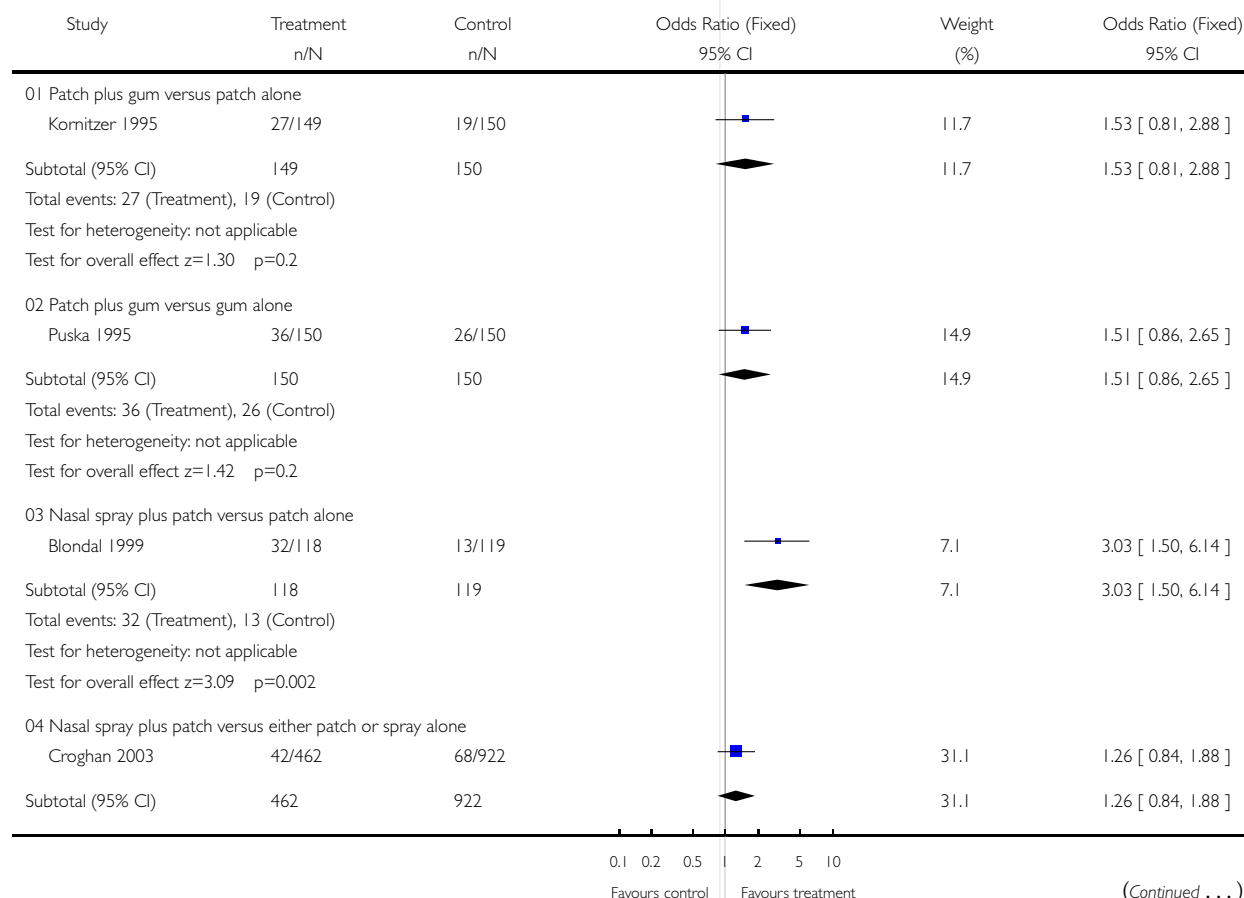


### Analysis 09.01. Comparison 09 Effect of combinations of different types of NRT, Outcome 01 Long term smoking cessation

