Combined pharmacotherapy and behavioural interventions for smoking cessation (Review)

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[Intervention Review]

Combined pharmacotherapy and behavioural interventions for smoking cessation

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ABSTRACT

Background

Both behavioural support (including brief advice and counselling) and pharmacotherapies (including nicotine replacement therapy (NRT), varenicline and bupropion) are effective in helping people to stop smoking. Combining both treatment approaches is recommended where possible, but the size of the treatment effect with different combinations and in different settings and populations is unclear.

Objectives

To assess the effect of combining behavioural support and medication to aid smoking cessation, compared to a minimal intervention or usual care, and to identify whether there are different effects depending on characteristics of the treatment setting, intervention, population treated, or take-up of treatment.

Search methods

We searched the Cochrane Tobacco Addiction Group Specialised Register in July 2012 for records with any mention of pharmacotherapy, including any type of NRT, bupropion, nortriptyline or varenicline.

Selection criteria

Randomized or quasi-randomized controlled trials evaluating combinations of pharmacotherapy and behavioural support for smoking cessation, compared to a control receiving usual care or brief advice or less intensive behavioural support. We excluded trials recruiting only pregnant women, trials recruiting only adolescents, and trials with less than six months follow-up.

Data collection and analysis

Search results were prescreened by one author and inclusion or exclusion of potentially relevant trials was agreed by both authors. Data was extracted by one author and checked by the other.

The main outcome measure was abstinence from smoking after at least six months of follow-up. We used the most rigorous definition of abstinence for each trial, and biochemically validated rates if available. We calculated the risk ratio (RR) and 95% confidence interval (CI) for each study. Where appropriate, we performed meta-analysis using a Mantel-Haenszel fixed-effect model.

Main results

Forty-one studies with a total of more than 20,000 participants met the inclusion criteria. A large proportion of studies recruited people in healthcare settings or with specific health needs. Most studies provided NRT. Behavioural support was typically provided by specialists in cessation counselling, who offered between four and eight contact sessions. The planned maximum duration of contact was typically more than 30 minutes but less than 300 minutes. Overall, studies were at low or unclear risk of bias, and findings were not sensitive to the exclusion of any of the three studies rated at high risk of bias in one domain. One large study (the Lung Health Study) contributed heterogeneity due to a substantially larger treatment effect than seen in other studies (RR 3.88, 95% CI 3.35 to 4.50). Since this study used a particularly intensive intervention which included extended availability of nicotine gum, multiple group sessions and long term maintenance and recycling contacts, the results may not be comparable with the interventions used in other studies, and hence it was not pooled in other analyses. Based on the remaining 40 studies (15,021 participants) there was good evidence for a benefit of combination pharmacotherapy and behavioural treatment compared to usual care or brief advice or less intensive behavioural support (RR 1.82, 95% CI 1.66 to 2.00) with moderate statistical heterogeneity (I^2 = 40%). The pooled estimate for 31 trials that recruited participants in healthcare settings (RR 2.06, 95% CI 1.81 to 2.34) was higher than for eight trials with community-based recruitment (RR 1.53, 95% CI 1.33 to 1.76). Pooled estimates were lower in a subgroup of trials where the behavioural intervention was provided by specialist counsellors versus trials where counselling was linked to usual care (specialist: RR 1.73, 95% CI 1.55 to 1.93, 28 trials; usual provider: RR 2.41, 95% CI 1.91 to 3.02, 8 trials) but this was largely attributable to the small effect size in two trials using specialist counsellors where the take-up of the planned intervention was low, and one usual provider trial with alarge effect. There was little indirect evidence that the relative effect of an intervention differed according to whether participants in a trial were required to be motivated to make a quit attempt or not. There was only weak evidence that studies offering more sessions had larger effects and there was not clear evidence that increasing the duration of contact increased the effect, but there was more evidence of a dose-response relationship when analyses were limited to trials where the take-up of treatment was high.

Authors' conclusions

Interventions that combine pharmacotherapy and behavioural support increase smoking cessation success compared to a minimal intervention or usual care. Further trials would be unlikely to change this conclusion. We did not find strong evidence from indirect comparisons that offering more intensive behavioural support was associated with larger treatment effects but this could be because intensive interventions are less likely to be delivered in full.

PLAIN LANGUAGE SUMMARY

Does a combination of smoking cessation medication and behavioural support help smokers to stop?

Behavioural support (such as brief advice and counselling) and medications (including varenicline, bupropion, and nicotine replacement therapies like patches or gum) help people quit smoking. Many guidelines recommend combining medication and behavioural support to help people stop smoking, but it is unclear if some combinations are more effective than others, or if the combination of medication and behavioural support works better in some settings or groups than in others.

This review includes 41 studies which compare combinations of behavioural support and medication to help smokers to stop compared to groups receiving usual care or less behavioural support. One large study found a very strong treatment effect; it had an intensive intervention which included extended availability of nicotine gum, multiple group sessions, and long term contact to help maintain abstinence or encourage additional quit attempts Because it was not typical of most treatment programmes, it was not included when we combined the results from the included studies although it shows that such intensive support can be very effective. Based on the remaining 40 studies, we found that using a combination of behavioural support and medication might typically increase the chances of a person successfully quitting smoking by 70 to 100 per cent compared to their chance of success if they just received brief advice or support. There was no clear evidence that providing more contact time increased the effect of the intervention, and there was only weak evidence that studies offering a larger number of behavioural support sessions had larger effects. However, when we only looked at studies where most people used the treatments offered, there was some evidence that intensive support was more effective.

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

Combined pharmacotherapy and behavioural interventions for smoking cessation

Patient or population: patients with smoking cessation
Settings: Community and healthcare settings
Intervention: Combined pharmacotherapy and behavioural interventions

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Combined pharmacotherapy and behavioural interventions				
Cessation at longest follow-up (all but Lung Health Study)	**83 per 1000**[1]	**151 per 1000** (138 to 166)	**RR 1.82** (1.66 to 2)	15021 (40 studies)	⊕⊕⊕⊕ **high**[2]	
Cessation at longest follow-up (Lung Health Study only) Follow-up: mean 12 months	**90 per 1000**	**350 per 1000** (302 to 406)	**RR 3.88** (3.35 to 4.5)	5887 (1 study)	⊕⊕⊕◯ **moderate**[3]	Substantially larger treatment effect than seen in other studies. Particularly intensive intervention, hence not included in main analysis

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

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

[1] Baseline risk calculated as mean control group risk for both comparisons

[2] Some evidence of asymmetry in a funnel plot; excess of small trials detecting larger effects. However, in a sensitivity analysis, removing smaller studies did not markedly decrease the pooled estimate.

[3] Downgraded due to indirectness. As this study had a particularly intensive intervention, the results may not be generalisable to real world treatment programmes.

BACKGROUND

Giving up smoking is the most effective way for people who smoke to reduce their risk of smoking related disease and premature death. Behavioural support and pharmacotherapies help people to stop smoking. Behavioural support interventions include written materials containing advice on quitting, multisession group therapy programmes or individual counselling sessions in person or by telephone. Providing standard self-help materials alone seems to have at best a small effect on success, but there is evidence of a benefit of individually tailored self-help materials or more intensive advice or counselling (Lancaster 2005a; Lancaster 2005b). Nicotine replacement therapy (NRT), varenicline, bupropion and nortriptyline all increase the long-term success of quit attempts (Hughes 2007; Stead 2008; Cahill 2012). Many clinical practice guidelines recommend that healthcare providers offer people who are prepared to make a quit attempt both classes of intervention on the basis that they may have an additive or even multiplicative effect. This approach assumes that the two types of treatment have complementary modes of action, and may independently improve the chances of maintaining long-term abstinence. However, it is recognised that many people who use pharmacotherapy will not take up the offer of intensive behavioural support. NRT products are available over the counter (OTC) without a prescription in many countries, and people who purchase them may not access any specific behavioural support. People who obtain prescriptions for pharmacotherapies are more likely to receive some support, but this may be focused on explaining proper use of the drug rather than on behavioural counselling. Surveys suggest that the proportion of people who use both types of treatment when attempting to stop smoking is low (Shiffman 2008, Kotz 2009b). The aim of this review is to assess the the effect of the combined intervention of pharmacotherapy and behavioural support, compared to using neither type of treatment, or receiving only brief advice or behavioural support.

Other Cochrane Tobacco Addiction reviews have evaluated the separate effects of behavioural and pharmaceutical interventions. In order to quantify these individual effects, these reviews restrict inclusion to trials where the intervention under investigation is unconfounded. By unconfounded, we mean that trials of pharmacotherapies had to provide the same amount of behavioural support (materials, advice, counselling contacts) to all participants whether they receive active treatment or a placebo or no medication. Likewise, when behavioural interventions are evaluated there must be no systematic difference in the offer of medications between the active and control arms of the trial.

The findings from reviews of unconfounded trials support the use of combined pharmacological and behavioural therapy, but do not provide a direct estimate of the size of the benefit to be expected from combining the two types of treatment. The aim of this review is to synthesize the evidence from trials that directly evaluate the use of an intervention combining pharmacotherapy and behavioural support, where the control condition includes neither pharmacotherapy nor the same intensity of behavioural support. The control will involve either usual care, or brief advice. If the pharmacotherapy and the behavioural support components exert independent effects on successful cessation, these trials might be expected to give considerably larger treatment effects than would be achieved from either the behavioural or the medication component alone. However, other factors may affect the size of this effect. In particular, pragmatic trials of interventions in healthcare settings may find smaller effects than placebo-controlled pharmacotherapy studies in research settings, as delivery of the intervention components may be lower. To address this, we set out to identify moderators that might lead to heterogeneity in effects of combined treatment, including the motivation of participants, the nature of the treatment setting, and the type of therapist. We also aimed to categorize by the intensity of behavioural support, based on number and duration of contacts, in order to evaluate whether the intensity of the behavioural support affected treatment success. Previous meta-analyses have suggested that there is a dose response, with more contacts improving outcomes amongst people receiving pharmacotherapy (Fiore 2008 table 6.23). We also considered the degree to which participants used both medication and behavioural components as a possible explanation for any heterogeneity.

For this review we identified trials of interventions that combined pharmacotherapies (NRT, varenicline, bupropion, nortriptyline) with behavioural support (tailored materials, brief advice, in person or telephone counselling) and that compared outcomes against a control group that received either usual care or a brief cessation component (i.e. advice to quit but no other behavioural support or medication common to the intervention). A companion review will evaluate whether more intensive behavioural support improves cessation outcomes for people using pharmacotherapy, using the direct evidence from trials that compare different levels of behavioural support for people receiving any type of pharmacotherapy for smoking cessation (Stead 2012).

OBJECTIVES

To assess the effect of combining behavioural support and medication to aid smoking cessation, compared to using neither, and to identify whether there are different effects depending on characteristics of the treatment setting, intervention, population treated, or take-up of treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized or quasi-randomized controlled trials. We did not exclude studies on the basis of publication status or language of publication.

Types of participants

We included trials that recruited people who smoke in any setting, with the exception of trials which only recruit pregnant women or adolescents. These populations are considered in specific reviews. Trial participants did not need to be selected according to their interest in quitting or their suitability for pharmacotherapy.

Types of interventions

We included interventions for increasing smoking cessation that included behavioural support and the availability of pharmacotherapy. We excluded trials where fewer than 20% of participants were eligible for or used pharmacotherapy. The provision of written information or brief instructions on correct use of the pharmacotherapy was not regarded as behavioural support. The control group should not have been systematically offered pharmacotherapy but we did not exclude studies where some control group participants obtained medication from other sources. Control group participants could be offered usual care, self-help materials or brief advice on quitting, but support had to have been of a lower intensity than that given to intervention participants.

Types of outcome measures

Following the standard methodology of the Cochrane Tobacco Addiction Group, the primary outcome is smoking cessation at the longest follow-up using the strictest definition of abstinence, that is, preferring sustained over point prevalence abstinence and using biochemically validated rates where available. We also noted any other abstinence outcomes reported and conducted sensitivity analyses if the choice of outcome affected the results of meta-analysis. We excluded trials reporting less than six months follow-up from the start of intervention.

Search methods for identification of studies

We identified trials from the Cochrane Tobacco Addiction Specialised Register (the Register). This is generated from regular searches of The Cochrane Library, MEDLINE, EMBASE, PsycINFO and Science Citation Index for trials of smoking cessation or prevention interventions. The most recent search of the register was in July 2012. At the time of the search the register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 7, 2012; MEDLINE (via OVID) from 1946 to update 20120622; EMBASE (via OVID) from 1974 to week 201227 and PsycINFO (via OVID) from 1967 to update 20120625. See the Tobacco Addiction Group Module in the Cochrane Library for full search strategies and list of other resources searched.

We searched the Register for records with any mention of pharmacotherapy including any type of nicotine replacement therapy, bupropion, nortriptyline or varenicline in title, abstract or indexing terms (see Appendix 1 for the final search strategy). We checked titles and abstracts to identify trials of interventions for smoking cessation that combined pharmacotherapy with behavioural support. We also checked the excluded study lists of reviews of behavioural therapies and pharmacotherapy for trials excluded because pharmacotherapy was confounded with additional behavioural support compared to the control group. Trials with a factorial design that varied both pharmacotherapy and behavioural conditions were also considered for inclusion. We also tested an additional MEDLINE search using the smoking related terms and design limits used in the standard register search and the MeSH terms 'combined modality therapy' or (Drug Therapy and (exp Behavior therapy or exp Counseling)). This search retrieved a subset of records already screened for the inclusion in the Register and was used to assess whether it might retrieve studies where there was no mention of a specific cessation pharmacotherapy in the title, abstract or indexing. We did not find any additional studies from this.

Data collection and analysis

Selection of studies

LS identified potentially relevant trial reports according to the criteria above. Areas of uncertainty were discussed with TL. LS extracted data, and data extraction was checked by TL.

Data extraction and management

We extracted the following information from trial reports:

- Country and setting of trial
- Method of recruitment, including any selection by motivation to quit
- Method of sequence generation
- Method of allocation concealment
- Characteristics of participants including gender, age, smoking rate
- Characteristics of intervention deliverer
- Intervention components: type, dose and duration of pharmacotherapy, type and duration of behavioural support
- Control group components
- Outcomes: primary outcome length of follow-up and definition of abstinence; other follow-ups and abstinence definitions; use of biochemical validation; loss to follow-up.

Assessment of risk of bias in included studies

Studies were evaluated on the basis of the randomization procedure and allocation concealment, incomplete outcome data assessment and any other bias (Schulz 2002a; Schulz 2002b; Higgins 2011). Publication bias was assessed using a funnel plot.

Measures of treatment effect

Trial effects were expressed as a relative risk (RR): (quitters in treatment group/total randomized to treatment group)/ (quitters in control group/total randomized to control group).

Dealing with missing data

Numbers lost to follow-up were reported by group where available. Following standard Cochrane Tobacco Addiction Group methods, people lost to follow-up were assumed to be smoking and included in the denominators for calculating the RR. Any deaths during follow-up were reported separately and excluded from denominators.

Assessment of heterogeneity

We considered pooling all trials comparing combined therapy to usual care/minimal intervention control if heterogeneity as assessed by the I^2 statistic (Higgins 2003) was less than 50%.

Data synthesis

For groups of trials where meta-analysis was judged appropriate, relative risks were pooled using a Mantel-Haenszel fixed-effect model, and a pooled estimate with 95% confidence intervals reported.
If trials had more than one intervention condition we compared the most intensive combination of behavioural support and pharmacotherapy to the control in the main analysis.

Subgroup analysis and investigation of heterogeneity

We undertook planned subgroup analyses by setting, participant selection, intervention provider, number of sessions, total duration of contact, and take-up of treatment. The subgroups are listed below.

Setting

- Recruited in healthcare settings
- Recruited as community volunteers

Participant selection

- Selected for willingness to make a quit attempt/ high take-up of pharmacotherapy
- Not selected for interest in quitting/ low take-up of pharmacotherapy
- Not explicitly selected but study procedures and participant characteristics suggested that most participants were willing to make a quit attempt

Provider

- Usual care provider
- Specialist in smoking cessation
- Peer group counsellor (ex-smoker)

Intensity

We conducted alternative analyses of intensity adapted from two of the categories used in the US Guidelines (Fiore 2008). We used planned contact time and number of sessions where possible. If this was variable or unclear we used any report of actual delivery. We categorised total amount of contact time as zero (if the only support was sent by mail), 1 to 30 minutes (collapsing one to three and 4 to 30 US guideline categories), 31 to 90, 91 to 300, and over 300 minutes.
Number of person-to-person sessions was categorised as zero, one to three (instead of zero to one and two to three as used in US guidelines), four to eight and over eight sessions.

Treatment take-up (compliance with medication and behavioural support)

We expected this group of trials to include some pragmatic studies where participants are offered treatment but did not use all the components offered. After pilot testing, we categorised studies into three groups:

- High - over 70% starting pharmacotherapy and receiving at least one session of support (where applicable)
- Moderate - Over 30% starting pharmacotherapy and over 50% receiving at least one session of support
- Low - less than 30% starting pharmacotherapy or less than 50% receive at least one session of support

We did not separate trials using different pharmacotherapies in initial analyses but we considered the type of pharmacotherapy as an explanation for remaining heterogeneity.
Where there was evidence from subgroup analyses of clinically relevant differences between categories in any of the subgroups above, we used meta regression (Stata) to explore whether any of the characteristics were effect modifiers. Since these analyses were not pre-specified they are hypothesis generating only.

Sensitivity analysis

We considered the sensitivity of the results to changes in the cut-off range for categories outlined above. If data for multiple outcomes were provided, we conducted sensitivity analyses if the choice of outcome affected the results. We also conducted sensitivity analyses removing smaller studies to assess possible impact of publication bias.

RESULTS

Description of studies

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

Results of the search

The register search retrieved approximately 2200 records. Most of the records that did report trials of interventions for smoking cessation were not relevant because they were placebo-controlled trials of pharmacotherapies, in which the behavioural support was the same for intervention and control conditions. We identified 41 studies for inclusion; many of these were identified via more than one study report. All reports related to a study are listed in the reference section with the primary report used for data extraction identified. Trials are identified by the first author and year of publication of the main study report. A further 69 studies are listed as excluded.

Included studies

We identified 41 studies that met all inclusion criteria with a total of more than 20,000 participants. Most have been published since 2000, with the earliest published in 1988. One trial had almost 6000 participants (Lung Health Study) and one over 2000 (Hollis 2007). Twenty-three trials had more than 100 participants in the intervention arm and most of the remainder had more than 50 in the intervention arm.

About half the studies were conducted in the USA. Of the others there were four from Canada (Wilson 1988; Reid 2003; Ratner 2004; Chouinard 2005), three from Australia (Vial 2002; Wakefield 2004; Baker 2006), three from Denmark (Tonnesen 2006; Villebro 2008; Thomsen 2010), two from Spain (Juarranz Sanz 1998; Rodriguez 2003), two from the UK (Molyneux 2003; Binnie 2007) and one each from Brazil (Otero 2006), Italy (Segnan 1991), the Netherlands (Kotz 2009), Sweden (Sadr Azodi 2009), Japan (Hanioka 2010) and Hong Kong (Chan 2010).

Details of can be found in the Characteristics of included studies table. Appendix 2 tabulates the following study characteristics: setting and provider; selection by motivation; number and total duration of contact categories; and level of take-up of treatment.

Trial setting and recruitment

A high proportion of trials were conducted in healthcare settings and/or recruited people with specific health needs. These included eight trials in hospital inpatients (Simon 1997; Lewis 1998; Vial 2002; Molyneux 2003; Reid 2003; Chouinard 2005; Mohiuddin 2007; Brandstein 2011); four in patients awaiting admission for surgery (Ratner 2004; Villebro 2008; Sadr Azodi 2009; Thomsen 2010); two in outpatient substance abuse treatment programmes (Cooney 2007; Reid 2008); two in mental health service settings (Baker 2006; Hall 2006); one in an AIDS clinic (Wewers 2000); two for people with cancer (Wakefield 2004; Duffy 2006); and one for cancer survivors (Emmons 2005). Six trials recruited patients of primary care clinics (Wilson 1988; Ockene 1991; Segnan 1991; Juarranz Sanz 1998; Katz 2004) or primary care and women's health clinics (Wewers 2009), and two recruited dental clinic patients (Binnie 2007; Hanioka 2010). One recruited Chinese men with erectile dysfunction (Chan 2010). Three recruited people identified as having mild airway obstruction (Lung Health Study; Kotz 2009) or COPD (Tonnesen 2006). One recruited employees at annual occupational health checks (Rodriguez 2003). Okuyemi 2007 recruited residents of low-income public housing departments. Schauffler 2001 recruited members of health maintenance organisations and Velicer 2006 recruited Veterans Administration medical centre patients, in both cases using proactive telephone contact. An 2006 recruited Veterans Administration medical centre patients by mail. Hall 2002, Otero 2006 and McCarthy 2008 recruited community volunteers motivated to quit and Hollis 2007 recruited callers to a quitline seeking cessation assistance.

