Cochrane Library

**Cochrane** Database of Systematic Reviews

# Interventions to increase adherence to medications for tobacco dependence (Review)

Hollands GJ, McDermott MS, Lindson-Hawley N, Vogt F, Farley A, Aveyard P

Hollands GJ, McDermott MS, Lindson-Hawley N, Vogt F, Farley A, Aveyard P.
Interventions to increase adherence to medications for tobacco dependence.
*Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD009164.
DOI: 10.1002/14651858.CD009164.pub2.

**www.cochranelibrary.com**


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

## TABLE OF CONTENTS





Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

[Intervention Review]

# Interventions to increase adherence to medications for tobacco dependence

Gareth J Hollands[1], Máirtín S McDermott[2], Nicola Lindson-Hawley[3], Florian Vogt[4], Amanda Farley[5], Paul Aveyard[6]

[1]Behaviour and Health Research Unit, University of Cambridge, Cambridge, UK. [2]School of Information Systems and Technology, University of Wollongong, Wollongong, Australia. [3]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK. [4]Institute of Pharmaceutical Science, King's College London, London, UK. [5]Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, UK. [6]Nuffield Department of Primary Care Health Sciences, Oxford University, Oxford, UK

Contact address: Gareth J Hollands, Behaviour and Health Research Unit, University of Cambridge, Forvie Site, Robinson Way, Cambridge, CB2 0SR, UK. gareth.hollands@medschl.cam.ac.uk.

**Editorial group:** Cochrane Tobacco Addiction Group.
**Publication status and date:** New, published in Issue 2, 2015.
**Review content assessed as up-to-date:** 25 October 2014.

**Citation:** Hollands GJ, McDermott MS, Lindson-Hawley N, Vogt F, Farley A, Aveyard P. Interventions to increase adherence to medications for tobacco dependence. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No.: CD009164. DOI: 10.1002/14651858.CD009164.pub2.

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## ABSTRACT

### Background

Pharmacological treatments for tobacco dependence, such as nicotine replacement therapy (NRT), have been shown to be safe and effective interventions for smoking cessation. Higher levels of adherence to these medications increase the likelihood of sustained smoking cessation, but many smokers use them at a lower dose and for less time than is optimal. It is therefore important to determine the effectiveness of interventions designed specifically to increase medication adherence. Such interventions may include further educating individuals about the value of taking medications and providing additional support to overcome problems with maintaining adherence.

### Objectives

The primary objective of this review was to assess the effectiveness of interventions to increase adherence to medications for smoking cessation, such as NRT, bupropion, nortriptyline and varenicline (and combination regimens). This was considered in comparison to a control group, typically representing standard care. Secondary objectives were to i) assess which intervention approaches are most effective; ii) determine the impact of interventions on potential precursors of adherence, such as understanding of the treatment and efficacy perceptions; and iii) evaluate key outcomes influenced by prior adherence, principally smoking cessation.

### Search methods

We searched the following databases using keywords and medical subject headings: Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*), MEDLINE (OVID SP) (1946 to July Week 3 2014), EMBASE (OVID SP) (1980 to Week 29 2014), and PsycINFO (OVID SP) (1806 to July Week 4 2014). The Cochrane Tobacco Addiction Group Specialized Register was searched on 9th July 2014. We conducted forward and backward citation searches.

### Selection criteria

Randomised, cluster-randomised or quasi-randomised studies in which participants using active pharmacological treatment for smoking cessation are allocated to an intervention arm or a control arm. Eligible participants were adult (18+) smokers. Eligible interventions


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

comprised any intervention that differed from standard care, and where the intervention content had a clear principal focus on increasing adherence to medications for tobacco dependence. Acceptable comparison groups were those that provided standard care, which depending on setting may comprise minimal support or varying degrees of behavioural support. Included studies used a measure of adherence behaviour that allowed some assessment of the degree of adherence.