Review: Nicotine replacement therapy for smoking cessation

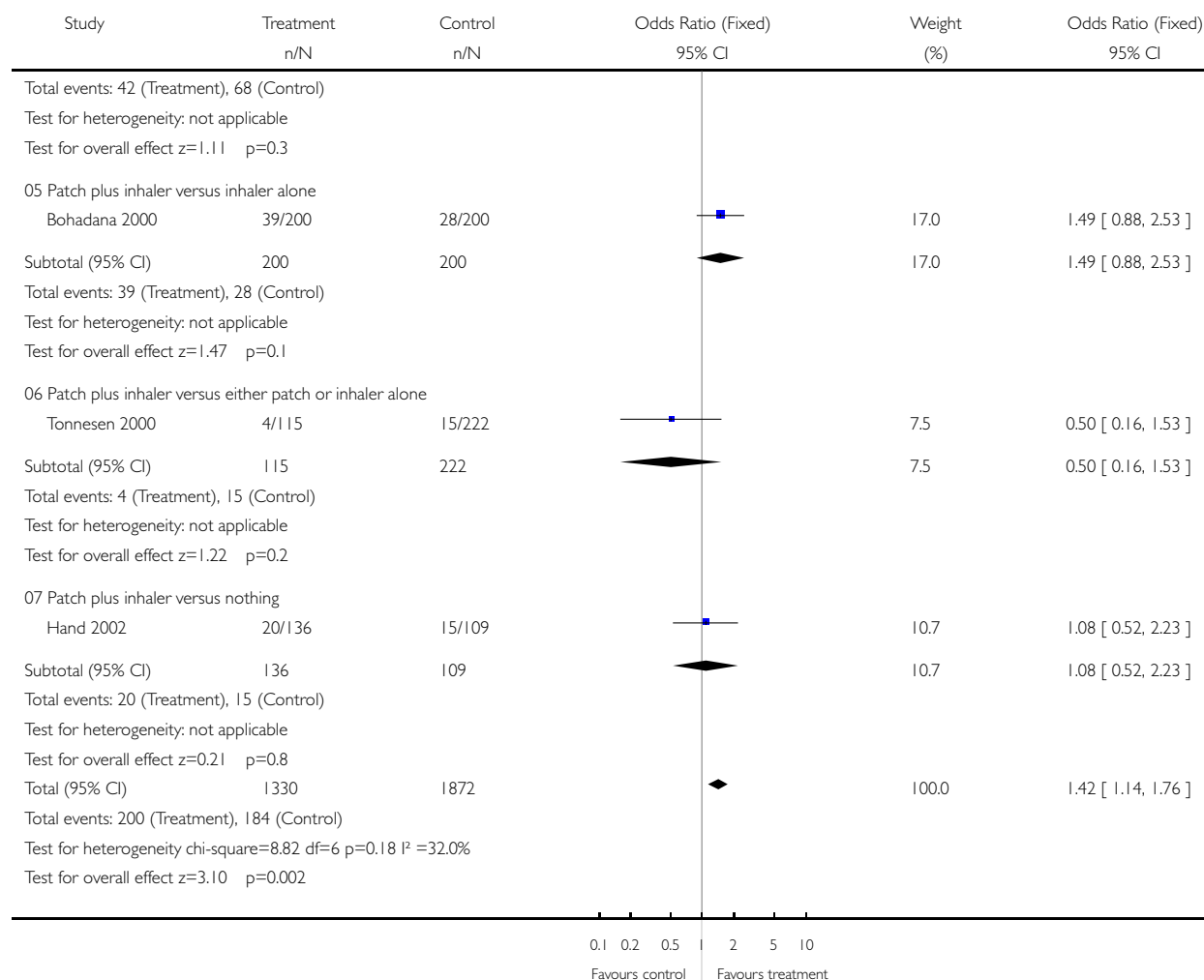
Comparison: 09 Effect of combinations of different types of NRT

Outcome: 01 Long term smoking cessation



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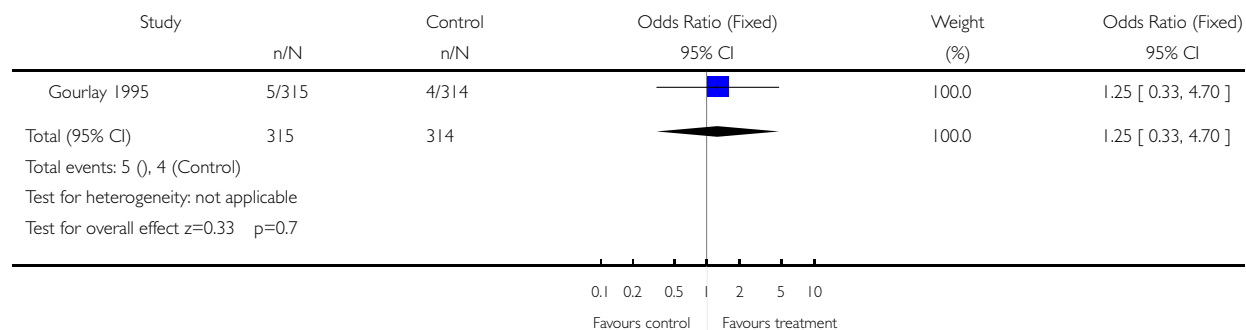