Selection by motivation to quit

We tried to classify trials according to whether or not willingness to make a quit attempt was required for study eligibility. In some studies motivation was an explicit requirement, including four trials that enrolled motivated volunteers for pharmacotherapy trials involving placebos (Hall 2002; Tonnesen 2006; McCarthy 2008; Kotz 2009). In some study reports there was no mention of motivation as a requirement for inclusion. Some of these trials did recruit some people with no plans to quit smoking. In others, the method of recruitment or the requirement to adhere to a protocol made it seem likely that only people interested in attempting to quit would enrol. We grouped the studies as follows:

- Motivation required (18 trials, 44%): Simon 1997; Lewis 1998; Wewers 2000; Hall 2002; Vial 2002; Reid 2003; Rodriguez 2003; An 2006; Baker 2006; Otero 2006; Tonnesen 2006; Cooney 2007; Hollis 2007; McCarthy 2008; Reid 2008; Kotz 2009: Chan 2010; Hanioka 2010
- Motivation not required but participants likely to have been interested in quitting (10 trials, 24%): Juarranz Sanz 1998;

Molyneux 2003; Wakefield 2004; Duffy 2006; Mohiuddin 2007; Okuyemi 2007; Villebro 2008; Sadr Azodi 2009, Wewers 2009; Brandstein 2011.

- Not selected by motivation (13 trials, 32%): Wilson 1988; Ockene 1991; Segnan 1991; Lung Health Study; Schauffler 2001; Katz 2004; Ratner 2004; Chouinard 2005; Emmons 2005; Hall 2006; Velicer 2006; Binnie 2007; Thomsen 2010.

Participant characteristics

Trials typically had between 35 to 65% female participants. Two trials recruited only women (Wewers 2009; Thomsen 2010) and one only men (Chan 2010). Three trials in the US Veterans Administration medical system had higher proportions of men (Simon 1997; Velicer 2006; Cooney 2007) as did one trial in Spanish workplaces (Rodriguez 2003). The average age ranged from low 40's to mid 50's. The age was younger in a trial amongst survivors of childhood cancer (Emmons 2005).

Provider characteristics

Most counselling and support was provided by specialist cessation counsellors or trained trial personnel. In a small subgroup the intervention was largely given by usual care providers including general practitioners/family physicians (Ockene 1991; Segnan 1991, Juarranz Sanz 1998), dental hygienists (Binnie 2007), dentists and dental hygienist (Hanioka 2010) or occupational physicians (Rodriguez 2003). Two studies used peer group counsellors (Emmons 2005; Wewers 2000) and one used trained lay advisers (Wewers 2009).

Intervention characteristics

The typical intervention involved multiple contacts with a specialist cessation adviser or counsellor, with most participants using some pharmacotherapy and receiving multiple contacts. However, there was a great deal of variation, including some interventions which involved making pharmacotherapy and behavioural components available to a large population in which take-up of treatment was low (Schauffler 2001), or providing a brief intervention to all participants and offering stepped care for those willing to set a quit date (Reid 2003; Katz 2004). One intervention was delivered entirely by mail or prerecorded phone messages, using an expert system for tailoring contact (Velicer 2006) and one by telephone counselling alone (Hollis 2007). All others included some face-to-face contact but additional sessions was sometimes provided by telephone. More than half the trials (n = 22, 54%) offered between four and eight sessions and around a quarter (n = 11, 27%) over eight sessions. The modal category for contact time was 91 to 300 minutes (n = 19, 46%), with 10 (24%) offering between 31 and 90 minutes and seven (17%) over 300 minutes. Since we categorised interventions according to the maximum contact, unless session duration was not described, the typical time per participant would have been smaller, even in studies where the take-up of treatment was high.

The treatment offered to the control group typically involved brief advice and self help materials.

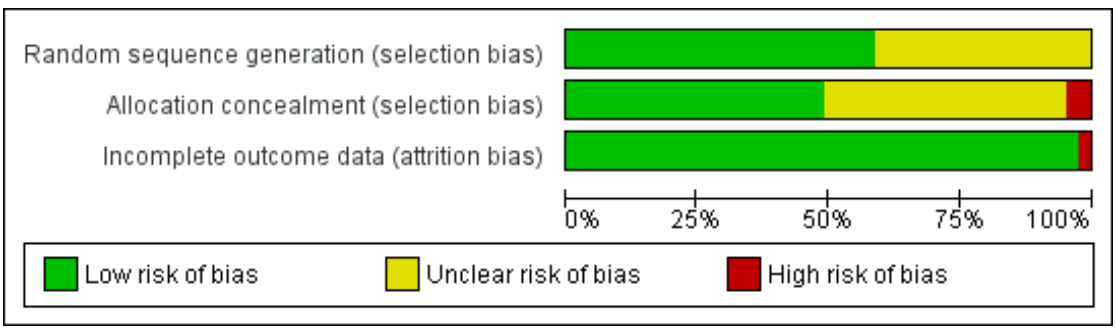
Excluded studies

We list 69 studies as excluded. In most of these there was no difference between treatment conditions in the use of pharmacotherapy, and the trial tested different types or amounts of adjunct behavioural support. These trials will contribute to a separate review (Stead 2012). A small number of studies did not report six month or longer follow-up. Reasons for exclusion can be found in the Characteristics of excluded studies table.

Risk of bias in included studies

Figure 1 presents review authors' judgements about each risk of bias item as percentages across all included studies. We did not judge any studies to be at risk of 'other' bias.

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

All studies reported that treatment allocation was random, with more than half explicitly describing an adequate method of generating the randomization schedule. Twenty-one (50%) reported a procedure for allocation concealment that we judged to be at a low risk of bias. One study (Wilson 1988) that used cluster randomisation by practice was judged to be at high risk of bias: participants were recruited by receptionists who could not be blind to practice condition, and there were baseline differences in consent rate and in motivation to quit between conditions. One study that recruited cancer patients with either smoking, alcohol or depression problems had more smokers in the intervention group suggesting possible recruitment bias (Duffy 2006).The other 20 trial reports gave too little information about allocation procedures to be certain that the risk of bias was low, and were hence judged to be at unclear risk of bias in this domain.

Blinding

We did not formally evaluate blinding of participants, providers or other personnel. It was almost always unclear whether or not participants would have known that they were in a control condition, but most controls did include advice and support for smoking cessation. Providers could not have been blind to treatment condition. Self-reported smoking status was biochemically validated at longest follow-up in 24 studies, with nine of these measuring cotinine and the remainder carbon monoxide (CO). Four studies either did not collect samples at final follow-up (Sadr Azodi 2009) or did not obtain samples from enough participants and did not report validated quit rates (Reid 2003; Katz 2004; Villebro 2008). Eight studies did not attempt any type of validation (Ockene 1991; Schauffler 2001; Emmons 2005; Otero 2006; Velicer 2006; Hollis 2007; Thomsen 2010; Brandstein 2011).

Incomplete outcome data

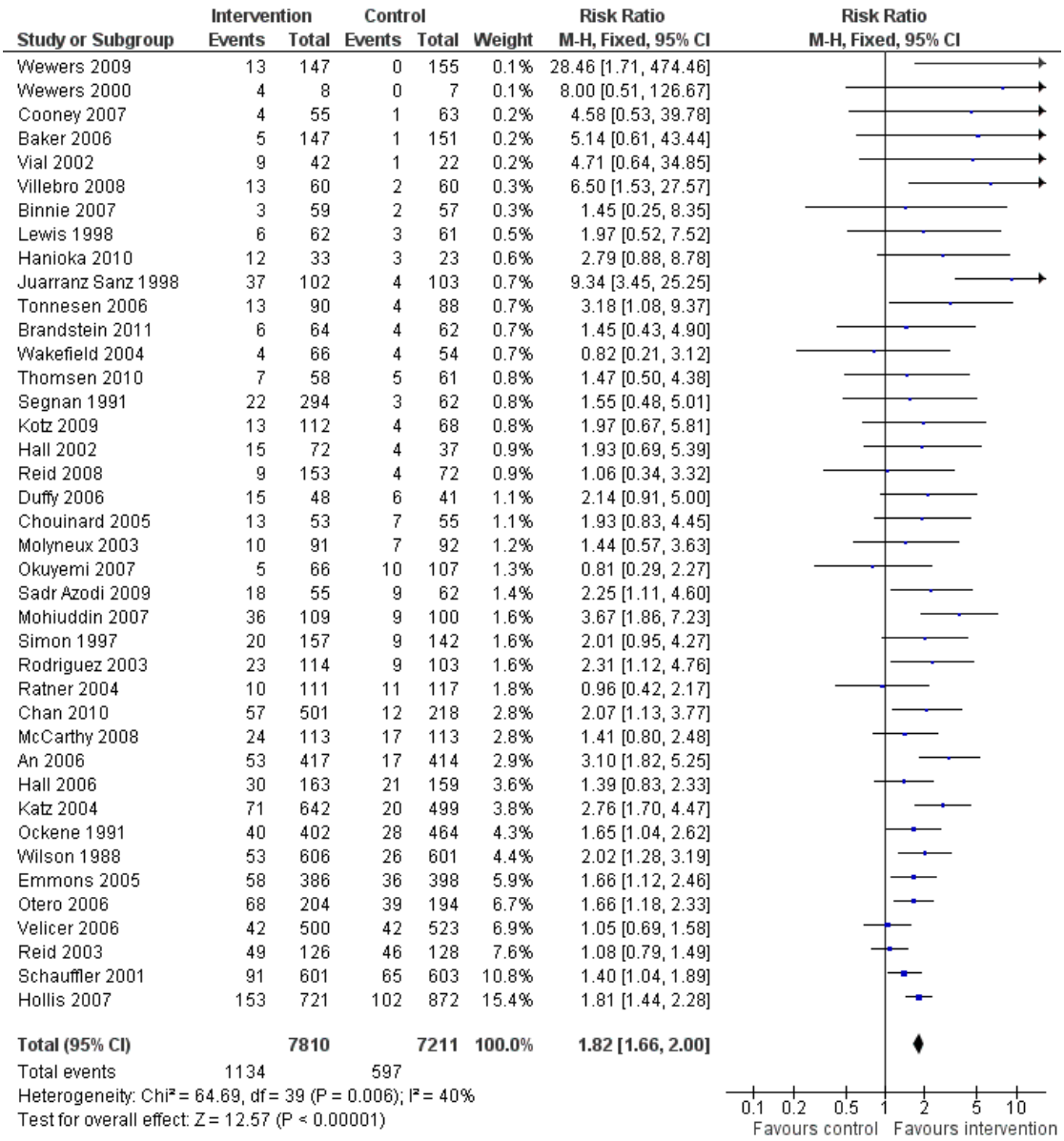
We classified one study at high risk of attrition bias because a number of control participants declined consent once told their treatment group (Hanioka 2010). In other studies, later dropouts were counted as continuing smokers, and all other trials were classified as low risk of bias due to loss to follow-up. Most trials lost less than 20% of each condition. There were a small number of trials in which the proportion lost to follow-up was over 20% and also differed between groups. Of the trials at potential risk of bias, Binnie 2007 and Villebro 2008 had high and differential losses, but since both were small trials any effect on the meta-analysis of different assumptions would be small. Hall 2006 and Hollis 2007 both had relatively high losses but both reported that different assumptions about the smoking status of those lost to follow-up would not be likely to alter their relative effects.

Effects of interventions

See: **Summary of findings for the main comparison** Combined pharmacotherapy and behavioural interventions for smoking cessation

A pooled estimate combining all 41 included studies using a Mantel-Haenszel fixed-effect model had a very high level of heterogeneity (I^2 = 78%, *data not shown*). This heterogeneity was attributable to the Lung Health Study which showed a very strong intervention effect (relative risk [RR] 3.88, 95% confidence interval [CI] 3.35 to 4.50). This study had a particularly intensive intervention; the behavioural component was a group-based 12 session course, and nicotine gum was available without charge for six months. Removing this study from the meta-analysis reduced heterogeneity (I^2 = 41%), and a benefit of intervention was still detected (RR 1.82, 95% CI 1.66 to 2.00, Figure 2, Analysis 1.1, Summary of findings for the main comparison). Only three trials (Wakefield 2004; Ratner 2004; Okuyemi 2007) had lower quit rates in the intervention than the control group and all had wide confidence intervals.

Figure 2. Combined intervention versus control. Cessation at longest follow-up.



There was some evidence of asymmetry in a funnel plot; there was an excess of small trials detecting larger effects, suggesting the possibility of publication or other bias. In a sensitivity analysis, removing smaller studies did not markedly decrease the pooled estimate.

Subgroup Analyses

Appendix 2 lists study characteristics used for subgroup analyses for each included study. All the subgroup analyses reported below exclude the Lung Health Study.

Effect of setting

The pooled estimate for trials that recruited participants in healthcare settings (RR 2.06, 95% CI 1.81 to 2.34, 31 trials, 9396 participants) was higher than that for trials that recruited volunteers in other settings (RR 1.53, 95% CI 1.33 to 1.76, 8 trials, 4906 participants) (Analysis 2.1). There were more small trials with large and significant effects in the healthcare subgroup, and a number of these had notably low quit rates in the control arms.

Effect of selection by motivation to quit

There was little evidence that the relative effect of the intervention differed according to whether participants were prepared to make a quit attempt or not (Analysis 3.1). The subgroup of participants selected for motivation had a slightly larger estimated effect (RR 1.83, 95% CI 1.60 to 2.10, 18 trials, 5903 participants) than the 'Not selected' subgroup (RR 1.58, 95% CI 1.37 to 1.83, 12 trials, 7474 participants) but confidence intervals overlapped. As would be expected, the typical control group quit rate was higher in trials where participants were more motivated than in trials in unselected participants. In the group of 10 trials that did not explicitly select for motivation, but where unmotivated participants seemed unlikely to be recruited, the effect size was larger (RR 2.92, 95% CI 2.18 to 3.91) and there was considerable heterogeneity (I^2 = 61%), for which there was no obvious explanation.

Effect of provider

The behavioural intervention was provided by specialists in cessation counselling in 28 of the trials. In eight trials, the support/counselling was given by a non specialist healthcare professional involved in usual care. In a further two trials behavioural support was provided by a peer counsellor, one of which was a very small pilot (Wewers 2000). One trial used trained lay advisers (Wewers 2009). One trial (Velicer 2006) had no person-to-person contact and behavioural support was provided by an 'expert system' generating individualised written materials and prerecorded telephone messages. The pooled estimate in the specialist care subgroup was smaller (RR 1.73, 95% CI 1.55 to 1.93, I^2 = 25%, 28 trials, 8733 participants) than the pooled estimate when counselling was linked to usual care (RR 2.41, 95% CI 1.91 to 3.02, I^2 = 39%, 8 trials, 4164 participants) (Analysis 4.1). Since this was an unexpected result we did an exploratory meta-regression controlling for type of provider, take-up of treatment and duration of contact; all were effect modifiers. Inspection of trial characteristics and sensitivity analyses suggested that two trials with low take-up of an intensive intervention from specialist providers (Schauffler 2001; Reid 2003) were reducing the effect size in the specialist subgroup. Analysis 8.1 shows that trials using specialist support where take-up of treatment was high had a higher effect estimate (RR 2.01, 95% CI 1.75 to 2.32). Also, one trial in the usual care provider group (Juarranz Sanz 1998) had the second largest effect of any trial in the review. Removing this study reduced the estimated RR in the usual care subgroup from 2.41 to 2.11 (95% CI 1.67 to 2.68). After excluding these three studies from the meta-regression there was no longer evidence of any effect modification by provider type, level of treatment take-up or duration.

Effect of intensity

We categorised trials by intended number of sessions and planned total duration of contact. Not all interventions prescribed a fixed number or standardised length of sessions, and not all participants received all planned contacts. Unsurprisingly there was some correlation between number of sessions and duration of contact; for example all interventions intended to provide at least 300 minutes of contact had at least four sessions scheduled. Where there was personal contact, there was only weak evidence that studies offering more sessions had larger effects (Analysis 5.1); the subgroup of trials offering eight or more sessions had the largest estimate (RR 2.09, 95% CI 1.57 to 2.79, 10 trials, 1474 participants) but CIs overlapped. One to three and four to eight session categories had almost the same effects. There was no clear evidence that increasing the duration of personal contact increased the effect either (Analysis 6.1). Estimates for each subgroup overlapped. Although there was heterogeneity in the 31 to 90 minute category, this was not attributable to any study with an unusually large effect. In an exploratory meta-regression neither number or duration alone or in combination were effect modifiers, nor was take-up in combination with these.

Effect of differences in treatment take-up

Only three trials were classified as 'low take-up of treatment' (Katz 2004; Reid 2003; Schauffler 2001), and in these the estimated effect was smaller, whilst there was little difference between the 12 that were moderate and 23 that were high (Analysis 7.1). When we restricted the studies in the number and duration subgroups

to those where take-up of treatment was 'high', the difference between subgroups increased with larger effects associated with greater intensity (Analysis 9.1; Analysis 10.1), but this was in part because, counterintuitively, estimates of effect became smaller in lower intensity conditions when low take-up trials were removed, as well as increasing in the higher intensity subgroups once only high take-up trials were included.

Direct tests of intensity of support

Two trials compared multiple intensities of support. In both cases the more intensive condition was compared to the control in the primary analysis. Hollis 2007 offered up to four additional telephone calls in the intensive counselling condition compared to a 30 to 40 minute motivational interview and a single follow-up call in the moderate condition but this did not significantly increase quit rates. Higher intensity participants had on average only about 14 minutes more contact. Otero 2006 randomized to one, two, three or four weekly hour-long sessions but pooled reported outcomes for one to two and three to four sessions. Direct comparisons of different intensities of behavioural therapy as adjuncts to pharmacotherapy are covered in a separate review (Stead 2012).

DISCUSSION

Behavioural support and certain pharmacotherapies increase the chance of successful cessation for people trying to quit. These effects have been confirmed by reviews of trials that synthesise the results of trials of both modalities of treatment. Nicotine replacement therapy (Stead 2008), bupropion and nortriptyline (Hughes 2007) and varenicline (Cahill 2012) increase quit rates. Group therapy (Stead 2005), individual counselling (Lancaster 2005b) and telephone counselling (Stead 2006) have all been shown to be successful ways of delivering behavioural support for cessation with some support for individually tailored written self-help materials (Lancaster 2005a). The effects of the two treatment modalities are largely assumed to be independent, although behavioural support may influence correct use of medication. Although guidelines support combining approaches where possible, the size of effect that might be expected when both therapies are combined has not been clear.

Summary of main results

In this review of 41 trials evaluating interventions that combine pharmacotherapy with behavioural support, we found, unsurprisingly, that the combination improves quit rates compared to no treatment or a minimum intervention (see Summary of findings for the main comparison). This finding is in accord with the evidence that each type of intervention is effective when evaluated independently. A strength of the evidence from these trials is that the results are largely consistent, with little evidence of clinically important heterogeneity even though they use a wide range of approaches in many different populations and settings.

One trial demonstrated a large benefit of a multimodal therapy. The Lung Health Study, conducted in the early 1990s, achieved a cessation rate of 35% at one year in the intervention group, compared with 9% for the control. The investigators also reported sustained benefits after five years, and demonstrated reduced mortality in the intervention group. As noted above, this was a particularly intensive intervention. Participants were offered maintenance sessions, and repeat treatment was available for those failing to quit. In addition, all participants had mild airway impairment, and intervention group participants were further randomized to use a bronchodilator or placebo inhaler. This component might have increased motivation for quitting, and the relatively high rates of cessation in the control group would support this.

The pooled estimate for the remaining 40 trials (RR 1.82, 95% CI 1.66 to 2.00) suggests that a combined intervention might typically increase cessation success by 70 to 100%. Most of the trials in this review offered one or more types of NRT, or bupropion. Based on estimates from Cochrane reviews of the effects for NRT alone (pooled estimate from 111 trials RR 1.58, 95% CI 1.50 to 1.66, Stead 2008) and bupropion (pooled estimate from 36 trials, RR 1.69, 95% CI 1.53 to 1.85, Hughes 2007), the additional benefit from the behavioural component might seem small. However it may be misleading to directly compare these estimates, and we did not attempt any formal statistical comparison.

There are important differences between the trials included in this review and typical pharmacotherapy studies that should be noted. Pharmacotherapy trials included in meta-analyses typically have a placebo control, but the control group also receives identical behavioural support to the active therapy group. The intensity may vary from brief advice on correct use of pharmacotherapy and provision of self-help materials, to multiple counselling sessions. The trial protocol may call for frequent contact with a clinical research centre, even if counselling contact is limited. Participants may have high expectations for the effect of treatment, but also the knowledge that they could be receiving placebo. In contrast, in the studies included in this review the control groups had limited support, but this typically involved advice that could be classified as a cessation intervention in other contexts. Additionally, it was generally unclear whether controls would have known the components of the active intervention and we did not attempt to assess the risk of bias from lack of blinding. In almost all the trials, intervention group participants would have known they were receiving active medication, but without the connotations of receiving a 'new' drug. Apart from the small number of included trials that were placebo-controlled factorial studies of medication and behavioural components (Hall 2006; Tonnesen 2006; McCarthy 2008), trials in this review had pragmatic designs and the intervention typically involved an offer of treatment. Actual use of medication and take-up of a full programme of behavioural support

was not uniform across trials.