**Data collection and analysis**

Two review authors searched for studies and independently extracted data for included studies. Risk of bias was assessed according to the Cochrane Handbook guidance. For continuous outcome measures, we report effect sizes as standardised mean differences (SMDs). For dichotomous outcome measures, we report effect sizes as relative risks (RRs). We obtained pooled effect sizes with 95% confidence intervals (CIs) using the fixed effects model.

**Main results**

Our search strategy retrieved 3165 unique references and we identified 31 studies as potentially eligible for inclusion. Of these, 23 studies were excluded at full-text screening stage or identified as studies awaiting classification subject to further information. We included eight studies involving 3336 randomised participants. The interventions were all additional to standard behavioural support and typically provided further information on the rationale for, and emphasised the importance of, adherence to medication, and supported the development of strategies to overcome problems with maintaining adherence.

Five studies reported on whether or not participants achieved a specified satisfactory level of adherence to medication. There was evidence that adherence interventions led to modest improvements in adherence, with a relative risk (RR) of 1.14 (95% CI, 1.02 to 1.28, P = 0.02, n = 1630). Four studies reported continuous measures of adherence to medication. Although the standardised mean difference (SMD) favoured adherence interventions, the effect was small and not statistically significant (SMD 0.07, 95% CI, -0.03 to 0.17, n = 1529). Applying the GRADE system, the quality of evidence for these results was assessed as moderate and low, respectively.

There was evidence that adherence interventions led to modest improvements in rates of cessation. The relative risk for achieving abstinence was similar to that for improved adherence. It was not significant in meta-analysis of four studies providing short-term abstinence: RR = 1.07 (95% CI 0.95 to 1.21, n = 1755), but there was statistically significant evidence of improved abstinence at six months or more from a different set of four studies: RR = 1.16 (95% CI, 1.01 to 1.34, P = 0.03, n = 3049). Applying the GRADE system, the quality of evidence for these results was assessed as low for both.

As interventions were similar in nature and the number of studies was low, it was not possible to investigate whether different types of intervention approaches were more effective than others. Relevant outcomes other than adherence or cessation were not reported.

There was no evidence that interventions to increase adherence to medication led to any adverse events. All included studies were assessed as at high or unclear risk of bias. This was often due to a lack of clarity in reporting - meaning assessments were unclear - rather than clear evidence of failing to sufficiently safeguard against the risk of bias.

**Authors' conclusions**

There is some evidence that interventions that devote special attention to improving adherence to smoking cessation medication through providing information and facilitating problem-solving can improve adherence, though the evidence for this is not strong and is limited in both quality and quantity. There is some evidence that such interventions improve the chances of achieving abstinence but again the evidence for this is relatively weak.

## PLAIN LANGUAGE SUMMARY

**Can we increase adherence to medications that help smokers to quit?**

Medications that help people to stop smoking such as nicotine replacement therapy (NRT) are safe and effective treatments for smoking cessation. However, people often do not take the medication they are prescribed as they should. In the current review, we examined whether there are effective approaches to increasing adherence to these treatments, which should improve smokers' chances of quitting. These approaches, or interventions, typically involve providing additional information about the medication and helping people to overcome any problems they have in taking it as prescribed.

A systematic search located eight studies of interventions to improve adherence, involving 3336 participants. Five studies assessed whether or not participants achieved a specified satisfactory level of medication taking, with statistical combination of the results


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

suggesting that the interventions led to modest improvements. Four studies assessed how much medication was taken, finding a small effect that may be due to chance. There was also some evidence that interventions to increase adherence to medication led to modest improvements in quitting smoking. The evidence that was included in the review was considered to be of low-to-moderate quality, suggesting that further research is necessary if we want to increase our confidence in these results.

In summary, there is some evidence that interventions that devote special attention to improving adherence to smoking cessation medication can increase this, though the evidence is not strong and is limited in both quality and quantity. There is also some evidence that these approaches improve the chances of quitting smoking but again this is relatively weak.