### Analysis 10.01. Comparison 10 Effect of nicotine patches in relapsed smokers, Outcome 01 Smoking cessation at six months

Review: Nicotine replacement therapy for smoking cessation

Comparison: 10 Effect of nicotine patches in relapsed smokers

Outcome: 01 Smoking cessation at six months

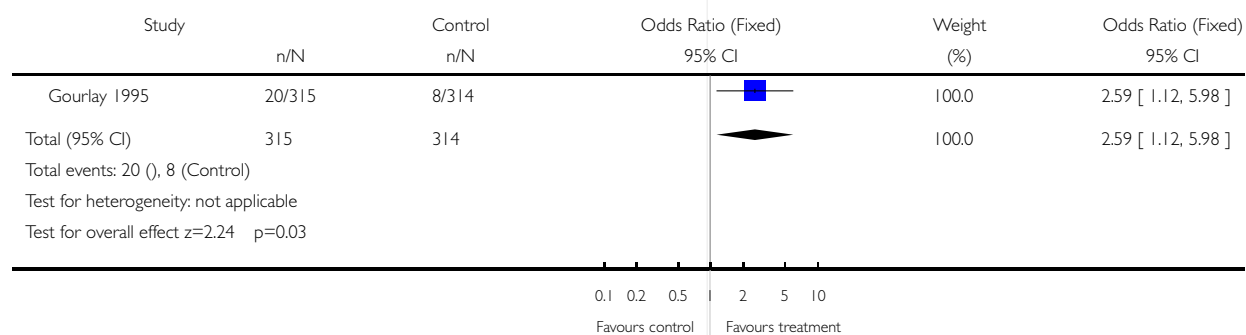


### Analysis 10.02. Comparison 10 Effect of nicotine patches in relapsed smokers, Outcome 02 Not smoking in 28 days before maximal followup

Review: Nicotine replacement therapy for smoking cessation

Comparison: 10 Effect of nicotine patches in relapsed smokers

Outcome: 02 Not smoking in 28 days before maximal followup

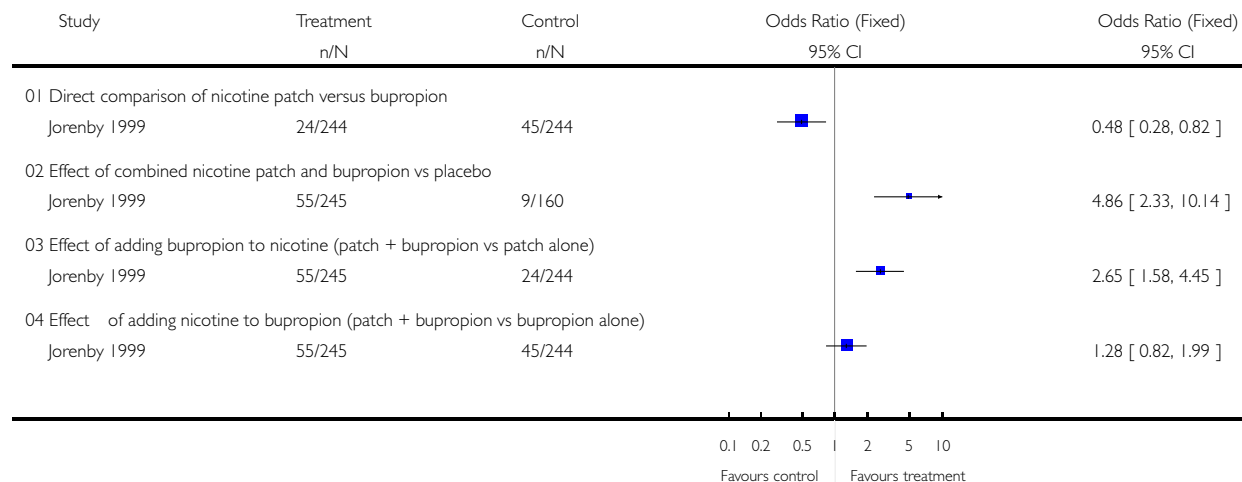


### Analysis 11.01. Comparison 11 Effect of combinations of nicotine patch and bupropion, Outcome 01 Smoking cessation at 12 months (continuous abstinence)