We found some evidence in subgroup analyses that studies offering more intensive support in which there was high participation in treatment had larger effect sizes. There is still uncertainty about the strength of the dose-response relationship for intensity of person-to-person contact. Almost all of the interventions in this review involved multiple sessions, with some studies providing or offering more than eight sessions and as much as eight hours of contact, although the typical intensity was much lower. We did not find clear evidence from indirect comparisons that increasing contact increased quit success but there was a trend in that direction. Stronger evidence for a trend might have been obscured by the multiple differences between trials. We used meta-regression for exploratory analyses of some potential effect modifiers but the relatively small number of trials and large number of variables reduces the power of this approach. We might not have been able to identify or quantify possible moderators. For example, more intensive support might have been tested in 'hard to treat' populations but it is not clear how this might be characterised. It seems unlikely that the number of supportive contacts and their length would have absolutely no effect on outcome, but our findings suggest that the added benefit from offering more intensive support may be small. One possible explanation is that the use of pharmacotherapy attenuates the importance of the behavioural support. Healthcare providers have an important role in convincing smokers of the importance of attempting to quit and making pharmacotherapy and behavioural support available. We did not find evidence from indirect comparison that counselling by trained specialists was critical for success; in fact the estimated treatment effect was higher in the smaller group of trials where the behavioural support was provided by non specialists, although we do not think great importance should be attached to this finding.

Overall completeness and applicability of evidence

These trials have been undertaken in a very wide range of settings using different providers of care and amongst different populations. The populations include people with mental illness and smoking related diseases. The relative homogeneity of their results therefore supports the general applicability of the evidence. Although most of the trials provided one or more types of NRT, and a small number offered bupropion, there is no reason to suppose that the results would not apply to interventions that offered varenicline.

Using a pharmacotherapy and accessing behavioural support will increase the chance of giving up smoking, but at the moment people who smoke are unlikely to use this combination when making a quit attempt. A US survey in 2003 found that only 5.9% of those making a quit attempt in the previous year had used combined behavioural and pharmacologic treatment (Shiffman 2008). An English study run from 2006 to 2008 found that 5% of people attempting to quit smoking had used both a pharmacotherapy and counselling provided by the UK Stop Smoking Services (Kotz 2009b).

Quality of the evidence

The majority of studies were judged to be at low or unclear risk of bias, and only three of the included studies were judged to be at high risk of bias in one or more domains. The results of the meta-analysis were not sensitive to the exclusion of any single trial. Excluding studies that did not use biochemical validation did not reduce the effect size. The largest study, Hollis 2007, was atypical in that all contact was telephone-based, it also had a potential methodological weakness due to losses to follow-up and lack of biochemical validation, although we did not judge these to put it at a high risk of bias. Excluding this study made little difference to the estimates.

Potential biases in the review process

We used the Cochrane Tobacco Addiction Specialised Register to identify studies. The Register includes reports of trials identified from the major bibliographic databases. There is no straightforward term for the type of intervention we were interested in, but we screened any trial report that mentioned a pharmacotherapy. It is possible that the Register does not include all relevant trial reports or that we failed to identify some. Our methods for data extraction and analysis are those used for other Cochrane reviews. The practice of imputing missing data as smoking is standard practice for primary and secondary research in smoking cessation and has the advantage that absolute cessation rates are not inflated by ignoring loss to follow-up. Bias in the relative effect will only be introduced if misclassification differs for people who are lost from the intervention condition compared to the control. If proportionately more of those who are lost in the control group are assumed to be smokers but have in fact quit then the treatment effect would be overestimated.

Agreements and disagreements with other studies or reviews

The results of this review are broadly in agreement with other reviews and guidelines (Hughes 1995; Reus 2008). US Guidelines (Fiore 2008) endorse a dose-response relationship for total amount of contact time (up to 300 minutes) and number of sessions, as well as session length. Their meta-analyses suggest clear trends although there were not necessarily significant differences between adjacent categories. There were however clear differences between for example 4 to 30 minutes of contact time (odds ratio (OR) 1.9, 95% CI 1.5 to 2.3) and 91 to 300 minutes (OR 3.2, 95% CI 2.3 to 4.6) (Fiore 2008 table 6.9) and between two to three

treatment sessions (OR 1.4, 95% CI 1.1 to 1.7) and over eight sessions (OR 2.3, 95% CI 2.1 to 3.0) (Fiore 2008 table 6.10). Our estimates comparing subgroups of trials classified by within trial differences in intensity show less clear evidence of a dose-response effect, although they do not exclude there being one.

AUTHORS' CONCLUSIONS

Implications for practice

Interventions that combine pharmacotherapy and behavioural support increase smoking cessation success in a wide range of settings and populations, compared to a minimal intervention or usual care. This suggests that clinicians should encourage smokers to use both types of aid. Offering more intensive behavioural support was not clearly shown to be associated with larger treatment effects; this may be because intensive interventions are more difficult to deliver consistently to participants.

Implications for research

It is unlikely that further trials will alter the main findings of this review, although they may contribute to further understanding about the effects of treatment in particular settings or in populations of smokers.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

An 2006

Methods	Setting: 5 Veterans Administration medical centres, USA Recruitment: by mail, prepared to quit in next 30 days
Participants	821 smokers interested in quitting (excludes 16 deaths, 1 withdrawal); 91% M, av. age 57, av. cpd 26. 26% had > 7d abstinence in previous year, 44% ever use of bupropion, 82% ever use NRT Provider: Specialist, telephone counsellors
Interventions	1. Mailed S-H and standard care; opportunity for intervention during routine cpd and referral to individual or group cessation programmes. NRT & bupropion avail on formulary 2. As 1, plus proactive TC, modified California helpline protocol, 7 calls over 2m, relapse sensitive schedule additional calls possible, multiple quit attempts. NRT & bupropion available, could be mailed directly after screening & primary provider approval for bupropion
Outcomes	Abstinence at 12m (sustained from 6m, 7-day PP also reported) Validation: none
Notes	Pharmacotherapy was available to control group, but intervention substantially increased use; 86% vs 30% reported use at 3m. Treatment effect greater for sustained quitting than PP

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 deaths (10 I; 6 C) & 1 withdrawal excluded from denominators. Other losses assumed smoking

Baker 2006

Methods	Setting: research clinics, Sydney & Newcastle, Australia Recruitment: referrals, mainly from community health agencies, interested in quitting

Baker 2006 (*Continued*)

Participants	298 smokers with non acute psychotic disorder; 48% F, av. age 37, av. cpd 30, 57% schizophrenia or schizo-affective disorder Provider: Trained cessation therapist
Interventions	1. Treatment as usual: Assessment interview & S-H books for patient & supporter 2. As 1 plus 8 x1-hour sessions (weekly x 6, 8 & 10wks), motivational interviewing & CBT & nicotine patch (21 mg for 8wks incl tapering)
Outcomes	Continuous abstinence at 12m (PP also reported) Validation: CO < 10 ppm
Notes	One participant claiming abstinence at 12m had CO >10 ppm attributable to continued cannabis use and was classified as abstinent. Unclear if this person in the continuously abstinent or PP category

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Participants were informed that they would be randomly assigned to one of two conditions at the end of the initial assessment interview, which was achieved simply by asking them to draw a sealed envelope from a set of envelopes in which there was initially an equal distribution of treatment/control allocations at each site.'
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes were opaque and if participants kept to allocated condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	17% lost to follow-up at 12m, no significant difference between groups

Binnie 2007

Methods	Setting: Periodontology clinic in dental hospital, Scotland Recruitment: Patients attending for treatment invited to enrol, not selected for motivation
Participants	116 smokers (excludes 1 death, 1 withdrawal), 13% pre-contemplators, 45% contemplators at baseline; 71% F, av. age ~42, median 20 cpd Provider: Trained dental hygienist
Interventions	1. Usual care 2. 5As based intervention from hygienist at visits for periodontal treatment. Median visits 6-7. Duration not specified. Free NRT (patch or gum) available, number using not specified

Binnie 2007 (*Continued*)

Outcomes	Sustained abstinence at 12 months (abstinent at 3, 6, 12m) Validation: Saliva cotinine < 20 ng/ml, CO at 3m & 6m.
Notes	Intervention did not define number and duration of sessions; classified as 4-8 sessions, 31-90 minutes. Number of people who received NRT not specified. Classifed as Moderate for treatment take-up; subgroup results not sensitive to recoding as High

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized using minimisation method
Allocation concealment (selection bias)	Low risk	'The randomisation process was set up by the project statistician and was implemented independently from the recruitment process.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 death, 1 withdrawal before treatment excluded from C denominator. Lost to follow-up: 26/59 (44%) I, 34/57 (60%) C. Losses included as smokers; exclusion would reduce point estimate, but CIs wide

Brandstein 2011

Methods	Setting: Single hospital, California, USA Recruitment: Inpatients who had quit smoking during hospitalisation (not explicitly selected for motivation for remain abstinent)
Participants	126 smokers of >10 cpd prior to hospitalizations Provider: Specialist, telephone counsellors (Bedside counselling from Respiratory Therapist for all participants)
Interventions	1. Enhanced Intervention: brief bedside counselling, 21 mg nicotine patch for 8 weeks (including tapering period) provided at discharge. Proactive telephone counselling from California Smokers' Helpline; initial call 30 min, up to x5 10-15 min contacts. Final contact ~ 2m post discharge 2. Usual care, same bedside counselling as 1
Outcomes	Self reported prolonged (180 day) abstinence at 6m Validation: None; all participants asked to provide a saliva sample 'as a way of enhancing self-report accuracy'
Notes	

Brandstein 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'The PI used computer generated randomization lists so that randomization was stratified by the RT [respiratory therapist] and subjects were allocated to treatment condition using blocks of four.'
Allocation concealment (selection bias)	Low risk	'Randomization took place after the RT collected baseline data, provided bedside counselling, and obtained consent; thus RTs were blind to group assignment during those procedures.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	37.5% I, 43.6% C lost at 6m, similar between groups. Counted as smokers in MA

Chan 2010

Methods	Setting: Clinics, Hong Kong Recruitment: Community volunteers & clinic patients, motivated to quit
Participants	719 male smokers with erectile dysfunction, av. age 49, av. cpd 20 Provider: Specialist counsellor
Interventions	1, Counselling at 0, 1, 4wks, ~15 min, NRT (patch or gum) for 2 wks. +/- 5 min adherence intervention (pooled for cessation outcomes) 2. Brief advice, 10 min, S-H materials
Outcomes	Abstinence at 6m (PP) Validation: cotinine 115 ng/mL, CO > 8ppm
Notes	Study stopped early before reaching target, when abstinence differences significant Not included in subgroup by setting as recruitment included both community volunteers and clinic patients

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned in 2 stages, no details reported
Allocation concealment (selection bias)	Unclear risk	No details given, 'single blind'

Incomplete outcome data (attrition bias) All outcomes	Low risk	24-30% lost to follow-up

Chouinard 2005

Methods	Setting: Canada Recruitment: Inpatients with cardiovascular disease (Myocardial Infarction, angina, Congestive Heart Failure) or Peripheral Vascular Disease, unselected by motivation
Participants	168 past-month smokers; 27% M, av.age 56, 60% in preparation or action SoC Provider: Research nurse (specialist)
Interventions	1. Counselling: 1 face to face session, 10-60 mins, av. 40 mins, based on Transtheoretical Model, included component to enhance social support from a significant family member, 6 telephone calls over 2m post-discharge. Advised to use pharmacotherapy, mainly NRT 2. In hospital counselling only (not used in analysis) 3. Usual care cessation advice (6% used pharmacotherapy)
Outcomes	Abstinence at 6m (sustained at 2m & 6m) Validation: Urine cotinine or CO
Notes	2 compared to 3 in main analysis. Sustained abstinence rate identical for 2 and 3. Classified as Moderate take-up; 39% used pharmacotherapy but 75% received 6 phone calls; subgroup results not sensitive to recoding as High

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Cluster randomized in groups of 3-6 'to prevent contamination between groups', method not described
Allocation concealment (selection bias)	Low risk	'Individuals not familiar with the study were in charge of the randomization procedure which included inserting the information into envelopes that were sealed and would be opened by the investigator only at the time of recruitment.'
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 death in intervention group and 3 ineligible for follow-up excluded from denominators in analysis

Cooney 2007

Methods	Setting: 2 Veterans Administration outpatient substance abuse programmes, USA Recruitment: Patients in treatment programme, interested in smoking cessation & alcohol treatment
Participants	118 smokers, ≥ 10 cpd, (excludes 15 early dropouts); 89% M, av. age 47, av. cpd 25 Provider: cessation specialist
Interventions	1. Brief advice; 5As model, 15 min session & 5 min follow-up, no offer of NRT 2. Intensive intervention; 3x 60 min individual sessions, free NRT (21 mg patch for up to 8 wks including tapering) Both delivered concurrently with 3 week intensive substance abuse programme (15 meetings)
Outcomes	Abstinence at 6 months (PP) Validation: CO < 10 ppm
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	9 I & 6 C pre-therapy dropouts excluded. Lost to follow-up: 9/55 (16%) I, 14/63 (22%) C. Losses included as smokers; exclusion would reduce point estimate, but CIs wide

Duffy 2006

Methods	Setting: ENT clinics at 4 hospitals, USA Recruitment: Patients with head & neck cancer who screened positive for smoking, alcohol problem or depression, not selected for motivation
Participants	89 current smokers used in MA, out of 184 trial participants who also included 26 quit within last month and 21 within last 6m. Demographics are for all participants; 16% F, av.age 57 Provider: Trained nurse specialist
Interventions	1. Telephone counselling and offer of NRT or bupropion or combination; 9-11 CBT based calls, linked to use of CBT workbook. Smokers with problem drinking or depression received counselling for these too. 2. Enhanced usual care with assessment and referral

Duffy 2006 (*Continued*)

Outcomes	Abstinence at 6m (self-reported sustained) Validation: none
Notes	Total contact time not stated but estimated as 91-300 mins based on sessions lasting 10 to 30 mins. Number of current smokers who were prescribed medication unclear, but likely to have been at least 30%. Classified as Moderate take-up; subgroup results not sensitive to recoding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	High risk	No details given. Smokers were a higher proportion of the intervention than control groups, and a higher proportion of those randomized than those who refused, raising possibility of selection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	22 in total (including non smokers) lost to follow-up, evenly distributed. Losses included as smokers

Emmons 2005

Methods	Setting: Childhood Cancer Survivors Study cohort, USA Recruitment: Smokers contacted via telephone to assess eligibility and enrol, not selected for motivation
Participants	794 smokers (excludes 2 deaths in control); 47% F, av. age 31, av. cpd 12, 18% precontemplators, 39% contemplators Provider: Peer, trained cancer survivor
Interventions	1. S-H control. Mailed manual (Clearing the Air) & letter from study physician 2. Peer counselling. Up to 6 calls in 7m period, by trained cancer survivor. Motivational, tailored to SoC. Free NRT available. Individually tailored materials before 1st call & other materials during intervention
Outcomes	Abstinence at 12m (7-day PP) Validation: none (warning that samples might be requested)
Notes	No data on average number of calls. Longer term follow-up, assessed at 2-4 years, reported in Emmons 2009. Not used in MA - sustained rates not reported. PP rates increased from 12m and remained higher in counselling group (20.6% vs 17.6%, P<.0003) 29% of intervention group requested and used NRT as part of intervention. At 8m 33% I and 8% C reported use of NRT in period

Emmons 2005 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up at 12m; 24% I, 19% C. All included as smokers in MA

Hall 2002

Methods	Setting: USA Recruitment: Community volunteers motivated to quit. Exclusion criteria included current MDD
Participants	220 smokers of ≥ 10 cpd (109 in relevant arms); 40-47% female, av. age 37-43, av. cpd 20-23; 33% had history of MDD Provider: masters level counsellors
Interventions	3 x 2 factorial design Pharmacotherapies: bupropion (300 mg/d for 12 wks), nortriptyline (up to 100 mg/d titrated to serum 50-150 ng/mL for 12 wks), or placebo 1. Medical Management (MM) control: physician advice, S-H, 10-20 min 1st visit, 5 min at 2, 6, 11wks) 2. Psychological Intervention (PI) as MM plus 5x 90 min group sessions at 4, 5, 5, 7, 11wks). Group size 3-11
Outcomes	PP at 1 yr (47wks post-quit date). Prolonged abstinence not reported by cell. Validation: CO ≤ 10 ppm, urine cotinine ≤ 60 ng/mL
Notes	Bupropion or nortriptyline with PI vs placebo with MM in main comparison

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, method not specified,
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	19% lost to follow-up at 1y, no difference by group, included in ITT analysis

Hall 2006

Methods	Setting: Four mental health O/P clinics, CA, USA Recruitment: Provider referral, invitation letters, fliers. Motivation to quit not required
Participants	322 psychiatric outpatients, daily smokers, treated for depression (unipolar); 70% F, av. age 42, av. cpd 15. Provider: cessation specialist
Interventions	1. Control: Referrals to SC programmes + SC guide 2. Intervention*:* (i) Counsellor-led 15-min computerized assessments and feedback at 3, 6, and 12m, using SoC framework (ii) For those in contemplation/preparation, offered SC programme of counselling (6 x 30 mins over 8 wks), + NRT, or bupropion (2nd line). SC programme made available to any Int pt requesting it, regardless of stage
Outcomes	7-day PP at 18m (Also reported at 3, 6, 12m) Validation: Expired CO $\leq$ 10 ppm
Notes	34% (53) entered cessation & had pharmacotherapy. Classified as Moderate take-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomized; "allocation list was computer-generated by statistical staff"
Allocation concealment (selection bias)	Low risk	"after completing the baseline assessment, interviewers randomly assigned participants to conditions from within stratified blocks, according to the number of cigarettes smoked per day and the participants' stage of change". Possibly not concealed, but risk of bias assessed as low
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses reported for all time points: 6m: I 23%, C 25%; 12m: I 31%, C 30%; 18m: I 25%, C 31%. Authors calculated propensity scores to estimate the effects of missing data on outcomes and there was no evidence that missing data caused bias. Main analyses in report used completers, losses treated as smoking in this MA

Hanioka 2010

Methods	Setting: 19 dental clinics, Japan Recruitment: Dental patients willing to stop smoking within 1 month
Participants	56 adult smokers attending dental clinics in Japan, 29% F, av, age ~48, av. cpd ~25 (excludes 14 I & 21 C who declined participation after randomization but before consent) Providers: Dentists & dental hygienists
Interventions	1. Free nicotine patches for 6 weeks, information about nicotine gum. 5 counselling visits at baseline, 2, 4, 8, & 12wks 2. No intervention
Outcomes	Abstinence at 12 m (3, 6, 12m continuous abstinence) Validation: Saliva cotinine < 20 ng/mL
Notes	Total duration of contact averaged 116 mins (87-146)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	Assignment cards in envelopes provided *a priori* to clinics; allocated as subjects agreed to participate but before consent
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants were given details of their treatment after allocation, and more control than intervention declined after allocation and before consent. 15 later dropouts included as smokers

Hollis 2007

Methods	Setting: Community-based telephone quitline programme, Oregon USA Recruitment: Callers invited to participate; assumed to be fully or partly motivated to quit
Participants	4614 smokers; 40% M, av. age 41, av. cpd 21. Provider: cessation specialist, telephone based
Interventions	Factorial design; 3 levels of counselling, +/- offer of up to 8 weeks of free nicotine patches. No face-to-face contact. 1. Control (Brief): 15 min call + referral material + tailored S-H materials. [Mean 1 session, 20 min contact time] 2. Moderate: 40 min call + brief call to encourage use of community services, tailored S-H materials. [Mean 2.0 sessions, 47 min contact]

Hollis 2007 (*Continued*)

	3. Intensive: As 2, plus offer of ≤ 4 additional calls. [Mean 2.9 sessions, 60 min contact] Each call incorporated MI techniques, stage assessment, RP as needed
Outcomes	Abstinence at 12m (30 day PP). Also assessed at 6m Validation: none
Notes	Of those offered NRT, 80% accepted the first 5-week regimen and 25%/28% requested a second 3-week refill and there were no differences across the three levels of behavioural intensity. 3 with NRT vs 1 without NRT used in main analysis, but little difference between moderate and intensive outcomes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a computer algorithm randomly assigned participants"
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	35% control, 30% intervention lost at 12 months, included in analyses as smokers. Authors report sensitivity analyses using imputation for missing data. Some evidence that effect of NRT, but not behavioural support, might be over estimated using missing = smoking assumption for all losses, but less evident when only 'active refusers' assumed to be smoking

Juarranz Sanz 1998

Methods	Setting: Primary care clinic, Spain Recruitment: Patients of clinic proactively recruited by phone, unclear whether motivation to quit required
Participants	205 smokers; 48% M, av. age 38, av. cpd 23 Provider: primary care provider
Interventions	1. Initial counselling 35 min, phone call 2d post quit date, visits at 2wks,1m, 3m, 6m. Nicotine patch for 8-12 wks, dose and duration tailored. 2. No intervention
Outcomes	Abstinence at 6m, self-reported prolonged Validation: CO ≤ 8 ppm
Notes	No further details could be obtained about the intervention provider

Juarranz Sanz 1998 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random, but possibly alternated
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 lost to follow-up, included as smokers