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

**Interventions to increase adherence compared to standard care for improving adherence to medications for tobacco dependence and abstinence from smoking**

**Patient or population: Adult smokers**
**Settings: Typically in-person clinical settings**
**Intervention: Interventions to increase adherence through providing information and facilitating problem-solving**
**Comparison: Standard care**

| Outcomes | Relative effect (95% CI) | Illustrative comparative risks (95% CI) | | No of Participants (studies) | Quality of the evidence (GRADE) |
|---|---|---|---|---|---|
| | | Assumed risk | Corresponding risk | | |
| | | Standard care | Interventions to increase adherence | | |
| Adherence to medications for tobacco dependence (dichotomous outcomes) | RR 1.14 (1.02 to 1.28) | Study population | | 1630 (5 RCTs) | ⊕⊕⊕◯ MODERATE [1] |
| | | 368 per 1000 achieve a specified satisfactory level of adherence | 419 per 1000 (375 to 471) achieve a specified satisfactory level of adherence | | |
| Adherence to medications for tobacco dependence (continuous outcomes) | SMD 0.07 (-0.03 to 0.17) | The mean level of adherence is 0 | The mean level of adherence is 0.07 standard deviations higher (0.03 lower to 0.17 higher) | 1529 (4 RCTs) | ⊕⊕◯◯ LOW [1,2] |
| Short-term abstinence from smoking (<6 months) | RR 1.07 (0.95 to 1.21) | Study population | | 1755 (4 RCTs) | ⊕⊕◯◯ LOW [1,3] |
| | | 363 per 1000 achieve abstinence | 389 per 1000 (345 to 439) achieve abstinence | | |
| Long-term abstinence from smoking (≥6 months) | RR 1.16 (1.01 to 1.34) | Study population | | 3049 (4 RCTs) | ⊕⊕◯◯ LOW [1,4] |
| | | 171 per 1000 achieve abstinence | 198 per 1000 (173 to 229) achieve abstinence | | |

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;

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]All studies are judged to be at high or unclear risk of bias which lowers confidence in estimate of effect
[2]Includes sufficient sample size for single adequately powered trial but 95% CI overlaps no effect and ranges from very small harm to small benefit
[3]Includes sufficient sample size for single adequately powered trial but 95% CI overlaps no effect and ranges from small harm to substantial benefit
[4]Substantial heterogeneity with inconsistency in point estimates and limited overlap of confidence intervals


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

# BACKGROUND

## Description of the condition

Smoking is the single largest preventable cause of disease and premature death worldwide, being a key causal factor in heart disease, stroke, chronic lung disease and cancers. Pharmacological treatments for tobacco dependence such as nicotine replacement therapy (NRT) are widely considered to be safe and effective interventions for smoking cessation. A systematic review found that participants using NRT were over 1.5 times more likely to achieve abstinence (Stead 2012a). Participants using bupropion, nortriptyline and varenicline are also more likely to stop smoking than those using placebo (Hughes 2014; Cahill 2012).

There is observational evidence that people who adhere to medication to a greater extent are more likely to achieve abstinence. One problem with interpreting such evidence is that people whose quit attempt is faltering may also choose not to adhere to their medication. However, even studies that control for this reverse causation still suggest that prior adherence promotes later abstinence (Shiffman 2007; Shiffman 2008; Hollands 2013). A recent review of this relationship, although highlighting the lack of high quality studies, suggests that the degree of adherence predicts subsequent abstinence (Raupach 2014). Observational evidence can, however, never prove causality. Trials that show that interventions to improve adherence also improve the rate of abstinence are stronger evidence for causality in this respect.

Studies show that many smokers who use medications for tobacco dependence do so at a lower dose and for less time than the evidence suggests is optimal (Shiffman 2008; Cheong 2010; Hays 2010; Swan 2010). For example, Burns and Levinson (Burns 2008) report that users of NRT, on average, continue medication for less than half the time for which it is prescribed. These findings provide another reason why assessing the effectiveness of interventions to improve adherence is important.