Review: Nicotine replacement therapy for smoking cessation

Comparison: 11 Effect of combinations of nicotine patch and bupropion

Outcome: 01 Smoking cessation at 12 months (continuous abstinence)

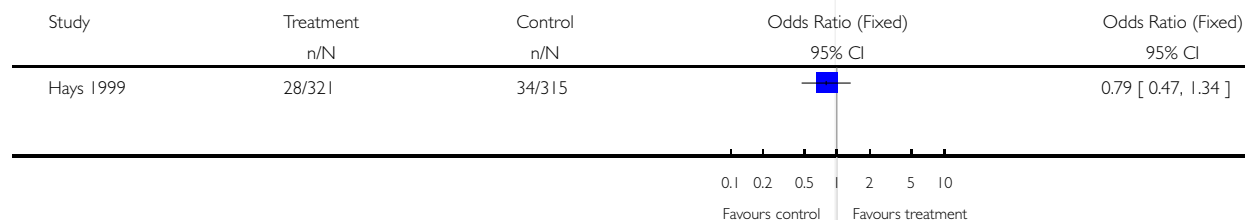


### Analysis 12.01. Comparison 12 Effect of Over the Counter setting, Outcome 01 Free nicotine patch versus paid patch (no support)

Review: Nicotine replacement therapy for smoking cessation

Comparison: 12 Effect of Over the Counter setting

Outcome: 01 Free nicotine patch versus paid patch (no support)