Katz 2004

Methods	Setting: 8 primary care clinics, USA Recruitment: smokers attending for non-emergency visits
Participants	1141 smokers (>1 cpd) 56% F, age 43/40, median cpd 20/15 Providers: Usual care clinicians & trained nurses
Interventions	1. Intervention based on AHRQ guidelines. Training in brief advice for intake clinicians, vital signs stamp. Patients willing to set TQD offered proactive telephone counselling (2 calls, pre & post TQD) by trained nurse, smokers of over 10 cpd offered NRT 2. Control. Information about guidelines, no specific advice on counselling
Outcomes	Sustained abstinence at 2m & 6m Validation: saliva cotinine. Poor response, similar return & misreport rates. Validated sustained rates not reported
Notes	Study also included a baseline assessment. Only data from smokers recruited during implementation period used here. Compliance: 183 intervention patients were willing to set a quit date so eligible for counselling and NRT; 148/642 (23%) had some counselling, 164/642 (25.5%) had NRT; 144 received both components. 29% of all intervention participant reported NRT use during follow-up versus 11% in control

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Cluster randomized by clinic, method not described
Allocation concealment (selection bias)	Low risk	Participants enrolled by completing an exit interview with researcher, not determined by clinic

Incomplete outcome data (attrition bias) All outcomes	Low risk	4-8% lost to follow-up

Kotz 2009

Methods	Setting: University research unit, Netherlands Recruitment: Volunteers from community & health centres, interested in quitting & reporting respiratory symptoms
Participants	296 people with at least 10 pack-yrs of smoking, and evidence of mild to moderate airflow limitation at spirometry; 39% F, av. age 54, av. cpd 23 Provider: respiratory nurse
Interventions	1. High intensity counselling (4 weekly 40 min individual sessions) & nortriptyline for 7 weeks. No information given about spirometry results. 2. As 1 including confrontational counselling about spirometry findings (not used in this review) 3. Referred to GP for low intensity smoking cessation treatment, no information about spirometry results
Outcomes	Prolonged abstinence at 52 weeks (weeks 5-52) Validation: urine cotinine < 50 ng/mL at 5, 26 & 52 weeks
Notes	1 vs 3 compared in analysis. Test of confrontational counselling not covered in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using computerised system, initially 1:1:1 ratio, then altered to 3:3:1 with block size 7
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	17% lost in 1 vs 22% in 3, included as smokers

Lewis 1998

Methods	Setting: hospital, USA Recruitment: inpatients (excluding some cardiac conditions) interested in quitting
Participants	185 hospitalised adults; self-reported 'regular use' for at least one year. 44% F, av. age 43, av. cpd 24 Provider: research nurse

Lewis 1998 (*Continued*)

Interventions	1. Minimal care (MC): motivational message from physician to quit plus pamphlet 2. Counselling and nicotine patch (CAP). 3. Counselling and placebo patch (CPP). (not included in this review) In addition groups 2 & 3 received a motivational message & instructions on patch use from physician, 4 sessions of telephone counselling by nurse based on cognitive behavioural therapy and motivational interviewing
Outcomes	Abstinence at 6m (7 day PP) Validation: CO $\leq$ 10 ppm
Notes	2 compared to 1 in this review. No information about compliance with treatment except 'Patch compliance was not related to outcome among patients'. Classified as Moderate take-up but subgroup results not sensitive to recoding as High. Also contributes to reviews of NRT, nursing and hospital interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized: predetermined computer-generated code
Allocation concealment (selection bias)	Low risk	Study staff blind to active/placebo patch condition so assignment code likely to have been blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported. 10 self-reported quitters refused CO validation and counted as smokers

Lung Health Study

Methods	Setting: 10 study centres, USA Recruitment: Healthy smokers with mild airway obstruction, not required to be interested in quitting
Participants	5887 smokers; 37% F, av. age 48, av. cpd 31 Providers: specialist counsellors
Interventions	1. Advice from study physician with stress on high risk of COPD, 12 group sessions over 10 weeks, beginning on quit day, initially 4 sessions/week, 2 mg nicotine gum available for 6 months, maintenance and recycling sessions offered long term. Cessation intervention participants also randomized to bronchodilator or placebo arms, pooled here. 2. Usual Care, no intervention

Lung Health Study (*Continued*)

Outcomes	Abstinence at 1 year (PP) (also assessed annually for 5 years, data not used here) Validation: CO at each visit, cotinine at 1y
Notes	Numbers quit at 1y estimated from graph. At 5y sustained abstinence rates reported to be approximately 22% vs 5%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized, computer generated separately for each centre, blocks of random permutations of varied length (Reported in Connett 1993)
Allocation concealment (selection bias)	Low risk	Centralised verification of eligibility & allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	~95% follow-up at 1y. Non attenders counted as smokers

McCarthy 2008

Methods	Setting: clinic, USA Recruitment: community volunteers motivated to enrol in trial of cessation medication
Participants	463 smokers (226 in relevant arms); 50% female, av. age 36-41 across arms, av.cpd 22 Providers: trained college-aged or bachelor's level staff, supervised by experienced counsellor
Interventions	Factorial trial of bupropion or placebo pharmacotherapy and counselling versus support 1. Bupropion & counselling; 8 x 10 min sessions, 2 prequit, TQD, 5 over 4 wks, additional office visits without counselling 2. Bupropion & psychoeducation (not used in this review) 3. Placebo & counselling (not used in this review) 4. Placebo & psychoeducation about medication, support & encouragement. Same no. of office visits, 80 mins less contact time than 1
Outcomes	7 day PP abstinence at 12m Validation: CO ≤10 ppm
Notes	1 vs 4 used as a test of combined intervention. Others arms do not contribute to this review. Classified as 91-300 mins because of additional contact time during office visits. Also contributes to Cochrane reviews of antidepressants (Hughes 2007) (collapsing behavioural conditions) and individual behavioural counselling (Lancaster 2005b) (collapsing pharmacotherapy)

Risk of bias

McCarthy 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Random number table'
Allocation concealment (selection bias)	Low risk	'Staff who screened and enrolled participants were unaware of the experimental condition to be assigned'
Incomplete outcome data (attrition bias) All outcomes	Low risk	In relevant arms 24 (11%) failed to attend quit date visit and 62 (27%) lost to follow-up at 12m, no difference by condition, all included as smokers in ITT analysis

Mohiuddin 2007

Methods	Setting: Hospital, USA Recruitment: Inpatients with diagnosis of acute coronary syndrome (including MI) or decompensated CHF, admitted to critical care unit, invited to participate, not selected for motivation to quit, but high rate of refusal amongst eligible patients
Participants	209 smokers; 37% F, av. age 55, av. cpd I 26, C 22 (p=.03); no information about baseline motivation Providers: Physician and trained tobacco counsellor or nurse
Interventions	All participants received standardised 30 min in-hospital counselling & S-H materials 1. Intervention: Inpatient counselling. Individualised pharmacotherapy (NRT and/or bupropion). Weekly group meetings (60 min session for up to 3m) with trained tobacco counsellor (content: behavioural counselling, social support, relaxation training, risk factor management). 2. Control: inpatient counselling & S-H only.
Outcomes	Sustained abstinence at 24m (PP abstinence and 12m outcomes also reported) Validation: CO
Notes	Pharmacotherapy used by 75% in intervention (bupropion 7%; NRT 28%; combination 40%) compared to 17% control (bupropion 1%; NRT 5%; combination 11%)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"using simple randomization, without block assignment"
Allocation concealment (selection bias)	Unclear risk	No details given

Mohiuddin 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	<5% lost to follow-up, included as smokers. 3 deaths in I and 12 in C also retained in denominators

Molyneux 2003

Methods	Setting: hospital, UK Recruitment: hospital inpatients, invited to participate, not selected for motivation to quit, but 'expected to comply with protocol' and high rate of refusal amongst eligible patients
Participants	274 smokers (183 in relevant arms) admitted to medical and surgical wards, smoked in last 28 days; 60% M, av. age 60, median cpd 17, 81% had previous quit attempt; no information about baseline motivation Providers: research doctor or nurse trained in cessation counselling
Interventions	1. Usual Care, no smoking advice 2. Brief (20 min) bedside counselling + advice leaflet + advice on NRT 3. As 2 plus 6 week course of patient's choice of NRT product (patch, gum, inhalator, sublingual tablet nasal spray)
Outcomes	Continuous abstinence at 12m Validation: CO < 10 ppm at 3 & 12m
Notes	3 vs 1 as test of combined brief counselling and offer of pharmacotherapy. 96% in condition 3 accepted NRT, few other participants obtained NRT. Also contributes to Cochrane reviews of individual counselling (Lancaster 2005b) (2 vs 1) and interventions in hospitalised patients (Rigotti 2012).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'List generated for each centre allocating equally in random permuted blocks of nine.'
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	68 (37%) lost to follow-up included as smokers in analysis

Ockene 1991

Methods	Setting: US primary care residency programme (physicians in training) Recruitment: unselected patients in 5 primary care clinics
Participants	1286 smoking patients not selected for motivation to quit Providers: 196 primary care physicians in training
Interventions	1. Advice only 2. Patient-centred counselling, written materials, asked to schedule follow-up visit, follow-up letter (not used in this review) 3. Patient-centred counselling and offer of prescription for nicotine gum (Each group was further randomized to minimal (no calls) or intensive follow-up by telephone (3 calls over 6m) from a health educator (HE) but no main effects or interactions were noted and no results were presented at 12 months so this factor is not analysed here)
Outcomes	Sustained abstinence at 12m (reported in Ockene 1994) (6 & 12m). PP also reported Validation: none
Notes	Adjusted rates used in analysis. All physicians received training in minimal vs intensive interventions and delivered them according to random allocation of patient. 12m PP abstinence showed no effect of intervention. 69% of group 3 accepted prescription and received at least 1 box of gum. Also contributes to Cochrane reviews of physician advice and NRT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, no further information provided
Allocation concealment (selection bias)	Unclear risk	Each physician delivered 1 of the 3 interventions according to instructions in a packet for each patient
Incomplete outcome data (attrition bias) All outcomes	Low risk	17% of total sample unreachable and treated as smokers in analyses. 25 others not included

Okuyemi 2007

Methods	Setting: 20 low-income public housing developments, USA Recruitment: residents attending community health fairs, no contraindications to NRT, not selected for motivation
Participants	173 smokers; ~70%F, av. age 43, av. cpd ~17. 'Although we did not screen for motivation as part of our study inclusion criteria, motivation to quit was moderately high in both groups at baseline' Providers: specialist counsellors

Okuyemi 2007 (*Continued*)

Interventions	Intervention: MI counselling in-person at weeks 0 & 3, phone on day 10, wk 5 & 20. 8 week supply of 4 mg nicotine gum Control: Same schedule of MI for increasing fruit & veg consumption, free supplies, cookbook
Outcomes	Abstinence at 6m (7-day PP) Validation: CO ≤10 ppm
Notes	No correction for clustering. Length of sessions not reported, estimated as 91-300 mins

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Cluster randomized by housing unit, stratified by elderly vs family development
Allocation concealment (selection bias)	Low risk	Treatment assignment was revealed to the research staff only after each health fair was completed. A timed e-mail was sent to the study coordinator at 6:00 p.m. after each health fair was complete along with a sealed envelope containing the randomization code
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 (28.8%) I, 23 (21.5%) C lost to follow-up, included as smokers

Otero 2006

Methods	Setting: community, Brazil Recruitment: volunteers, wanting to quit
Participants	1199 smokers (includes 254 non-attenders); 63% female, av.age 42, 46% smoked >20 cpd Providers: trained doctors, nurses or psychologists
Interventions	Factorial design; NRT or no NRT, and 5 levels of behavioural support collapsed into 3 for reported analyses. Nicotine patch 21mg or 14mg based on dependence, for 8wks including tapering 1. Single 20 min session - classified as brief intervention control in meta-analysis 2. Cognitive behavioural, 1 or 2 weekly x1 hr group sessions 3. As 2, with 3 or 4 weekly sessions. Maintenance or recycling sessions provided to all groups at 3, 6, 12m
Outcomes	Abstinence at 12m (7 day PP) Validation: none

Otero 2006 (*Continued*)

Notes	Condition 3 with either dose of patch compared to condition 1 without patch in primary meta-analysis. Similar outcomes for condition 2 as for 3. Classified in 1-3 session, 91-300 minute subgroups 29% of no-patch group participants asked for nicotine patch after the 3m follow-up

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized, stratified by age & sex, by independent specialist
Allocation concealment (selection bias)	Low risk	Trial administrators blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Non-participants and losses to follow-up included as smokers

Ratner 2004

Methods	Setting: Preadmission clinic, teaching hospital, Canada Recruitment: Smokers awaiting surgery, not selected for motivation
Participants	237 smokers; 52% F, av. age 49, av. cpd 12; 16.5% precontemplators, 35% contemplators Provider: research nurse
Interventions	Intervention: Initiated 1-3 weeks before surgery: 15 min face-to-face counselling, materials, nicotine gum, quit kit, hotline number. Post-operative visit, 9 telephone calls, weekly for 1 m, biweekly for 2 m Control: usual care
Outcomes	Abstinence at 12m (7 day PP) Validation: cotinine <100 ng/mL based on mailed 'Nicotest' strips,. Self reported non smokers failing to return strips are classified as smokers in this analysis. 'it was not possible to verify whether participants had tested their own urine'
Notes	No information on % using NRT or other medication, classified as moderate take-up of treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Sealed envelopes opened after baseline data collection

Incomplete outcome data (attrition bias) All outcomes	Low risk	30 I & 29 C lost to follow-up treated as smokers. 9 deaths excluded from denominators

Reid 2003

Methods	Setting: Cardiac hospital, Canada Recruitment: Inpatients with myocardial infarction, coronary artery bypass graft, coronary angioplasty, coronary angiography, motivated to quit
Participants	254 current smokers (smoked in month before admission); av. age 54 yrs Providers: specialist nurse counsellors
Interventions	Intervention: Brief nurse counselling at bedside (5-10 mins) + booklet . Nurse call at 4 wks; if smoking, offered 3 x 20 min in-person counselling sessions (wks 4,8,12) and nicotine patch recommended for 8 wks. Nonsmokers reinforced and reminded about relapse prevention Control: Brief nurse counselling (5-10 mins) + self-help booklet (same in hospital as intervention group)
Outcomes	Abstinence at 12m (7-day PP) Validation: Random sample of 25 self-reported non-smokers asked for CO validation; 91% validated, similar in both arms. Results not adjusted for this
Notes	Classified as 4-8 sessions, 31-90 mins. Classified as low take-up because only 26% scheduled to receive 4 week intervention due to continued smoking

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization stratified by diagnosis on admission, degree of nicotine dependence using random numbers table
Allocation concealment (selection bias)	Low risk	Concealed until after assessment and initial counselling
Incomplete outcome data (attrition bias) All outcomes	Low risk	19.5% I 9.5% C lost to follow-up treated as smokers. 2 deaths included using last smoking status

Reid 2008

Methods	Setting: drug & alcohol dependence treatment centres, USA Recruitment: outpatients with current drug or alcoholic dependence or methadone maintained, interested in quitting
Participants	225 smokers (≥10 CPD), 49% F, av. age 41, av. cpd 21 Providers: Specialist counsellors
Interventions	1. Intervention: Nicotine patch for 8wks, Intensive behavioral therapy; 9 group sessions over 7wks, mood management & CBT components. 2. Treatment as usual (offered cessation treatment after end of trial)
Outcomes	Abstinence at 26wks (PP) Validation: CO ≤ 10 ppm
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization in 2:1 ratio 'computer generated, using permuted blocks of six, stratified by site and sex'
Allocation concealment (selection bias)	Low risk	'study statistician, who had no other contact with site study staff, performed the randomization, and staff were blind as to stratification and block size strategies'
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 intervention and 4 control participants did not complete treatment. Denominator used for abstinence rates unclear, but results not sensitive to different assumptions

Rodriguez 2003

Methods	Setting: 3 worksites, Spain. Recruitment: at annual medical check-up, motivated to quit smoking
Participants	218 smokers; 14% M, av. age 43 Provider: occupational physician
Interventions	1. Intervention: 5-8 mins structured counselling + further contacts at 2 days, 15 days & 3m. NRT based on Fagerstrom score; < 5 counselling only; 5-7 8 wks x14 mg nicotine patch; > 7 4 wks x 21 mg, 4wks x 14mg, 4wks x 7mg. Could be increased if necessary. 2. Control: minimal (30-60 secs) sporadic unstructured advice, usually at annual medical check up

Rodriguez 2003 (*Continued*)

Outcomes	Continuous abstinence (7 day PP at each assessment) at 12m. Validation: expired CO <= 10 ppm at each assessment
Notes	Control group participants also contacted at 2 & 15 days and most appear to have also made quit attempts. Classified as moderate treatment take-up

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Numbered sealed opaque envelopes, opened after enrolment
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 death in intervention group excluded from denominator, no other reported losses to follow-up

Sadr Azodi 2009

Methods	Setting: Pre-surgical clinics, 3 hospitals, Sweden Recruitment: Smokers due to undergo elective surgery for primary hernia repair, laparoscopic cholecystectomy or hip or knee prosthesis. Not selected for motivation to quit, but unwillingness to quit smoking a major reason for refusal to enrol
Participants	117 smokers; 47% F, av. age 55, av. cpd 15; no information about baseline motivation Provider: trained nurse counsellor
Interventions	Intervention: weekly counselling 4 wks pre- to 4 wks post-op, face-to-face or by telephone, free choice of NRT product, Control: Standard care
Outcomes	Abstinence at 12m. Post operative complications were primary trial outcomes Validation: CO ≤10 ppm at 2-3 weeks post op, no validation at 12m
Notes	Smoking cessation was validated by CO in exhaled air.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block randomization
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes

Sadr Azodi 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	7/55 (13%) I 10/62 (16%) C lost to 12-month follow-up, treated as smokers

Schauffler 2001

Methods	Setting: 2 health maintenance organisations (HMOs), USA Recruitment: Members of HMOs recruited by phone, no obligation to quit
Participants	1204 smokers (excludes 342 who did not return consent form). No demographic information provided Providers: specialist counsellors
Interventions	1. Notification of access to smoking cessation treatment covered by HMO: free NRT (patch or gum ordered by phone, dose tailored to smoking history) and free American Lung Association programmes (4-7 sessions over 2-4 weeks) 2. Self-help kit including video & pamphlet
Outcomes	Abstinence at 12m from introduction of benefit (PP). No quit date set so period since quit day not known Validation: none
Notes	Low use of treatment: 25% I vs 14% C study completers reported use of NRT during study period. 1.2% I vs 1.1% C reported participation in a behavioural programme

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	randomized, method not described
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% discontinued & 15% lost to follow-up, similar across groups. Paper calculates % quit excluding discontinuations; all losses counted as smokers in this MA, giving marginally more conservative RR

Segnan 1991

Methods	Setting: 44 general practices, Italy Recruitment: Consecutive eligible patients attending on study days (unselected)
Participants	923 smoking general practice attenders aged 20-60; ~35% F, av. age ~45, av. cpd ~15 Providers: GPs who had undergone a 3-hr training session

Segnan 1991 (*Continued*)

Interventions	1. Advice and leaflet 2. Repeated counselling (follow-up at 1, 3, 6, 9m) (not used in this review) 3. Repeated counselling plus nicotine gum 4. Repeated counselling plus spirometry (not used in this review)
Outcomes	Sustained abstinence at 12m (sustained for 3m by self-report) Validation: Urinary cotinine < 100 ng/mg
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Blocked treatment allocation based on a sequence of random numbers'
Allocation concealment (selection bias)	Low risk	'closed, numbered envelopes ... provided to each GP at the beginning of the study ... envelopes were indistinguishable from the outside ... research staff checked physicians' compliance with the procedure for assignment by comparing envelope numbers and dates of recruitment'
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% refused, 7% untraced at 12m, included as smokers

Simon 1997

Methods	Setting: Veterans Administration hospital, USA Recruitment: smokers undergoing non-cardiac surgery, prepared to make quit attempt
Participants	324 smokers (smoked within 2 wks of admission); 98% M, av. age 54, av. cpd 20 Providers: public health educator
Interventions	Intervention: single counselling session (30-60 min) prior to discharge, 5 follow-up counselling calls over 3m (based on social learning theory and stages of change). Video, prescription for NRT (gum or patch, dose not stated, for 3m) if no contraindications. Control: Brief pre-discharge counselling (10 min) and S-H materials
Outcomes	Abstinence at 12m (7 day PP) Validation: serum or saliva cotinine < 15 ng/ml. 6 self reports confirmed only by 'significant other' classified as smokers in the meta-analysis. 2 NRT users classed as quit
Notes	Approx 65% intervention and 17% control used NRT. Not associated with quitting in either group

Simon 1997 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Random list of assignments'
Allocation concealment (selection bias)	Low risk	'Sealed opaque envelopes opened on formal enrolment'
Incomplete outcome data (attrition bias) All outcomes	Low risk	25 (8%) lost to follow-up included as smokers, 11 (7%) intervention & 14 (9%) control group deaths excluded from denominators in report and in this meta-analysis

Thomsen 2010

Methods	Setting: 3 surgical units, Denmark Recruitment: Women scheduled for breast cancer surgery in near future, not selected for motivation
Participants	130 women with breast cancer; av. age 57, av. cpd NS Providers: specialist counsellor
Interventions	1. Counselling session 45-90 mins, using MI. NRT offered free of charge perioperatively 2. Usual care control, no systematic advice
Outcomes	Sustained abstinence at 12m (from 2 days pre-op, blinded telephone interviews) Validation: none
Notes	No information on number of participants who used NRT, so not included in subgroup for take-up of treatment. All intervention group received counselling

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, stratified by dept and procedure, method not stated
Allocation concealment (selection bias)	Unclear risk	No details reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 I and 3 C withdrew before receiving any intervention, excluded from denominators. 1 death in control group excluded, other dropouts treated as smokers in this analysis

Tonnesen 2006

Methods	Setting: 7 chest clinics, Denmark Recruitment: outpatient attender motivated to enrol in trial of cessation medication
Participants	370 smokers of >1 cpd with COPD (178 in arms of interest); 52% F, av. age 61, av. cpd 20 Providers: 20 nurses with cessation experience, trained to support medication use and provide standardised counselling
Interventions	Factorial trial. Nicotine sublingual tablet versus placebo and high versus low support 1. High support: 7 x 20-30min clinic visits (0, 2, 4, 8, 12 wks, 6m, 12m) & 5 x 10min phone calls (1, 6, 10 wks, 4½m, 9m), total contact time 4½ hrs. 2. Low support: 4 clinic visits (0, 2 wks, 6m, 12m) & 6 phone calls (1, 4, 6, 9, 12 wks, 9m), total time 2½ hrs
Outcomes	Sustained abstinence at 12m (validated at all visits from wk 2, PP also reported) Validation: CO < 10 ppm
Notes	NRT and high support versus placebo and low support used for meta-analysis.Therapists were not full time specialist counsellors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization list at each centre
Allocation concealment (selection bias)	Unclear risk	Allocation process not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	82 (22%) of total in trial lost to follow-up, 14 deaths, all included as smokers (support condition not specified for dropouts or deaths)

Velicer 2006

Methods	Setting: Community, USA Recruitment: Proactive approach by telephone to smokers at Veterans Administration medical center, not selected for motivation
Participants	2054 smokers (1023 in relevant arms); 23% F, av age 51, 40% precontemplators, 40% contemplators, 20% preparers Provider: expert system only
Interventions	1. Stage-based S-H manuals; participants sent manual for current stage and next stage on 2. As 1 plus 6wks nicotine patch if in appropriate stage, reassessed for NRT eligibility at 6 & 10m

Velicer 2006 (*Continued*)

	3. As 2 plus one expert system feedback report 4. As 3 plus regular automated telephone counselling using prerecorded messages
Outcomes	Abstinence at 30m, sustained for 6m Validation: none, telephone assessors blind to condition
Notes	None of the interventions involved any personal contact. 4 vs 1 used as test of combined intervention. In condition 4 79% received NRT, 60% used the telephone system at least once

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based random number generator
Allocation concealment (selection bias)	Low risk	Allocation done after completion of survey. Randomized participants who did not return consent form are excluded from further analyses
Incomplete outcome data (attrition bias) All outcomes	Low risk	39% lost incl 8% refused by 30m, no significant differences between groups. Different treatments of missing data reported not to have altered pattern of results

Vial 2002

Methods	Setting: Single hospital, Australia Recruitment: inpatients, motivated to quit
Participants	102 (only 64 followed to 6m), 44% F, av. age 52 Providers: pharmacists
Interventions	1. Initial counselling session from hospital pharmacist, up to 16 further weekly meetings after discharge, nicotine patch dispensed weekly at visits. 2. Initial counselling from hospital pharmacist, further sessions with a community pharmacist, same availability of patch 3. Minimal intervention, brief advice only
Outcomes	Continuous abstinence at 12 months Validation: CO $\leq$ 8 ppm
Notes	1 & 2 versus 3

Risk of bias

Vial 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomized, block size 10
Allocation concealment (selection bias)	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Due to time constraints only 64 of the randomized participants had been enrolled early enough to be followed at 12m, of whom 19 could not be reached

Villebro 2008

Methods	Setting: Pre-surgical assessment clinic, Denmark Recruitment: Smokers due to undergo elective hip or knee replacement surgery, not selected for motivation
Participants	120 daily smokers; 57% F, av. age 65, av. cpd 15; no information about baseline motivation Provider: trial nurse specialist
Interventions	Intervention: weekly counselling from 6-8 weeks prior to surgery to 10 days post-op. Individualised NRT. Strong encouragement to quit but option to reduce consumption by ≥50%. Control: Standard care
Outcomes	Abstinence 1 year after surgery Validation: CO only for those who participated in focus group interviews
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified block randomisation
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/60 I & 15/60 C not reached at 1y, included as smokers

Wakefield 2004

Methods	Setting: Radiation therapy, medical oncology & haematology departments of a single hospital, Australia Recruitment: cancer patients, not selected for interest in quitting, but number refused enrolment due to lack of interest
Participants	137 smokers; 38% F, av. age 52, av. cpd 21 Provider: Counsellor
Interventions	1. Motivational interviewing by single counsellor, unspecified number and duration of sessions, advice to use NRT if motivated and smoking >15 cpd. 2. Brief advice, SH materials
Outcomes	Abstinence at 6m, prolonged for 3m Validation: cotinine < 400 nmol/mmol or CO < 8 ppm if using NRT
Notes	Average of 11 contacts, 18 min duration, 209 mins total contact/patient. 81% of intervention and 42% of controls reported use of NRT by 6m

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'randomized'
Allocation concealment (selection bias)	Unclear risk	no details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	32 (23%) lost to follow-up, included as smokers. 17 deaths excluded from denominators

Wewers 2000

Methods	Setting: AIDS clinical trial unit, Ohio, USA Recruitment: HIV seropositive volunteers, interested in quitting
Participants	15 male smokers, av. age 40, av. cpd 27 Provider: peer educator
Interventions	Intervention: Initial session, TQD set, SH materials, wk3 visit, nicotine patch 24 + 4wk) , weekly telephone contact from peer educator for 8wk Control: mailed SH, written quit advice from nurse
Outcomes	Continuous abstinence 8 months post intervention (no smoking since quit date) Validation: CO <8 ppm
Notes	Pilot study

Wewers 2000 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'randomly assigned'
Allocation concealment (selection bias)	Unclear risk	no details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 control reached at 8 months but 7 known to be smoking at 8 weeks so no impact on continuous abstinence outcomes

Wewers 2009

Methods	Setting: 14 primary care and women's health clinics, Ohio, USA Recruitment: Women who had attended clinics in past 2y invited to enrol. Not explicitly selected for motivation
Participants	302 women. Av. age not stated, majority under 50, av. cpd 17.2 for intervention, 19.4 for control, p = 0.05 Provider: trained lay health adviser
Interventions	1. Intervention from health adviser. 8x 30-40 min sessions over 12wks. Nicotine patch 21 mg for 8wks 2. Letter from physician advising cessation, S-H guide
Outcomes	Abstinence at 12m (prolonged) (PP was primary trial outcome) Validation: Saliva cotinine < 14 ng/mL
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	'Randomly assigned' but mentions a biostatistics core staff member suggesting central randomisation
Allocation concealment (selection bias)	Low risk	Baseline data collection and eligibility assessed using computer assisted interview before random assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses higher in intervention (22.4%) than control (14.8%) but all missing assumed smoking

Wilson 1988

Methods	Setting: 70 family practices, Canada Recruitment: smokers attending regular appointments, not selected for motivation
Participants	1207 patients in 46 practices (in relevant arms); ~64% F, majority aged 25-44, approx 1/3 smoked >20 cpd Providers: Physician (usual care)
Interventions	1. Trained physician asked for a decision to set quit date. At quit date appointment explained correct use of 2 mg gum, x4 supportive follow-ups over 2m. All visits ~10 min. Prescription for nicotine gum 2. Untrained physician offered gum prescription, no other advice or follow-up (not used in this review) 3. Usual care
Outcomes	Abstinence at 12m (sustained for 3m) Validation: saliva cotinine $\leq$ 0.057 µmol/L, or saliva thiocyanate $\leq$ µ1724 mol/L if the patient was still using nicotine gum
Notes	Intervention patients more motivated to quit, so adjusted mean cessation rates used. For meta-analysis we estimated number of quitters without a correction for clustering within practices; the number of clusters was large, cluster size small (average 28 patients/cluster) and cessation rates did not vary significantly among practices within treatment groups. Less than 65% of intervention used any gum, 27% used only a few pieces

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Cluster randomized by practice
Allocation concealment (selection bias)	High risk	Receptionists recruited the first one or two eligible smokers each day. Usual care group physicians were not alerted but other physicians prompted to offer intervention. Recruitment consent rates lower for intervention (76%) than control (91%), and baseline differences in motivation to quit
Incomplete outcome data (attrition bias) All outcomes	Low risk	4.5% classified as smokers, who might have quit

AHRQ - Agency for Healthcare Research; av - average; C - control; CO - carbon monoxide; COPD - chronic obstructive pulmonary disease; CBT - cognitive behavioural therapy; cpd - cigarettes per day; d - day; F - female; GP - general practitioner; I - intervention; m - month(s); M - male; MA - meta-analysis; MDD - major depressive disorder; MI - motivational interviewing; NRT - nicotine replacement therapy; NS - not specified; O/P - outpatient; PI - principal investigator; PP - point prevalence abstinence; RP - relapse prevention; RR - risk ratio; SC - smoking cessation; S-H - self-help; SoC - Stage of Change; TC - telephone counselling; TQD - target quit date; wk(s) - week(s)

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

Study	Reason for exclusion
Ahluwalia 2006	Factorial trial crossing nicotine gum/ placebo and two counselling approaches. Matched intensity so no minimal intervention control relevant to this review. (See Lancaster 2005b, Individual behavioural counselling for smoking cessation)
Alterman 2001	Comparison of three levels of behaviour support as adjuncts to NRT
Andrews 2007	Cluster randomized with only two clusters so not possible to estimate the intraclass correlation
Aveyard 2007	Comparison of two levels of behaviour support as adjuncts to NRT
Bernstein 2011	Short follow-up (three months)
Bock 2008	Main intervention was motivational interviewing. Both intervention and control participants interested in quitting were offered NRT
Boyle 2007	Comparison of two levels of behaviour support as adjuncts to pharmacotherapy
Brown 2007	Factorial trial of bupropion/placebo and mood management CBT or standard cessation CBT. Both behavioural interventions were intensive
BTS 1983	Difference between levels of behavioural support was provision of self-help materials
Buchanan 2004	Only three months follow-up
Bushnell 1997	All participants offered free NRT. Comparison between two types of support programme
Campbell 1995	Short-follow-up (end of treatment at 16 weeks). Delayed intervention control
Carmody 2012	Usual care involved referral to a programme that provided counselling and pharmacotherapy
Chan 2011	Planned as a trial of smoking reductionusing NRT and counselling; participants selected for lack of motivation to quit. (Did report cessation outcomes, inclusion would not affect conclusions.)
Christenhusz 2007	All participants offered bupropion, test of different intensities of counselling
Costello 2011	All participants received NRT and a behavioural intervention. Compared two intensities of counselling. Also excluded from Behavioural Adjuncts review because only 5 weeks follow-up
Cropsey 2008	Waiting list control with delayed intervention. Outcomes reported for early and delayed intervention participants together
Ellerbeck 2009	All participants received offers of free pharmacotherapy, test of different levels of telephone counselling

(*Continued*)

Ferguson 2012	Some level of pharmacotherapy available to both intervention and control arms
Fiore 2004	All participants offered NRT, test of different types of counselling
Gariti 2009	Factorial trial comparing two levels of counselling intensity in combination with one of two pharmacotherapies
Ginsberg 1992	All participants offered NRT, test of different levels of behavioural support
Gordon 2010	Very little difference in use of pharmacotherapy between interventions (based on 3As or 5As) and control; 30% prescribed pharmacotherapy in intervention vs 20% in control
Hall 1987	No low intensity control. Factorial trial of nicotine gum or placebo and high or low intensity behavioural support. The low intensity treatment involved five 60 minute meetings
Hall 1994	No low intensity control. Trial compared two high intensity behavioural interventions as adjuncts to NRT in a selected population
Hall 1996	No low intensity control. Factorial trial comparing two high intensity interventions, and nicotine gum versus placebo
Hall 1998	No low intensity control. Factorial trial comparing two high intensity interventions (as used in Hall 1994), and nortriptyline versus placebo.
Hall 2004	No low intensity control. Factorial trial comparing extended behavioural intervention and nortriptyline as adjuncts to nicotine patch
Hall 2009	No low intensity control. Factorial trial comparing brief and extended behavioural intervention and nortriptyline or placebo as adjuncts to nicotine patch
Hall 2011	All participants received bupropion and behavioural support, trial of extended support
Hegaard 2003	Study population pregnant smokers, not eligible
Hokanson 2006	Intervention consisted of motivational interviewing and offer of pharmacotherapy. Control group received advice to quit smoking as part of diabetes education programme. Similar numbers of subjects in both groups sought medication (bupropion or NRT) so does not test a combined approach
Huber 1988	No minimal intervention control; test of nicotine gum versus behavioural support versus combination
Huber 2003	Both nicotine gum groups had high intensity behavioural support. Control was a waiting list
Ingersoll 2009	Only 3 months follow-up. Test of motivational interviewing as adjunct to nicotine patch therapy
Japuntich 2006	All participants received bupropion, trial of adjunct internet support
Jorenby 1995	All participants received nicotine patch. Factorial trial of dosage and level of behavioural support

(*Continued*)

Joseph 2004	Intervention and control did not differ on use of pharmacotherapy or intensity of behavioural support. Test of timing in relation to alcohol dependence treatment
Joyce 2008	Test of reimbursement for pharmacotherapy and counselling
Katz 2002	Non randomized pilot study for Katz 2004. Before & after study in one clinic with four clinics as controls
Kinnunen 2008	All participants received nicotine gum and brief counselling. Tested efficacy of additional exercise intervention or a matched contact condition that did not involve further counselling
Lacasse 2008	Only 18% of intervention participants received NRT. Trial in hospital inpatients, detected no effect of 5As behavioural intervention including brief counselling and postdischarge phone calls
Lando 1997	Test of telephone counselling as adjunct to NRT
Levine 2010	No minimal intervention control; behavioural interventions were matched for intensity, specifically tested a weight related intervention
Lifrak 1997	Comparison of two levels of behavioural support as adjuncts to NRT
MacLeod 2003	Test of telephone counselling as adjunct to NRT
Marshall 1985	All participants received nicotine gum. Trial of additional follow-up
Martin 1997	No minimal support condition; behavioural conditions differed in theoretical basis but not intensity
Mochizuki 2004	Only three months follow-up. Small study of pharmacist advice as adjunct to NRT
Nilsson 1996	Only four months follow-up. Intervention was offer of group support and free NRT
Okuyemi 2006	All participants received same intensity of motivational interviewing, group sessions and offer of NRT. Tested different targets for motivational interviewing
Park 2011	Non randomized, historical control design.
Rovina 2009	All participants received either a behavioural intervention, pharmacotherapy, or combination. See review of behavioural adjuncts (Stead 2012).
Schmitz 2007	All participants received same intensity of group based therapy, compared cognitive behavioural to supportive approaches. See Cochrane review of group based behavioural therapies (Stead 2005).
Schnoll 2005	Behavioural interventions similar in intensity as adjuncts to nicotine patch, and only three months follow-up
Shiffman 2000	Short follow-up (12 weeks from start of treatment). Study of computer tailored materials as adjunct to nicotine gum

(*Continued*)

Shiffman 2001	Short follow-up (12 weeks from start of treatment). Study of computer tailored materials as adjunct to nicotine patch
Simon 2003	Comparison of two levels of behavioural support as adjuncts to NRT
Smith 2001	Comparison of three levels of behavioural support as adjuncts to NRT
Sorensen 2003	Short follow-up (pre-operative period)
Stein 2006	Comparison of two levels of behavioural support as adjuncts to NRT
Strecher 2005	Short follow-up (12 weeks from start of treatment). Study of web-based tailored materials as adjunct to nicotine patch
Swan 2003	All participants received bupropion, factorial trial of dose and intensity of behavioural support
Ward 2001	Compared two group-based behavioural interventions similar in intensity as adjuncts to nicotine patch, see Stead 2005 'Group behaviour therapy programmes for smoking cessation'
Wiggers 2006	All participants received NRT, test of additional behavioural support
Wolfenden 2005	Only three month follow-up. Test of multifaceted intervention including offer of NRT at preoperative clinics
Wolfenden 2008	Not fully randomized; pilot study in which part of the control group was a historical control, from follow-up of a previous trial
Wu 2009	All participants received NRT, test of additional behavioural support
Yu 2006	Short follow-up (12 weeks from start of treatment). Test of behavioural support adjunct to NRT

CBT - cognitive behavioural therapy; NRT - nicotine replacement therapy

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

Cummins 2012

Trial name or title	Smoking cessation in Hospitalized Smokers NCT01289275
Methods	Randomized 2 x2 factorial study
Participants	Hospitalised patients from 2 San Diego County helath-care systems
Interventions	Provision of nicotine patch at discharge/ no NRT. Proactive telephone counselling from California Quitline/ no counselling

Cummins 2012 (*Continued*)

Outcomes	Abstinence at 2 and 6 months
Starting date	August 2011
Contact information	Shu-Hong Zhu: szhu@ucsd.edu
Notes	Brandstein 2011 was a pilot for this study

Wong 2008

Trial name or title	The Chinese Community Smoking Cessation Project
Methods	Prospective, randomized clinical trial, set in the Chinese community in San Francisco, CA, USA
Participants	464 Chinese Americans with medical conditions, av. 9 cpd
Interventions	Intervention: physician advice, in-person counselling with nicotine replacement therapy, 5 telephone calls Control: physician advice and self-help manual only Recruitment and intervention and control treatments were culturally tailored
Outcomes	Biochemically validated self reported abstinence at 6, 12 and 24 months
Starting date	Ran from 2001 to 2007
Contact information	Candice C. Wong, Candice.Wong@ucsf.edu
Notes	Study completed but full trial report not available at time of writing

DATA AND ANALYSES

Comparison 1. Primary analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	40	15021	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.66, 2.00]
2 Lung Health Study	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Subgroups by setting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	40		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Recruited in health care setting	31	9396	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.81, 2.34]
1.2 Recruited from community settings	8	4906	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.33, 1.76]
1.3 Lung Health Study (community)	1	5887	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [3.35, 4.50]

Comparison 3. Subgroup by selection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	41		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Selected for motivation	18	5903	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.60, 2.10]
1.2 Not explicitly selected	10	1644	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [2.18, 3.91]
1.3 Not selected	12	7474	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.37, 1.83]
1.4 Lung Health Study (unselected)	1	5887	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [3.35, 4.50]

Comparison 4. Subgroup by provider

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	41		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Usual care provider	8	4164	Risk Ratio (M-H, Fixed, 95% CI)	2.41 [1.91, 3.02]
1.2 Specialist cessation provider	28	8733	Risk Ratio (M-H, Fixed, 95% CI)	1.73 [1.55, 1.93]
1.3 Peer supporter	2	799	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.19, 2.58]
1.4 Lay health adviser	1	302	Risk Ratio (M-H, Fixed, 95% CI)	28.46 [1.71, 474.46]
1.5 Mail contact only	1	1023	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.58]
1.6 Lung Health Study (specialist)	1	5887	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [3.35, 4.50]

Comparison 5. Subgroup by number of sessions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	41		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 0 sessions	1	1023	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.58]
1.2 1-3 sessions	7	3544	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.56, 2.38]
1.3 4-8 sessions	22	8980	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.63, 2.05]
1.4 Over 8 sessions	10	1474	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.57, 2.79]
1.5 Lung Health Study (over 8 sessions)	1	5887	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [3.35, 4.50]

Comparison 6. Subgroup by duration of contact

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	41		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 No personal contact scheduled	1	1023	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.69, 1.58]
1.2 up to 30 minutes	4	1622	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.23, 2.45]
1.3 31-90 minutes	10	6261	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [1.64, 2.18]
1.4 91-300 minutes	19	4006	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [1.64, 2.32]
1.5 Over 300 minutes	6	2109	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.36, 2.24]
1.6 Lung Health Study (over 300 mins)	1	5887	Risk Ratio (M-H, Fixed, 95% CI)	3.88 [3.35, 4.50]

Comparison 7. Subgroup by take-up of treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	38		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 High take-up of treatment	23	7518	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.74, 2.28]
1.2 Moderate take-up of treatment	12	3762	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.64, 2.43]
1.3 Low take-up of treatment	3	2599	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.25, 1.86]

Comparison 8. Subgroup by treatment take-up, specialist support only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	28		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 High take-up of treatment	19	6225	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [1.75, 2.32]
1.2 Moderate take-up of treatment	7	1233	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [1.23, 2.25]
1.3 Low take-up of treatment	2	1458	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.02, 1.58]

Comparison 9. Subgroup by number of sessions, high take-up only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	23		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 1-3 sessions	5	2284	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.37, 2.22]
1.2 4-8 sessions	11	4141	Risk Ratio (M-H, Fixed, 95% CI)	2.06 [1.71, 2.47]
1.3 Over 8 sessions	7	1093	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.63, 3.21]

Comparison 10. Subgroup by duration of contact, high take-up only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cessation at longest follow-up	23		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 up to 30 minutes	3	1405	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.08, 2.36]
1.2 31-90 minutes	2	2312	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [1.49, 2.30]
1.3 91-300 minutes	14	2960	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.74, 2.62]
1.4 Over 300 minutes	4	841	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [1.63, 4.25]