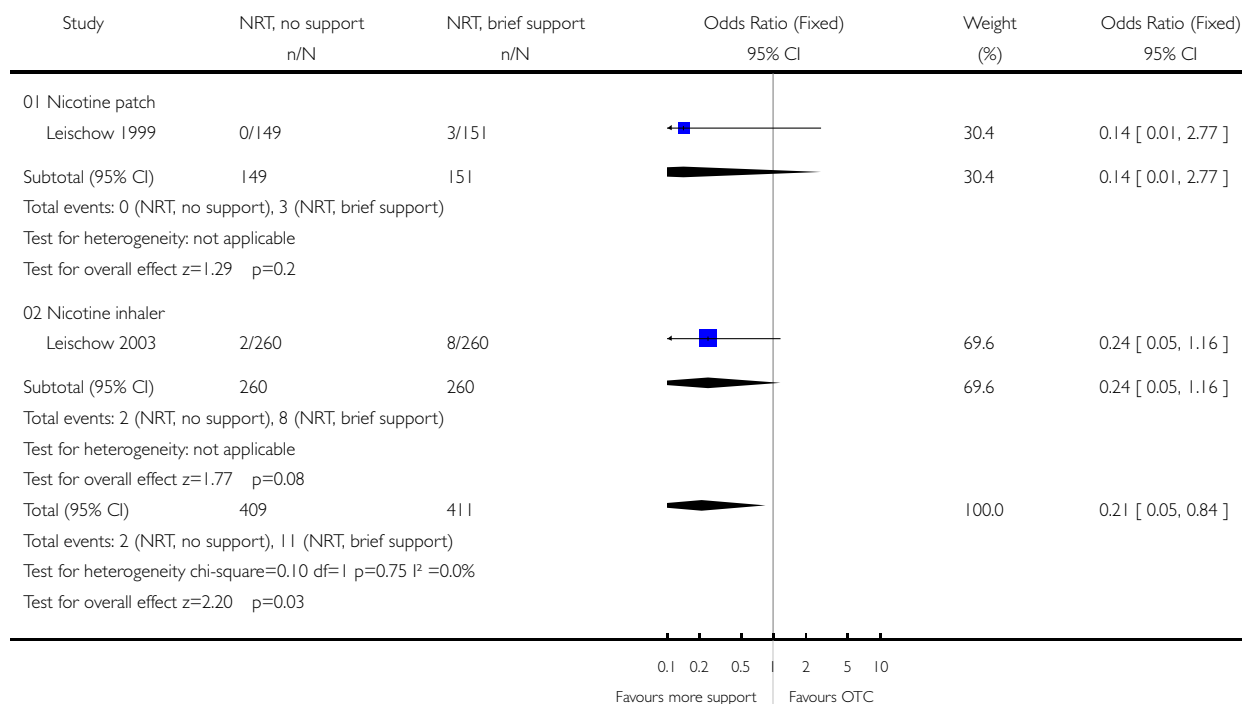


## Analysis 12.02. Comparison 12 Effect of Over the Counter setting, Outcome 02 Smoking cessation using NRT without support versus physician prescribed NRT (all NRT purchased)

Review: Nicotine replacement therapy for smoking cessation

Comparison: 12 Effect of Over the Counter setting

Outcome: 02 Smoking cessation using NRT without support versus physician prescribed NRT (all NRT purchased)