Analysis 1.1. Comparison 1 Primary analysis, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 1 Primary analysis

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wewers 2009	13/147	0/155		0.1 %	28.46 [1.71, 474.46]
Wewers 2000	4/8	0/7		0.1 %	8.00 [0.51, 126.67]
Cooney 2007	4/55	1/63		0.2 %	4.58 [0.53, 39.78]
Baker 2006	5/147	1/151		0.2 %	5.14 [0.61, 43.44]
Vial 2002	9/42	1/22		0.2 %	4.71 [0.64, 34.85]
Villebro 2008	13/60	2/60		0.3 %	6.50 [1.53, 27.57]
Binnie 2007	3/59	2/57		0.3 %	1.45 [0.25, 8.35]
Lewis 1998	6/62	3/61		0.5 %	1.97 [0.52, 7.52]
Hanioka 2010	12/33	3/23		0.6 %	2.79 [0.88, 8.78]
Juarranz Sanz 1998	37/102	4/103		0.7 %	9.34 [3.45, 25.25]
Tonnesen 2006	13/90	4/88		0.7 %	3.18 [1.08, 9.37]
Brandstein 2011	6/64	4/62		0.7 %	1.45 [0.43, 4.90]
Wakefield 2004	4/66	4/54		0.7 %	0.82 [0.21, 3.12]
Thomsen 2010	7/58	5/61		0.8 %	1.47 [0.50, 4.38]
Segnan 1991	22/294	3/62		0.8 %	1.55 [0.48, 5.01]
Kotz 2009	13/112	4/68		0.8 %	1.97 [0.67, 5.81]
Hall 2002	15/72	4/37		0.9 %	1.93 [0.69, 5.39]
Reid 2008	9/153	4/72		0.9 %	1.06 [0.34, 3.32]
Duffy 2006	15/48	6/41		1.1 %	2.14 [0.91, 5.00]
Chouinard 2005	13/53	7/55		1.1 %	1.93 [0.83, 4.45]
Molyneux 2003	10/91	7/92		1.2 %	1.44 [0.57, 3.63]
Okuyemi 2007	5/66	10/107		1.3 %	0.81 [0.29, 2.27]
Sadr Azodi 2009	18/55	9/62		1.4 %	2.25 [1.11, 4.60]
Mohiuddin 2007	36/109	9/100		1.6 %	3.67 [1.86, 7.23]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Simon 1997	20/157	9/142		1.6 %	2.01 [0.95, 4.27]
Rodriguez 2003	23/114	9/103		1.6 %	2.31 [1.12, 4.76]
Ratner 2004	10/111	11/117		1.8 %	0.96 [0.42, 2.17]
Chan 2010	57/501	12/218		2.8 %	2.07 [1.13, 3.77]
McCarthy 2008	24/113	17/113		2.8 %	1.41 [0.80, 2.48]
An 2006	53/417	17/414		2.9 %	3.10 [1.82, 5.25]
Hall 2006	30/163	21/159		3.6 %	1.39 [0.83, 2.33]
Katz 2004	71/642	20/499		3.8 %	2.76 [1.70, 4.47]
Ockene 1991	40/402	28/464		4.3 %	1.65 [1.04, 2.62]
Wilson 1988	53/606	26/601		4.4 %	2.02 [1.28, 3.19]
Emmons 2005	58/386	36/398		5.9 %	1.66 [1.12, 2.46]
Otero 2006	68/204	39/194		6.7 %	1.66 [1.18, 2.33]
Velicer 2006	42/500	42/523		6.9 %	1.05 [0.69, 1.58]
Reid 2003	49/126	46/128		7.6 %	1.08 [0.79, 1.49]
Schauffler 2001	91/601	65/603		10.8 %	1.40 [1.04, 1.89]
Hollis 2007	153/721	102/872		15.4 %	1.81 [1.44, 2.28]
Total (95% CI)	**7810**	**7211**		**100.0 %**	**1.82 [1.66, 2.00]**

Total events: 1134 (Intervention), 597 (Control)

Heterogeneity: Chi?? = 64.69, df = 39 (P = 0.01); I?? =40%

Test for overall effect: Z = 12.57 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Primary analysis, Outcome 2 Lung Health Study.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 1 Primary analysis

Outcome: 2 Lung Health Study

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Lung Health Study	1373/3923	177/1964		3.88 [3.35, 4.50]

Analysis 2.1. Comparison 2 Subgroups by setting, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 2 Subgroups by setting

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Recruited in health care setting					
An 2006	53/417	17/414		5.5 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.3 %	5.14 [0.61, 43.44]
Binnie 2007	3/59	2/57		0.7 %	1.45 [0.25, 8.35]
Brandstein 2011	6/64	4/62		1.3 %	1.45 [0.43, 4.90]
Chouinard 2005	13/53	7/55		2.2 %	1.93 [0.83, 4.45]
Cooney 2007	4/55	1/63		0.3 %	4.58 [0.53, 39.78]
Duffy 2006	15/48	6/41		2.1 %	2.14 [0.91, 5.00]
Emmons 2005	58/386	36/398		11.5 %	1.66 [1.12, 2.46]
Hall 2006	30/163	21/159		6.9 %	1.39 [0.83, 2.33]
Hanioka 2010	12/33	3/23		1.1 %	2.79 [0.88, 8.78]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Juarranz Sanz 1998	37/102	4/103		1.3 %	9.34 [3.45, 25.25]
Katz 2004	71/642	20/499		7.3 %	2.76 [1.70, 4.47]
Lewis 1998	6/62	3/61		1.0 %	1.97 [0.52, 7.52]
Mohiuddin 2007	36/109	9/100		3.0 %	3.67 [1.86, 7.23]
Molyneux 2003	10/91	7/92		2.3 %	1.44 [0.57, 3.63]
Ockene 1991	40/402	28/464		8.4 %	1.65 [1.04, 2.62]
Ratner 2004	10/111	11/117		3.5 %	0.96 [0.42, 2.17]
Reid 2003	49/126	46/128		14.8 %	1.08 [0.79, 1.49]
Reid 2008	9/153	4/72		1.8 %	1.06 [0.34, 3.32]
Rodriguez 2003	23/114	9/103		3.1 %	2.31 [1.12, 4.76]
Sadr Azodi 2009	18/55	9/62		2.7 %	2.25 [1.11, 4.60]
Segnan 1991	22/294	3/62		1.6 %	1.55 [0.48, 5.01]
Simon 1997	20/157	9/142		3.1 %	2.01 [0.95, 4.27]
Thomsen 2010	7/58	5/61		1.6 %	1.47 [0.50, 4.38]
Tonnesen 2006	13/90	4/88		1.3 %	3.18 [1.08, 9.37]
Vial 2002	9/42	1/22		0.4 %	4.71 [0.64, 34.85]
Villebro 2008	13/60	2/60		0.6 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		1.4 %	0.82 [0.21, 3.12]
Wewers 2000	4/8	0/7		0.2 %	8.00 [0.51, 126.67]
Wewers 2009	13/147	0/155		0.2 %	28.46 [1.71, 474.46]
Wilson 1988	53/606	26/601		8.5 %	2.02 [1.28, 3.19]
Subtotal (95% CI)	**4920**	**4476**		**100.0 %**	**2.06 [1.81, 2.34]**
Total events: 666 (Intervention), 302 (Control)					
Heterogeneity: Chi?? = 53.17, df = 30 (P = 0.01); I?? =44%					
Test for overall effect: Z = 11.06 (P < 0.00001)					
2 Recruited from community settings					
Hall 2002	15/72	4/37		1.9 %	1.93 [0.69, 5.39]
Hollis 2007	153/721	102/872		33.8 %	1.81 [1.44, 2.28]
Kotz 2009	13/112	4/68		1.8 %	1.97 [0.67, 5.81]
McCarthy 2008	24/113	17/113		6.2 %	1.41 [0.80, 2.48]
Okuyemi 2007	5/66	10/107		2.8 %	0.81 [0.29, 2.27]
Otero 2006	68/204	39/194		14.6 %	1.66 [1.18, 2.33]
Schauffler 2001	91/601	65/603		23.8 %	1.40 [1.04, 1.89]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Velicer 2006	42/500	42/523		15.0 %	1.05 [0.69, 1.58]
Subtotal (95% CI)	**2389**	**2517**		**100.0 %**	**1.53 [1.33, 1.76]**
Total events: 411 (Intervention), 283 (Control)					
Heterogeneity: Chi?? = 7.89, df = 7 (P = 0.34); I?? =11%					
Test for overall effect: Z = 5.95 (P < 0.00001)					
3 Lung Health Study (community)					
Lung Health Study	1373/3923	177/1964		100.0 %	3.88 [3.35, 4.50]
Subtotal (95% CI)	**3923**	**1964**		**100.0 %**	**3.88 [3.35, 4.50]**
Total events: 1373 (Intervention), 177 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 18.11 (P < 0.00001)					
Test for subgroup differences: Chi?? = 83.90, df = 2 (P = 0.00), I?? =98%					

Analysis 3.1. Comparison 3 Subgroup by selection, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 3 Subgroup by selection

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Selected for motivation					
An 2006	53/417	17/414		6.1 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.4 %	5.14 [0.61, 43.44]
Chan 2010	57/501	12/218		6.0 %	2.07 [1.13, 3.77]
Cooney 2007	4/55	1/63		0.3 %	4.58 [0.53, 39.78]
Hall 2002	15/72	4/37		1.9 %	1.93 [0.69, 5.39]
Hanioka 2010	12/33	3/23		1.3 %	2.79 [0.88, 8.78]
Hollis 2007	153/721	102/872		33.2 %	1.81 [1.44, 2.28]
Kotz 2009	13/112	4/68		1.8 %	1.97 [0.67, 5.81]
Lewis 1998	6/62	3/61		1.1 %	1.97 [0.52, 7.52]
McCarthy 2008	24/113	17/113		6.1 %	1.41 [0.80, 2.48]
Otero 2006	68/204	39/194		14.4 %	1.66 [1.18, 2.33]
Reid 2003	49/126	46/128		16.4 %	1.08 [0.79, 1.49]
Reid 2008	9/153	4/72		2.0 %	1.06 [0.34, 3.32]
Rodriguez 2003	23/114	9/103		3.4 %	2.31 [1.12, 4.76]
Simon 1997	20/157	9/142		3.4 %	2.01 [0.95, 4.27]
Tonnesen 2006	13/90	4/88		1.5 %	3.18 [1.08, 9.37]
Vial 2002	9/42	1/22		0.5 %	4.71 [0.64, 34.85]
Wewers 2000	4/8	0/7		0.2 %	8.00 [0.51, 126.67]
Subtotal (95% CI)	**3127**	**2776**		**100.0 %**	**1.83 [1.60, 2.10]**
Total events: 537 (Intervention), 276 (Control)					
Heterogeneity: Chi?? = 22.04, df = 17 (P = 0.18); I?? =23%					
Test for overall effect: Z = 8.87 (P < 0.00001)					
2 Not explicitly selected					
Brandstein 2011	6/64	4/62		7.5 %	1.45 [0.43, 4.90]
Duffy 2006	15/48	6/41		12.0 %	2.14 [0.91, 5.00]
Juarranz Sanz 1998	37/102	4/103		7.4 %	9.34 [3.45, 25.25]

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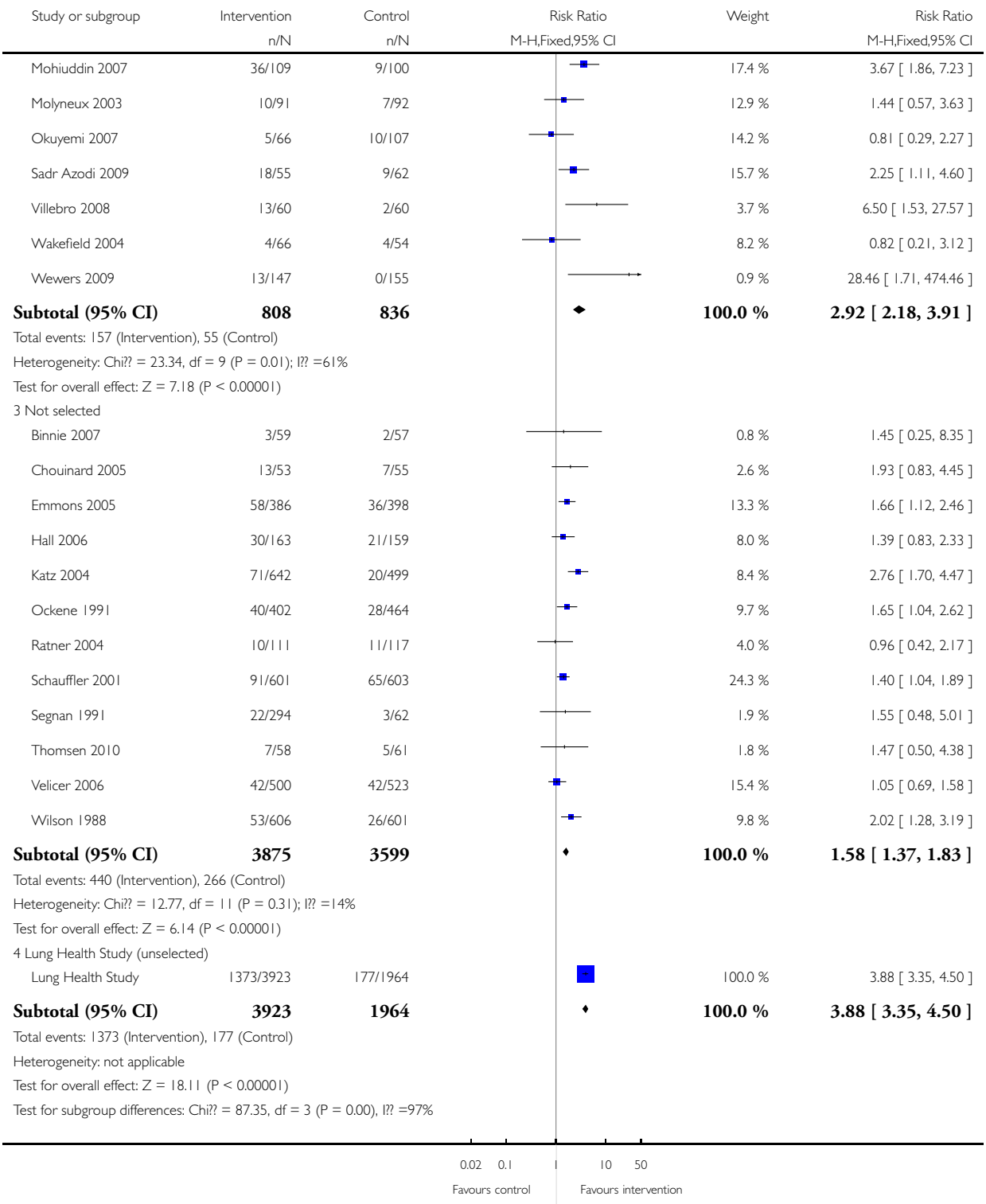

Analysis 4.1. Comparison 4 Subgroup by provider, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 4 Subgroup by provider

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Usual care provider					
Binnie 2007	3/59	2/57		2.1 %	1.45 [0.25, 8.35]
Hanioka 2010	12/33	3/23		3.6 %	2.79 [0.88, 8.78]
Juarranz Sanz 1998	37/102	4/103		4.0 %	9.34 [3.45, 25.25]
Katz 2004	71/642	20/499		22.8 %	2.76 [1.70, 4.47]
Ockene 1991	40/402	28/464		26.4 %	1.65 [1.04, 2.62]
Rodriguez 2003	23/114	9/103		9.6 %	2.31 [1.12, 4.76]
Segnan 1991	22/294	3/62		5.0 %	1.55 [0.48, 5.01]
Wilson 1988	53/606	26/601		26.5 %	2.02 [1.28, 3.19]
Subtotal (95% CI)	**2252**	**1912**		**100.0 %**	**2.41 [1.91, 3.02]**
Total events: 261 (Intervention), 95 (Control)					
Heterogeneity: Chi?? = 11.51, df = 7 (P = 0.12); I?? =39%					
Test for overall effect: Z = 7.53 (P < 0.00001)					
2 Specialist cessation provider					
An 2006	53/417	17/414		4.0 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.2 %	5.14 [0.61, 43.44]
Brandstein 2011	6/64	4/62		1.0 %	1.45 [0.43, 4.90]
Chan 2010	57/501	12/218		4.0 %	2.07 [1.13, 3.77]
Chouinard 2005	13/53	7/55		1.6 %	1.93 [0.83, 4.45]
Cooney 2007	4/55	1/63		0.2 %	4.58 [0.53, 39.78]
Duffy 2006	15/48	6/41		1.5 %	2.14 [0.91, 5.00]
Hall 2002	15/72	4/37		1.3 %	1.93 [0.69, 5.39]
Hall 2006	30/163	21/159		5.0 %	1.39 [0.83, 2.33]
Hollis 2007	153/721	102/872		21.9 %	1.81 [1.44, 2.28]
Kotz 2009	13/112	4/68		1.2 %	1.97 [0.67, 5.81]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lewis 1998	6/62	3/61		0.7 %	1.97 [0.52, 7.52]
McCarthy 2008	24/113	17/113		4.0 %	1.41 [0.80, 2.48]
Mohiuddin 2007	36/109	9/100		2.2 %	3.67 [1.86, 7.23]
Molyneux 2003	10/91	7/92		1.6 %	1.44 [0.57, 3.63]
Okuyemi 2007	5/66	10/107		1.8 %	0.81 [0.29, 2.27]
Otero 2006	68/204	39/194		9.5 %	1.66 [1.18, 2.33]
Ratner 2004	10/111	11/117		2.5 %	0.96 [0.42, 2.17]
Reid 2003	49/126	46/128		10.8 %	1.08 [0.79, 1.49]
Reid 2008	9/153	4/72		1.3 %	1.06 [0.34, 3.32]
Sadr Azodi 2009	18/55	9/62		2.0 %	2.25 [1.11, 4.60]
Schauffler 2001	91/601	65/603		15.4 %	1.40 [1.04, 1.89]
Simon 1997	20/157	9/142		2.2 %	2.01 [0.95, 4.27]
Thomsen 2010	7/58	5/61		1.2 %	1.47 [0.50, 4.38]
Tonnesen 2006	13/90	4/88		1.0 %	3.18 [1.08, 9.37]
Vial 2002	9/42	1/22		0.3 %	4.71 [0.64, 34.85]
Villebro 2008	13/60	2/60		0.5 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		1.0 %	0.82 [0.21, 3.12]
Subtotal (95% CI)	**4517**	**4216**		**100.0 %**	**1.73 [1.55, 1.93]**
Total events: 756 (Intervention), 424 (Control)					
Heterogeneity: Chi?? = 35.97, df = 27 (P = 0.12); I?? =25%					
Test for overall effect: Z = 9.75 (P < 0.00001)					
3 Peer supporter					
Emmons 2005	58/386	36/398		98.5 %	1.66 [1.12, 2.46]
Wewers 2000	4/8	0/7		1.5 %	8.00 [0.51, 126.67]
Subtotal (95% CI)	**394**	**405**		**100.0 %**	**1.75 [1.19, 2.58]**
Total events: 62 (Intervention), 36 (Control)					
Heterogeneity: Chi?? = 1.23, df = 1 (P = 0.27); I?? =19%					
Test for overall effect: Z = 2.86 (P = 0.0042)					
4 Lay health adviser					
Wewers 2009	13/147	0/155		100.0 %	28.46 [1.71, 474.46]
Subtotal (95% CI)	**147**	**155**		**100.0 %**	**28.46 [1.71, 474.46]**
Total events: 13 (Intervention), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.33 (P = 0.020)					
5 Mail contact only					
Velicer 2006	42/500	42/523		100.0 %	1.05 [0.69, 1.58]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**500**	**523**		**100.0 %**	**1.05 [0.69, 1.58]**
Total events: 42 (Intervention), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					
6 Lung Health Study (specialist)					
Lung Health Study	1373/3923	177/1964		100.0 %	3.88 [3.35, 4.50]
Subtotal (95% CI)	**3923**	**1964**		**100.0 %**	**3.88 [3.35, 4.50]**
Total events: 1373 (Intervention), 177 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 18.11 (P < 0.00001)					
Test for subgroup differences: Chi?? = 93.10, df = 5 (P = 0.00), I?? =95%					

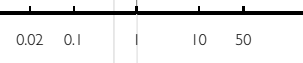
Analysis 5.1. Comparison 5 Subgroup by number of sessions, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 5 Subgroup by number of sessions

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 0 sessions					
Velicer 2006	42/500	42/523		100.0 %	1.05 [0.69, 1.58]
Subtotal (95% CI)	**500**	**523**		**100.0 %**	**1.05 [0.69, 1.58]**
Total events: 42 (Intervention), 42 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.22 (P = 0.83)					
2 1-3 sessions					
Chan 2010	57/501	12/218		14.2 %	2.07 [1.13, 3.77]
Cooney 2007	4/55	1/63		0.8 %	4.58 [0.53, 39.78]
Katz 2004	71/642	20/499		19.1 %	2.76 [1.70, 4.47]



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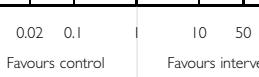
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Molyneux 2003	10/91	7/92		5.9 %	1.44 [0.57, 3.63]
Ockene 1991	40/402	28/464		22.0 %	1.65 [1.04, 2.62]
Otero 2006	68/204	39/194		33.9 %	1.66 [1.18, 2.33]
Thomsen 2010	7/58	5/61		4.1 %	1.47 [0.50, 4.38]
Subtotal (95% CI)	**1953**	**1591**		**100.0 %**	**1.93 [1.56, 2.38]**
Total events: 257 (Intervention), 112 (Control)					
Heterogeneity: Chi?? = 4.59, df = 6 (P = 0.60); I?? =0.0%					
Test for overall effect: Z = 6.07 (P < 0.00001)					
3 4-8 sessions					
An 2006	53/417	17/414		4.5 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.3 %	5.14 [0.61, 43.44]
Binnie 2007	3/59	2/57		0.5 %	1.45 [0.25, 8.35]
Brandstein 2011	6/64	4/62		1.1 %	1.45 [0.43, 4.90]
Chouinard 2005	13/53	7/55		1.8 %	1.93 [0.83, 4.45]
Emmons 2005	58/386	36/398		9.4 %	1.66 [1.12, 2.46]
Hall 2002	15/72	4/37		1.4 %	1.93 [0.69, 5.39]
Hall 2006	30/163	21/159		5.6 %	1.39 [0.83, 2.33]
Hanioka 2010	12/33	3/23		0.9 %	2.79 [0.88, 8.78]
Hollis 2007	153/721	102/872		24.4 %	1.81 [1.44, 2.28]
Juarranz Sanz 1998	37/102	4/103		1.1 %	9.34 [3.45, 25.25]
Kotz 2009	13/112	4/68		1.3 %	1.97 [0.67, 5.81]
Lewis 1998	6/62	3/61		0.8 %	1.97 [0.52, 7.52]
Okuyemi 2007	5/66	10/107		2.0 %	0.81 [0.29, 2.27]
Reid 2003	49/126	46/128		12.1 %	1.08 [0.79, 1.49]
Rodriguez 2003	23/114	9/103		2.5 %	2.31 [1.12, 4.76]
Sadr Azodi 2009	18/55	9/62		2.2 %	2.25 [1.11, 4.60]
Schauffler 2001	91/601	65/603		17.2 %	1.40 [1.04, 1.89]
Segnan 1991	22/294	3/62		1.3 %	1.55 [0.48, 5.01]
Simon 1997	20/157	9/142		2.5 %	2.01 [0.95, 4.27]
Wewers 2009	13/147	0/155		0.1 %	28.46 [1.71, 474.46]
Wilson 1988	53/606	26/601		6.9 %	2.02 [1.28, 3.19]
Subtotal (95% CI)	**4557**	**4423**		**100.0 %**	**1.83 [1.63, 2.05]**
Total events: 698 (Intervention), 385 (Control)					
Heterogeneity: Chi?? = 37.61, df = 21 (P = 0.01); I?? =44%					



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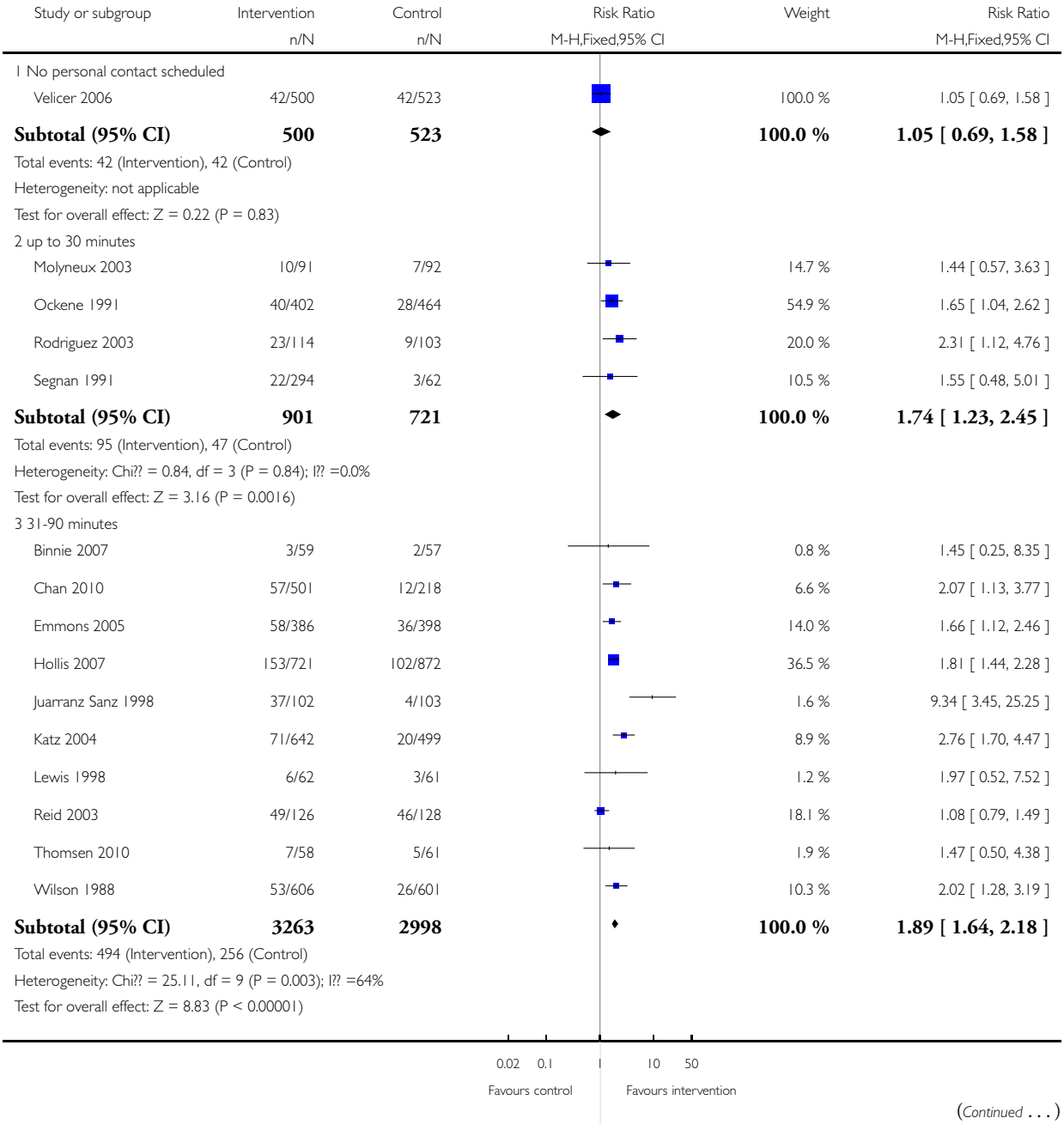
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 10.15 (P < 0.00001)					
4 Over 8 sessions					
Duffy 2006	15/48	6/41		10.6 %	2.14 [0.91, 5.00]
McCarthy 2008	24/113	17/113		27.7 %	1.41 [0.80, 2.48]
Mohiuddin 2007	36/109	9/100		15.3 %	3.67 [1.86, 7.23]
Ratner 2004	10/111	11/117		17.5 %	0.96 [0.42, 2.17]
Reid 2008	9/153	4/72		8.9 %	1.06 [0.34, 3.32]
Tonnesen 2006	13/90	4/88		6.6 %	3.18 [1.08, 9.37]
Vial 2002	9/42	1/22		2.1 %	4.71 [0.64, 34.85]
Villebro 2008	13/60	2/60		3.3 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		7.2 %	0.82 [0.21, 3.12]
Wewers 2000	4/8	0/7		0.9 %	8.00 [0.51, 126.67]
Subtotal (95% CI)	**800**	**674**		**100.0 %**	**2.09 [1.57, 2.79]**
Total events: 137 (Intervention), 58 (Control)					
Heterogeneity: Chi?? = 15.75, df = 9 (P = 0.07); I?? =43%					
Test for overall effect: Z = 5.02 (P < 0.00001)					
5 Lung Health Study (over 8 sessions)					
Lung Health Study	1373/3923	177/1964		100.0 %	3.88 [3.35, 4.50]
Subtotal (95% CI)	**3923**	**1964**		**100.0 %**	**3.88 [3.35, 4.50]**
Total events: 1373 (Intervention), 177 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 18.11 (P < 0.00001)					
Test for subgroup differences: Chi?? = 81.20, df = 4 (P = 0.00), I?? =95%					

Analysis 6.1. Comparison 6 Subgroup by duration of contact, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 6 Subgroup by duration of contact

Outcome: 1 Cessation at longest follow-up



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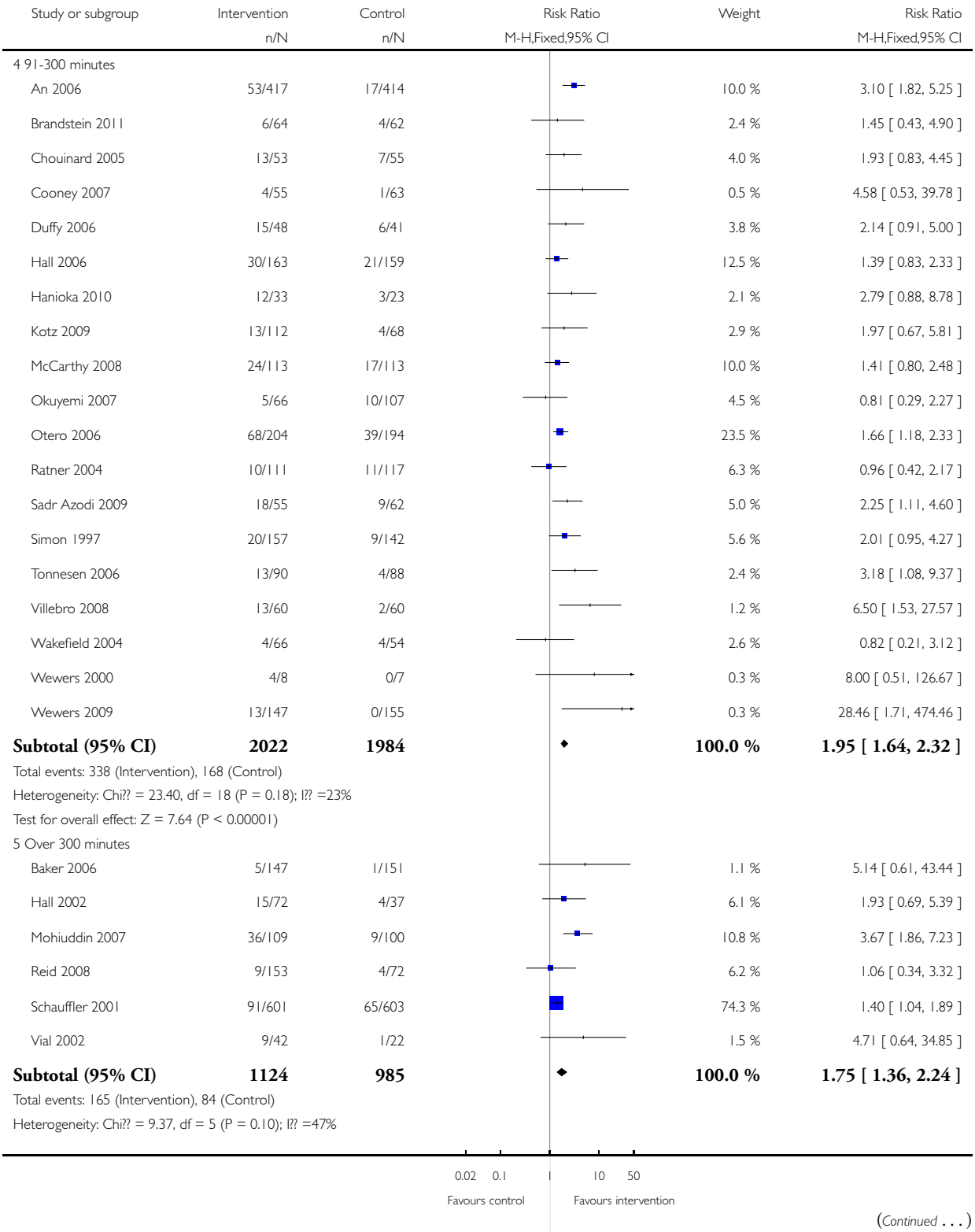

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 91-300 minutes					
An 2006	53/417	17/414		10.0 %	3.10 [1.82, 5.25]
Brandstein 2011	6/64	4/62		2.4 %	1.45 [0.43, 4.90]
Chouinard 2005	13/53	7/55		4.0 %	1.93 [0.83, 4.45]
Cooney 2007	4/55	1/63		0.5 %	4.58 [0.53, 39.78]
Duffy 2006	15/48	6/41		3.8 %	2.14 [0.91, 5.00]
Hall 2006	30/163	21/159		12.5 %	1.39 [0.83, 2.33]
Hanioka 2010	12/33	3/23		2.1 %	2.79 [0.88, 8.78]
Kotz 2009	13/112	4/68		2.9 %	1.97 [0.67, 5.81]
McCarthy 2008	24/113	17/113		10.0 %	1.41 [0.80, 2.48]
Okuyemi 2007	5/66	10/107		4.5 %	0.81 [0.29, 2.27]
Otero 2006	68/204	39/194		23.5 %	1.66 [1.18, 2.33]
Ratner 2004	10/111	11/117		6.3 %	0.96 [0.42, 2.17]
Sadr Azodi 2009	18/55	9/62		5.0 %	2.25 [1.11, 4.60]
Simon 1997	20/157	9/142		5.6 %	2.01 [0.95, 4.27]
Tonnesen 2006	13/90	4/88		2.4 %	3.18 [1.08, 9.37]
Villebro 2008	13/60	2/60		1.2 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		2.6 %	0.82 [0.21, 3.12]
Wewers 2000	4/8	0/7		0.3 %	8.00 [0.51, 126.67]
Wewers 2009	13/147	0/155		0.3 %	28.46 [1.71, 474.46]
Subtotal (95% CI)	**2022**	**1984**		**100.0 %**	**1.95 [1.64, 2.32]**
Total events: 338 (Intervention), 168 (Control)					
Heterogeneity: Chi?? = 23.40, df = 18 (P = 0.18); I?? =23%					
Test for overall effect: Z = 7.64 (P < 0.00001)					
5 Over 300 minutes					
Baker 2006	5/147	1/151		1.1 %	5.14 [0.61, 43.44]
Hall 2002	15/72	4/37		6.1 %	1.93 [0.69, 5.39]
Mohiuddin 2007	36/109	9/100		10.8 %	3.67 [1.86, 7.23]
Reid 2008	9/153	4/72		6.2 %	1.06 [0.34, 3.32]
Schauffler 2001	91/601	65/603		74.3 %	1.40 [1.04, 1.89]
Vial 2002	9/42	1/22		1.5 %	4.71 [0.64, 34.85]
Subtotal (95% CI)	**1124**	**985**		**100.0 %**	**1.75 [1.36, 2.24]**
Total events: 165 (Intervention), 84 (Control)					
Heterogeneity: Chi?? = 9.37, df = 5 (P = 0.10); I?? =47%					

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 4.41 (P = 0.000010)					
6 Lung Health Study (over 300 mins)					
Lung Health Study	1373/3923	177/1964		100.0 %	3.88 [3.35, 4.50]
Subtotal (95% CI)	**3923**	**1964**		**100.0 %**	**3.88 [3.35, 4.50]**
Total events: 1373 (Intervention), 177 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 18.11 (P < 0.00001)					
Test for subgroup differences: Chi?? = 80.83, df = 5 (P = 0.00), I?? =94%					

Analysis 7.1. Comparison 7 Subgroup by take-up of treatment, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 7 Subgroup by take-up of treatment

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High take-up of treatment					
An 2006	53/417	17/414		6.0 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.3 %	5.14 [0.61, 43.44]
Brandstein 2011	6/64	4/62		1.4 %	1.45 [0.43, 4.90]
Chan 2010	57/501	12/218		5.9 %	2.07 [1.13, 3.77]
Cooney 2007	4/55	1/63		0.3 %	4.58 [0.53, 39.78]
Hall 2002	15/72	4/37		1.9 %	1.93 [0.69, 5.39]
Hanioka 2010	12/33	3/23		1.2 %	2.79 [0.88, 8.78]
Hollis 2007	153/721	102/872		32.6 %	1.81 [1.44, 2.28]
Kotz 2009	13/112	4/68		1.8 %	1.97 [0.67, 5.81]

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McCarthy 2008	24/113	17/113		6.0 %	1.41 [0.80, 2.48]
Mohiuddin 2007	36/109	9/100		3.3 %	3.67 [1.86, 7.23]
Molyneux 2003	10/91	7/92		2.5 %	1.44 [0.57, 3.63]
Ockene 1991	40/402	28/464		9.2 %	1.65 [1.04, 2.62]
Okuyemi 2007	5/66	10/107		2.7 %	0.81 [0.29, 2.27]
Otero 2006	68/204	39/194		14.1 %	1.66 [1.18, 2.33]
Reid 2008	9/153	4/72		1.9 %	1.06 [0.34, 3.32]
Sadr Azodi 2009	18/55	9/62		3.0 %	2.25 [1.11, 4.60]
Segnan 1991	22/294	3/62		1.7 %	1.55 [0.48, 5.01]
Tonnesen 2006	13/90	4/88		1.4 %	3.18 [1.08, 9.37]
Villebro 2008	13/60	2/60		0.7 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		1.6 %	0.82 [0.21, 3.12]
Wewers 2000	4/8	0/7		0.2 %	8.00 [0.51, 126.67]
Wewers 2009	13/147	0/155		0.2 %	28.46 [1.71, 474.46]
Subtotal (95% CI)	**3980**	**3538**		**100.0 %**	**1.99 [1.74, 2.28]**
Total events: 597 (Intervention), 284 (Control)					
Heterogeneity: Chi?? = 25.78, df = 22 (P = 0.26); I?? =15%					
Test for overall effect: Z = 10.11 (P < 0.00001)					
2 Moderate take-up of treatment					
Binnie 2007	3/59	2/57		1.5 %	1.45 [0.25, 8.35]
Chouinard 2005	13/53	7/55		5.0 %	1.93 [0.83, 4.45]
Duffy 2006	15/48	6/41		4.8 %	2.14 [0.91, 5.00]
Emmons 2005	58/386	36/398		26.0 %	1.66 [1.12, 2.46]
Hall 2006	30/163	21/159		15.6 %	1.39 [0.83, 2.33]
Juarranz Sanz 1998	37/102	4/103		2.9 %	9.34 [3.45, 25.25]
Lewis 1998	6/62	3/61		2.2 %	1.97 [0.52, 7.52]
Ratner 2004	10/111	11/117		7.9 %	0.96 [0.42, 2.17]
Rodriguez 2003	23/114	9/103		6.9 %	2.31 [1.12, 4.76]
Simon 1997	20/157	9/142		6.9 %	2.01 [0.95, 4.27]
Vial 2002	9/42	1/22		1.0 %	4.71 [0.64, 34.85]
Wilson 1988	53/606	26/601		19.2 %	2.02 [1.28, 3.19]
Subtotal (95% CI)	**1903**	**1859**		**100.0 %**	**2.00 [1.64, 2.43]**
Total events: 277 (Intervention), 135 (Control)					
Heterogeneity: Chi?? = 16.11, df = 11 (P = 0.14); I?? =32%					

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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 6.93 (P < 0.00001)					
3 Low take-up of treatment					
Katz 2004	71/642	20/499		16.9 %	2.76 [1.70, 4.47]
Reid 2003	49/126	46/128		34.3 %	1.08 [0.79, 1.49]
Schauffler 2001	91/601	65/603		48.8 %	1.40 [1.04, 1.89]
Subtotal (95% CI)	**1369**	**1230**		**100.0 %**	**1.52 [1.25, 1.86]**
Total events: 211 (Intervention), 131 (Control)					
Heterogeneity: Chi?? = 10.55, df = 2 (P = 0.01); I?? =81%					
Test for overall effect: Z = 4.13 (P = 0.000037)					
Test for subgroup differences: Chi?? = 5.32, df = 2 (P = 0.07), I?? =62%					

Analysis 8.1. Comparison 8 Subgroup by treatment take-up, specialist support only, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 8 Subgroup by treatment take-up, specialist support only

Outcome: 1 Cessation at longest follow-up

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 High take-up of treatment					
An 2006	53/417	17/414		6.9 %	3.10 [1.82, 5.25]
Baker 2006	5/147	1/151		0.4 %	5.14 [0.61, 43.44]
Brandstein 2011	6/64	4/62		1.6 %	1.45 [0.43, 4.90]
Chan 2010	57/501	12/218		6.7 %	2.07 [1.13, 3.77]
Cooney 2007	4/55	1/63		0.4 %	4.58 [0.53, 39.78]
Hall 2002	15/72	4/37		2.1 %	1.93 [0.69, 5.39]
Hollis 2007	153/721	102/872		37.2 %	1.81 [1.44, 2.28]