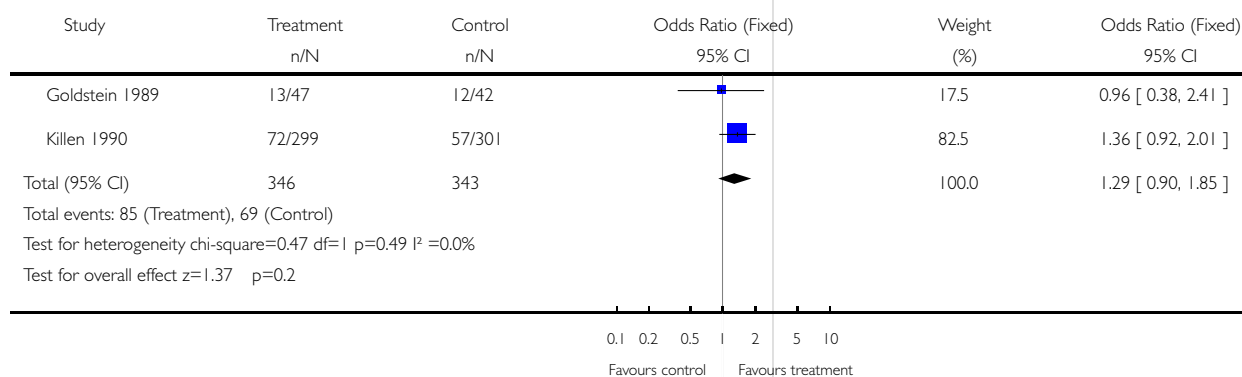


## Analysis 13.01. Comparison 13 Fixed versus ad lib schedule of gum, Outcome 01 Smoking cessation

Review: Nicotine replacement therapy for smoking cessation

Comparison: 13 Fixed versus ad lib schedule of gum

Outcome: 01 Smoking cessation



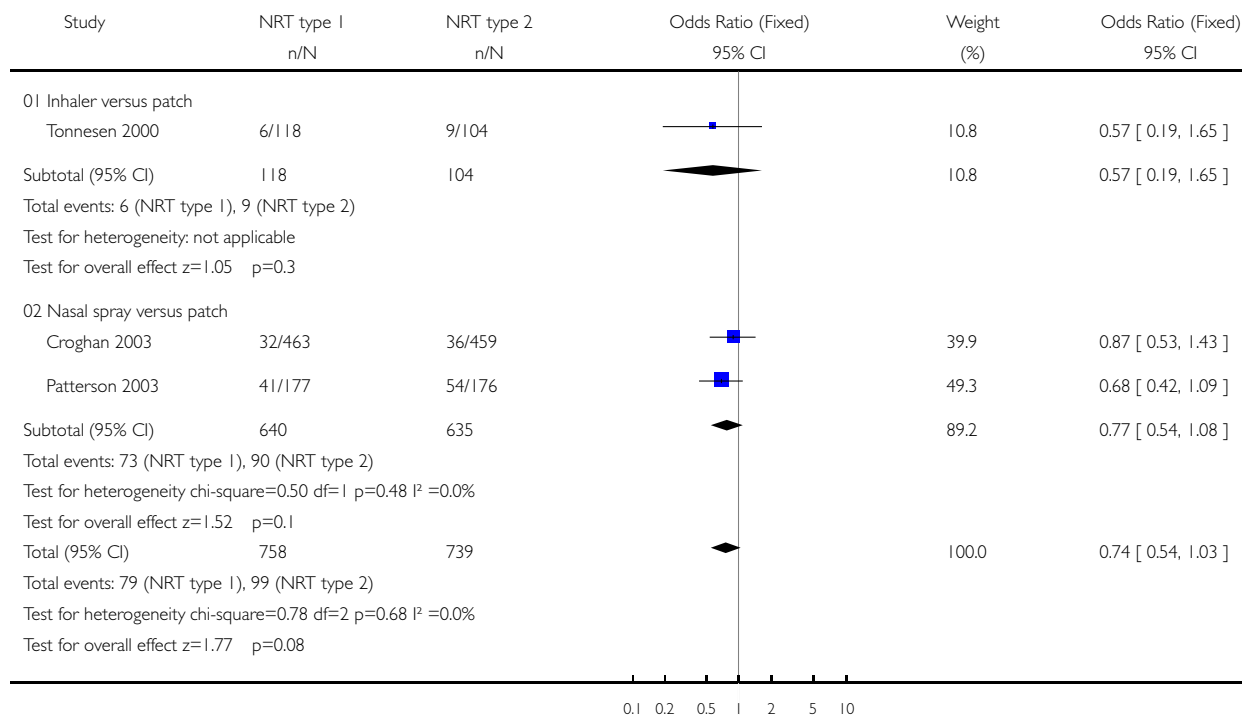


### Analysis 14.01. Comparison 14 Direct comparisons between NRT types, Outcome 01 Smoking cessation

Review: Nicotine replacement therapy for smoking cessation

Comparison: 14 Direct comparisons between NRT types

Outcome: 01 Smoking cessation

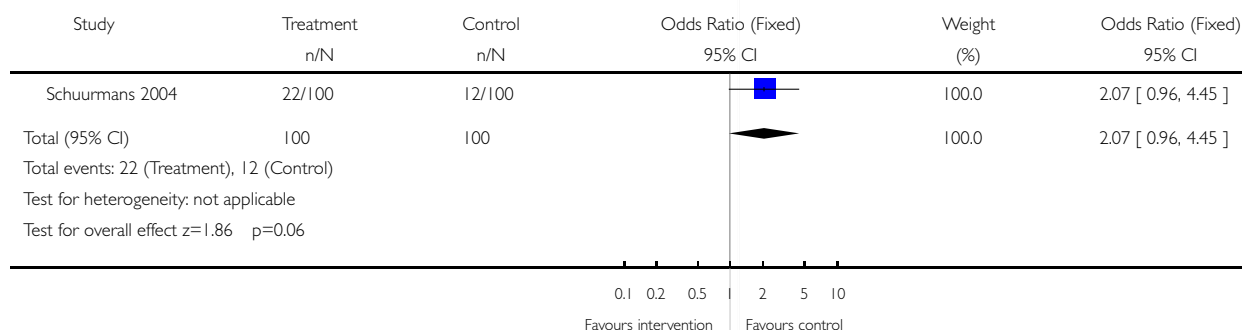