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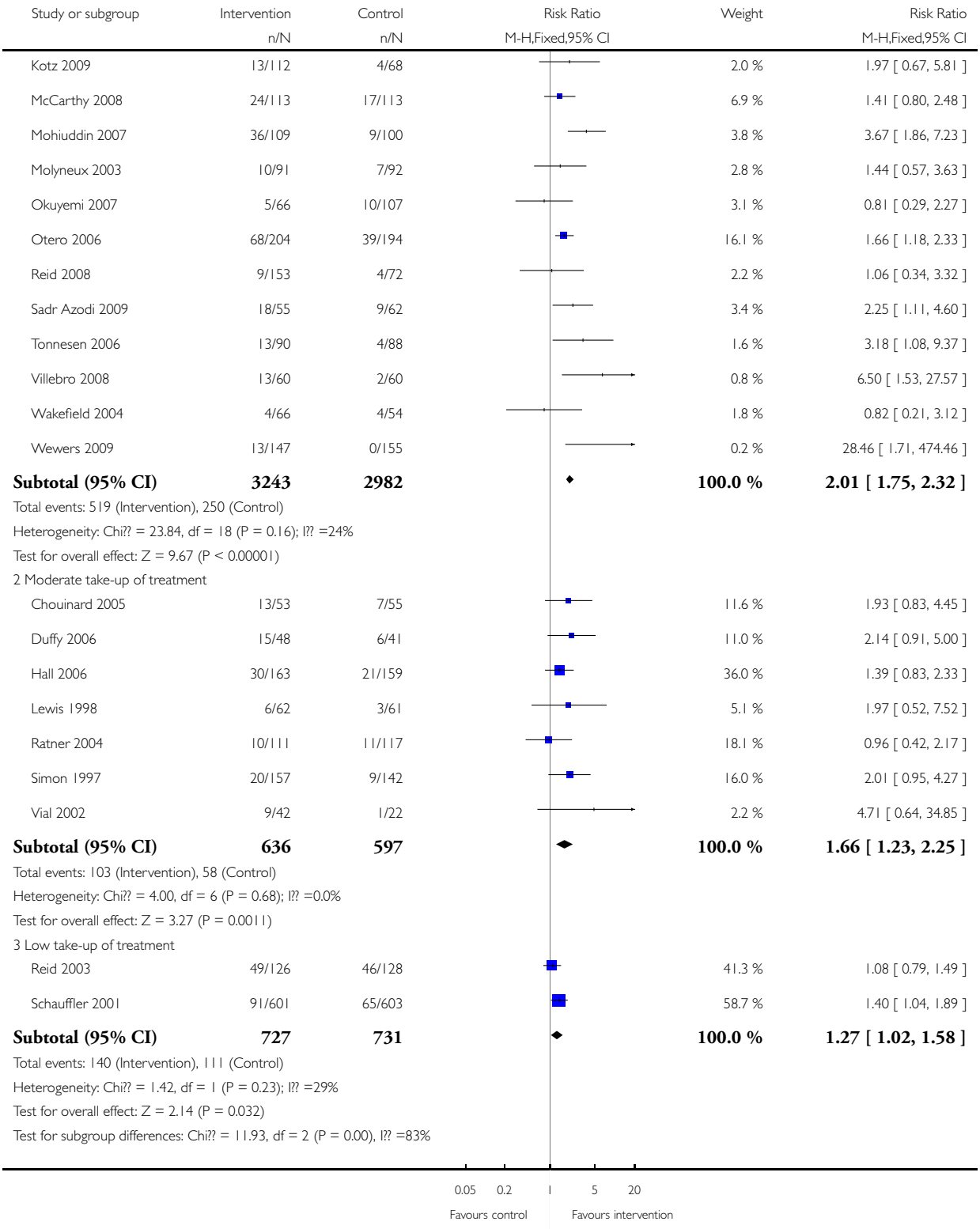
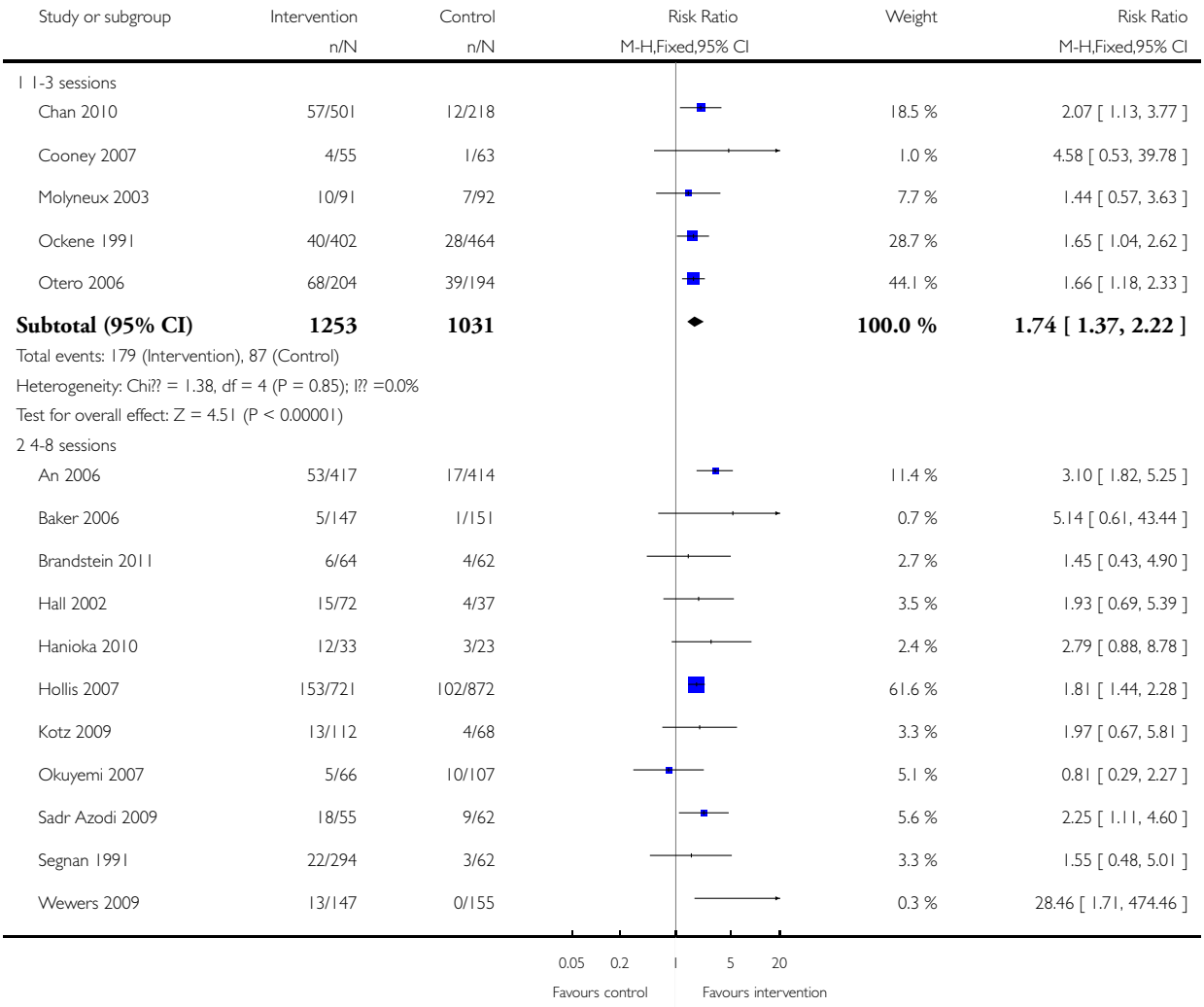


Analysis 9.1. Comparison 9 Subgroup by number of sessions, high take-up only, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 9 Subgroup by number of sessions, high take-up only

Outcome: 1 Cessation at longest follow-up



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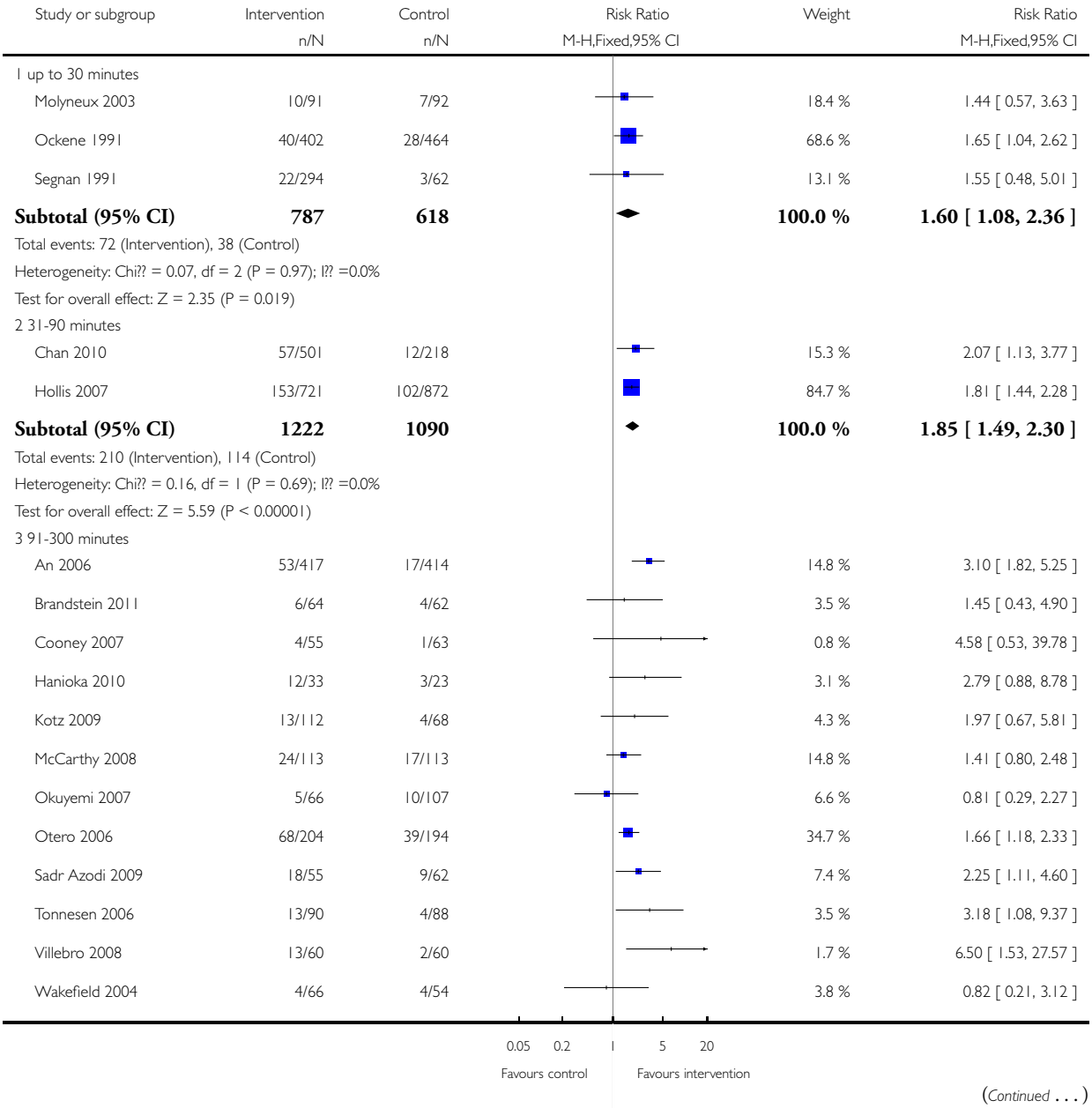
Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**2128**	**2013**	◆	**100.0 %**	**2.06 [1.71, 2.47]**
Total events: 315 (Intervention), 157 (Control)					
Heterogeneity: Chi?? = 11.53, df = 10 (P = 0.32); I?? =13%					
Test for overall effect: Z = 7.76 (P < 0.00001)					
3 Over 8 sessions					
McCarthy 2008	24/113	17/113		39.7 %	1.41 [0.80, 2.48]
Mohiuddin 2007	36/109	9/100		21.9 %	3.67 [1.86, 7.23]
Reid 2008	9/153	4/72		12.7 %	1.06 [0.34, 3.32]
Tonnesen 2006	13/90	4/88		9.5 %	3.18 [1.08, 9.37]
Villebro 2008	13/60	2/60		4.7 %	6.50 [1.53, 27.57]
Wakefield 2004	4/66	4/54		10.3 %	0.82 [0.21, 3.12]
Wewers 2000	4/8	0/7		1.2 %	8.00 [0.51, 126.67]
Subtotal (95% CI)	**599**	**494**	◆	**100.0 %**	**2.29 [1.63, 3.21]**
Total events: 103 (Intervention), 40 (Control)					
Heterogeneity: Chi?? = 11.84, df = 6 (P = 0.07); I?? =49%					
Test for overall effect: Z = 4.79 (P < 0.00001)					
Test for subgroup differences: Chi?? = 1.91, df = 2 (P = 0.38), I?? =0.0%					

Analysis 10.1. Comparison 10 Subgroup by duration of contact, high take-up only, Outcome 1 Cessation at longest follow-up.

Review: Combined pharmacotherapy and behavioural interventions for smoking cessation

Comparison: 10 Subgroup by duration of contact, high take-up only

Outcome: 1 Cessation at longest follow-up



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Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wewers 2000	4/8	0/7		0.5 %	8.00 [0.51, 126.67]
Wewers 2009	13/147	0/155		0.4 %	28.46 [1.71, 474.46]
Subtotal (95% CI)	**1490**	**1470**		**100.0 %**	**2.14 [1.74, 2.62]**
Total events: 250 (Intervention), 114 (Control)					
Heterogeneity: Chi?? = 19.49, df = 13 (P = 0.11); I?? =33%					
Test for overall effect: Z = 7.24 (P < 0.00001)					
4 Over 300 minutes					
Baker 2006	5/147	1/151		4.7 %	5.14 [0.61, 43.44]
Hall 2002	15/72	4/37		25.0 %	1.93 [0.69, 5.39]
Mohiuddin 2007	36/109	9/100		44.5 %	3.67 [1.86, 7.23]
Reid 2008	9/153	4/72		25.8 %	1.06 [0.34, 3.32]
Subtotal (95% CI)	**481**	**360**		**100.0 %**	**2.63 [1.63, 4.25]**
Total events: 65 (Intervention), 18 (Control)					
Heterogeneity: Chi?? = 4.08, df = 3 (P = 0.25); I?? =27%					
Test for overall effect: Z = 3.95 (P = 0.000079)					
Test for subgroup differences: Chi?? = 3.37, df = 3 (P = 0.34), I?? =11%					

APPENDICES

Appendix 1. Register Search

Version of the search used in the Cochrane Register of Studies:
1 NRT:TI,AB,KW 679
2 (nicotine NEAR (replacement OR patch* OR transdermal OR gum OR lozenge* OR sublingual OR inhaler* OR inhalator* OR oral OR nasal OR spray)):TI,AB,KW 1796
3 (Bupropion OR zyban OR wellbutrin):TI,AB,KW,MH,EMT 546
4 (varenicline OR champix OR chantix):TI,AB,KW,MH,EMT 278
5 combined modality therapy:MH,KW 213
6 ((behavio?r therapy) AND (drug therapy)):KW,MH,EMT,TI,AB 62
7 ((counsel*) AND (*drug therapy)):KW,MH,EMT,TI,AB 185
8 #1 OR #2 OR #3 OR #4 OR #5 2454
9 #6 OR #7 OR #8 2509
10 #9 AND INREGISTER 2200

Appendix 2. Summary of included study characteristics

Study	Recruitment setting/ Provider	Selected for motivation to quit	Sessions/ Duration	Take-up
An 2006	Veterans Administration medical centres/ Cessation specialist (telephone counsellor)	Selected	4-8 / 91-300 mins	High
Baker 2006	Community Health Agencies/ Cessation specialist	Selected	4-8 / >300 mins	High
Binnie 2007	Periodontology clinic/ Dental Hygienist (UC)	Not selected	4-8 / 31-90 mins	Moderate
Brandstein 2011	Hospital inpatients/ Cessation specialist (telephone counsellor)	Not explicit	4-8 / 91-300 mins	High
Chan 2010	Clinic patients and volunteers/ Cessation specialist	Selected	1-3 / 31-90 mins	High
Chouinard 2005	Hospital inpatients/ Cessation specialist (reseach nurse)	Not selected	4-8 / 91-300 mins	Moderate
Cooney 2007	Substance abuse programmes/ Cessation specialist	Selected	1-3 / 91-300 mins	High
Duffy 2006	ENT clinic cancer patients/ Cessation specialist	Not selected	>8 / 91-300 mins	Moderate
Emmons 2005	Childhood cancer survivors study/ Peer counsellor	Not selected	4-8 / 31-90 mins	Moderate
Hall 2002	Community/ Cessation specialist	Selected	4-8 />300 mins	High
Hall 2006	Mental health clinics/ Cessation specialist	Not selected	4-8 / 91-300 mins	Moderate
Hanioka 2010	Dental clinics/ Dentists and dental hy-	Selected	4-8 / 91-300 mins	High

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	gienists (UC)			
Hollis 2007	Community/ Cessation specialist (telephone counsellor)	Selected	4-8 / 31-90 mins	High
Juarranz Sanz 1998	Primary Care Clinic/ General practitioner (UC)	Not explicit	4-8 / 31-90 mins	Moderate
Katz 2004	Primary Care Clinic/ UC (low take-up of specialist referral)	Not selected	1-3 / 31-90	Low
Kotz 2009	Community/ Cessation specialist (respiratory nurse)	Selected	4-8 / 91-300 mins	High
Lewis 1998	Hospital inpatients/ Cessation specialist (research nurse)	Selected	4-8 / 31-90 mins	Moderate
Lung Health Study	Community/ Cessation specialist	Not selected	>8 / >300	High
McCarthy 2008	Community/ Cessation specialist	Selected	>8 / 91-300	High
Mohiuddin 2007	Hospital inpatients/ Cessation specialist	Not explicit	>8 / >300	High
Molyneux 2003	Hospital inpatients/ Cessation specialist	Not explicit	1-3 / up to 30 mins	High
Ockene 1991	Primary Care Clinic/ Physician resident (UC)	Not selected	1-3 / up to 30 mins	High
Okuyemi 2007	Community/ Cessation specialist	Not explicit	4-8 / 91-300 mins	High
Otero 2006	Community/ Cessation specialist	Selected	1-3 / 91-300	High
Ratner 2004	Preadmission clinic/ Specialist (Trained nurse)	Not selected	>8 / 91-300	Moderate
Reid 2003	Hospital inpatients/ Specialist (nurse counsel-	Selected	4-8 / 31-90 mins	Low

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	lor)			
Reid 2008	Drug & alcohol dependence treatment/ Cessation specialist	Selected	>8 / >300 mins	High
Rodriguez 2003	Worksite occupation health/ Occupational physician (UC)	Selected	4-8 / up to 30 mins	Moderate
Sadr Azodi 2009	Presurgical clinics/ Cessation specialist	Not explicit	4-8 / 91-300 mins	High
Schauffler 2001	Community/ Cessation specialist	Not selected	4-8 / >300 mins	Low
Segnan 1991	Primary Care Clinics/ GP (UC)	Not selected	4-8 / up to 30 mins	High
Simon 1997	Hospital inpatients/ Cessation specialist	Selected	4-8 / 91-300 mins	Moderate
Thomsen 2010	Surgical clinics/ Cessation specialist	Not selected	1-3 / 31-90 mins	Unclear
Tonnesen 2006	Outpatient chest clinic/ Specialist (trained nurse)	Selected	>8 / 91-300 mins	High
Velicer 2006	Community/ Expert system, no provider	Not selected	No personal contact	N/A
Vial 2002	Hospital inpatients/ Specialist (Pharmacist)	Selected	>8 / >300 mins	Moderate
Villebro 2008	Presurgical clinic/ Specialist (trial nurse)	Not explicit	>8 / 91-300 mins	High
Wakefield 2004	Cancer treatment units/ Specialist (trial co-ordinator)	Not explicit	>8 / 91-300 mins	High
Wewers 2000	AIDS clinical trial unit/ Peer counsellor	Selected	>8 / 91-300 mins	High
Wewers 2009	Primary Care Clinics/ Lay health adviser	Not explicit	4-8 / 91-300 mins	High

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Wilson 1988	Primary Care Clinics/ Family physician (UC)	Not selected	4-8 / 31-90 mins	Moderate

HISTORY

Protocol first published: Issue 1, 2010

Review first published: Issue 10, 2012

CONTRIBUTIONS OF AUTHORS

LS & TL jointly conceived the review and wrote the protocol. LS designed the search strategy and prescreened results. Both authors agreed on the inclusion of studies. The authors jointly drafted the text and are responsible for the analyses and conclusions.

DECLARATIONS OF INTEREST

No conflicts of interest to report.

SOURCES OF SUPPORT

Internal sources

- Department of Primary Care Health Sciences, University of Oxford, UK.

External sources

- NHS, National Institute of Health Research, UK.
- National School for Health Research, School for Primary Care Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A second planned objective of the review was to evaluate the effect of increasing behavioural support for people using pharmacotherapy. This will now be addressed in a companion review (Stead 2012).

The categories used for some subgroup analyses were altered: we distinguished between no person-to-person contact and between one and three sessions rather than using the US Guideline categories of zero to one and two to three, and collapsed one to three minutes and 4 to 30 minutes for contact time. We added categories of peer group counsellor and lay counsellor to provider type, and we added a category of studies that did not explicitly select for motivation but where study procedures or participant characteristics suggested that participants were typically motivated to quit.

We did not use a brief/moderate/intensive subgroup analysis because it did not help discriminate between studies.