### Analysis 15.01. Comparison 15 Effect of pretreatment with nicotine patch, Outcome 01 Smoking cessation

Review: Nicotine replacement therapy for smoking cessation

Comparison: 15 Effect of pretreatment with nicotine patch

Outcome: 01 Smoking cessation

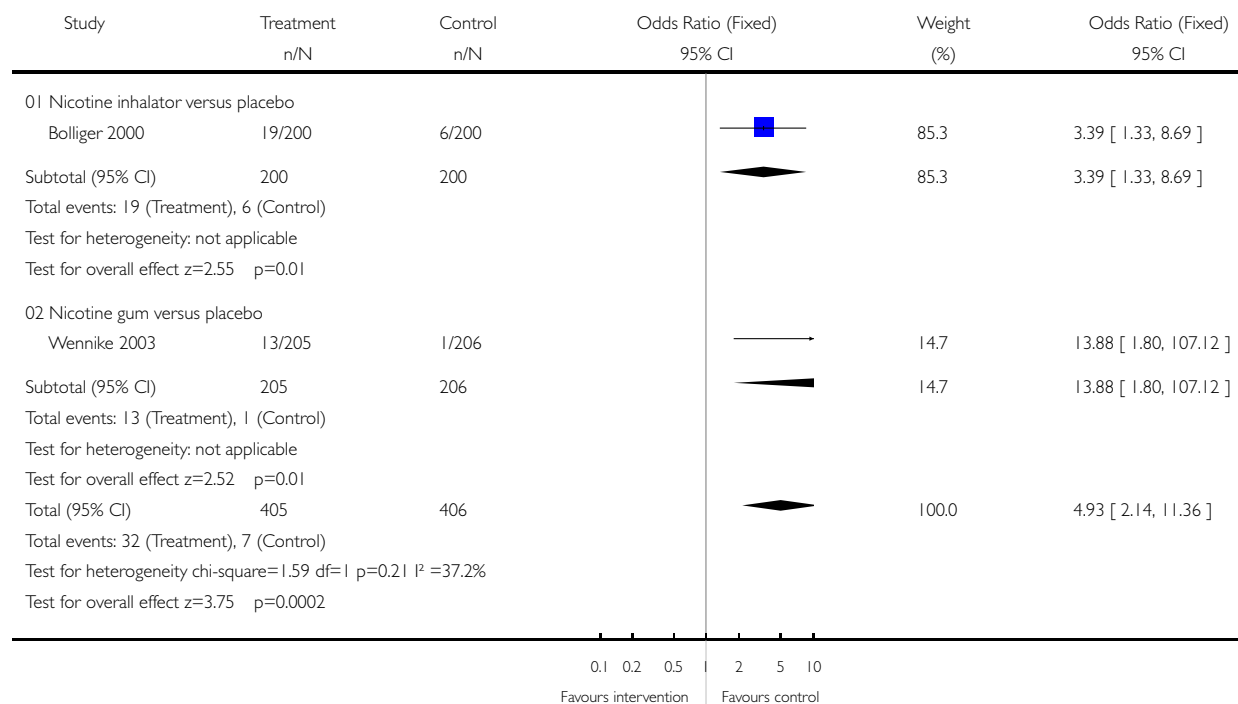


# **Analysis 16.01. Comparison 16 NRT for smoking reduction., Outcome 01 Sustained reduction to <50% of baseline cigarette consumption at longest follow-up**

Review: Nicotine replacement therapy for smoking cessation

Comparison: 16 NRT for smoking reduction.

Outcome: 01 Sustained reduction to <50% of baseline cigarette consumption at longest follow-up

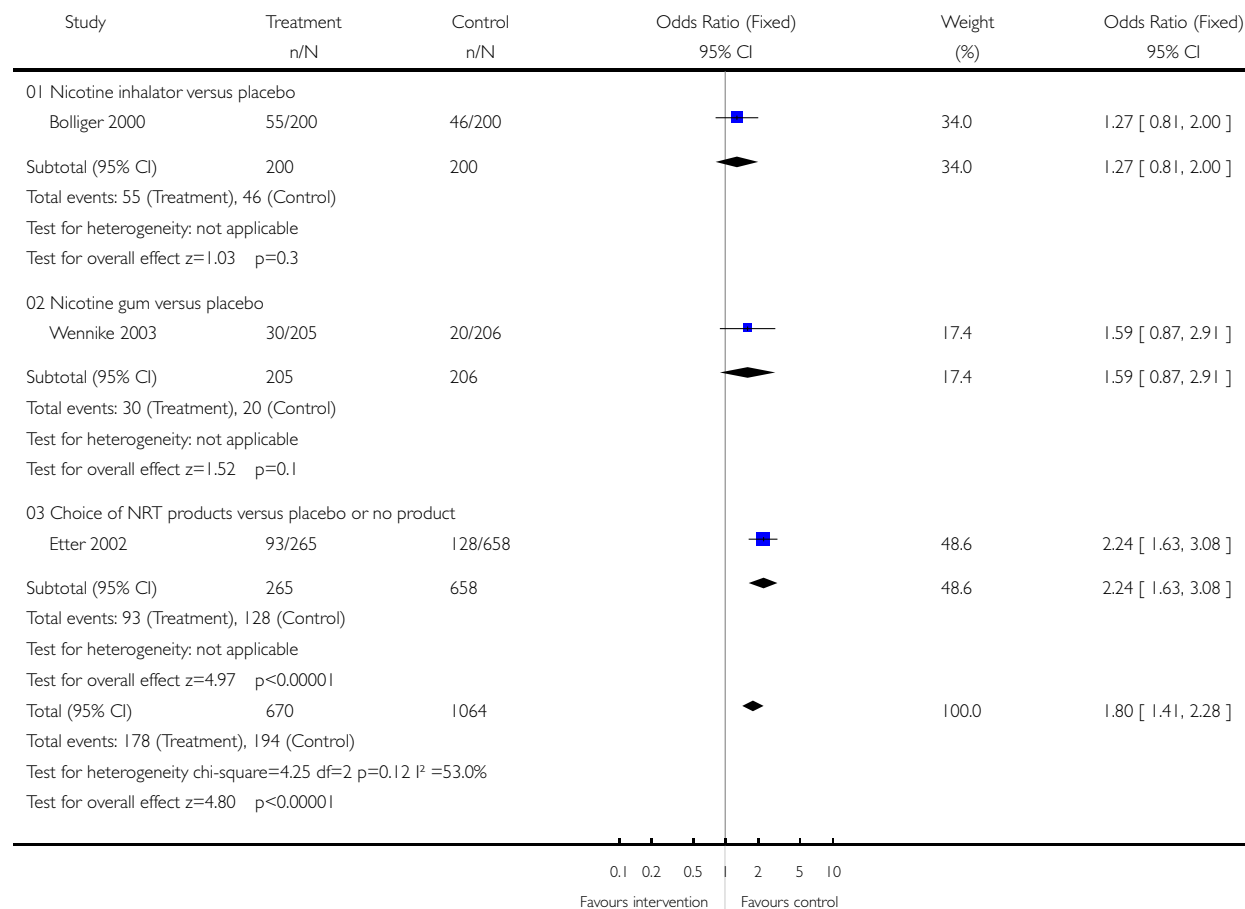


## Analysis 16.02. Comparison 16 NRT for smoking reduction., Outcome 02 Point prevalence reduction to <50% of baseline cigarette consumption at longest follow-up

Review: Nicotine replacement therapy for smoking cessation

Comparison: 16 NRT for smoking reduction.

Outcome: 02 Point prevalence reduction to <50% of baseline cigarette consumption at longest follow-up

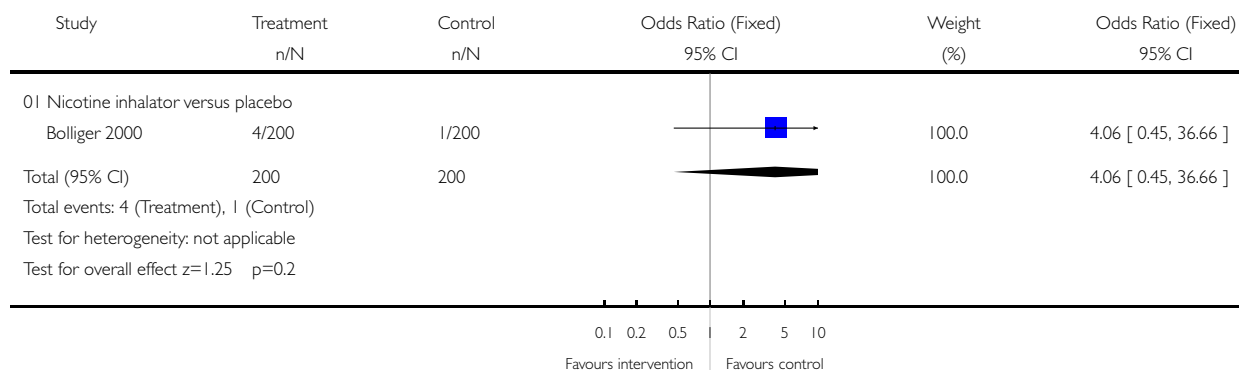


### Analysis 16.03. Comparison 16 NRT for smoking reduction., Outcome 03 Sustained abstinence at longest follow-up

Review: Nicotine replacement therapy for smoking cessation

Comparison: 16 NRT for smoking reduction.

Outcome: 03 Sustained abstinence at longest follow-up



### Analysis 16.04. Comparison 16 NRT for smoking reduction., Outcome 04 Point prevalence abstinence at longest follow-up

Review: Nicotine replacement therapy for smoking cessation

Comparison: 16 NRT for smoking reduction.

Outcome: 04 Point prevalence abstinence at longest follow-up