## Description of the intervention

Interventions that specifically aim to increase adherence to prescribed medications vary widely in their content and characteristics (Haynes 2008). Examples may include, but are not limited to, improved or increased information provision, monitoring and feedback concerning performance, reminders, and psychological therapy or counselling (see Appendix 1 for more details). In the specific context of medications for tobacco dependence, general behavioural support for smoking cessation may include components that target increasing medication adherence. Interventions that are additional to standard behavioural support and that devote special attention to improving adherence may also be delivered. Such interventions may include further educating individuals about the value of taking medications and providing additional support to overcome problems with maintaining adherence.

## Why it is important to do this review

As far as we are aware, no published systematic reviews address this question. Reviews of studies of behavioural support interventions (such as Lancaster 2008; Stead 2005; Stead 2012b), which may include elements that target medication adherence, are not designed to disentangle the specific effects of those components that focus on increasing adherence. Previous reviews of interventions designed to increase adherence have focused on specific patient groups or treatment contexts, or have not covered smoking cessation treatments (Nieuwlaat 2014). A specific review of the topic is valuable because we cannot be certain that findings relating to adherence to other medications are generalisable to smoking cessation medications, as these provide a unique treatment context with specific compliance issues. For example, smoking cessation treatment is relatively short term and its use dictated by a specific behaviour (if an individual resumes smoking, medication use typically ends) rather than an illness. Additionally, the drawbacks of failing to adhere are less significant than they may be in the treatment of illness. For example, individuals may successfully quit smoking without adhering to therapy, or if they fail to adhere and continue to smoke, they may not feel that they have lost anything or experienced any adverse effects. Finally, there is evidence to suggest that it may be more difficult to persuade individuals of the benefits of using smoking cessation medications compared with other health conditions. Hammond and colleagues (Hammond 2004) found that over a third of smokers reported that use of pharmacotherapies (NRT or bupropion) would either make no difference or actually reduce the likelihood of quitting smoking. Smokers who perceived cessation assistance methods to be beneficial were more likely to use medication in the future. Some users may perceive risks of harm to their health from the medication that outweigh the potential benefits.

# OBJECTIVES

The primary objective of the review was to assess the effectiveness of interventions aiming to increase adherence to medications for smoking cessation, such as NRT, bupropion, nortriptyline and varenicline (and combination regimens). This was considered in comparison to a control group, typically representing standard care. Secondary objectives were to i) assess which intervention approaches are most effective; ii) determine the impact of interventions on potential precursors of adherence, such as understanding of the treatment and efficacy perceptions; and iii) evaluate key outcomes influenced by prior adherence, principally smoking cessation.

# METHODS


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Criteria for considering studies for this review

### Types of studies

Randomised, cluster-randomised or quasi-randomised studies in which participants using active pharmacological treatment for smoking cessation were allocated to an intervention arm or a control arm. Pharmacological treatments comprised those that are prescribed to increase cessation rates (e.g. NRT, bupropion, nortriptyline, varenicline and combination regimens).

### Types of participants

Adult individuals (18 years and over) defined as smokers at point of entry into the trial.

### Types of interventions

Interventions to increase adherence may vary significantly in their nature, with a workable taxonomy provided in a previous Cochrane review (Haynes 2008). This taxonomy is provided in Appendix 1. The nature of the interventions considered in the current review was not specified beyond reference to exclusion criteria.

Eligible interventions comprised any intervention that differed from standard care administered to smokers, and where the differing intervention content had a clear principal focus on increasing adherence to medications for tobacco dependence, reflected in described content and stated aims. We did not include interventions that systematically alter the active pharmacological characteristics of a given medication, such as dose strength, length of treatment or means of delivery. Interventions that include the use of financial incentives were not eligible. Acceptable comparison groups were those that provided standard or usual care. Depending on setting, this can comprise minimal support or varying degrees of behavioural support.

### Types of outcome measures

To be considered for inclusion, studies must have used a measure of adherence behaviour allowing some assessment of the degree of adherence. This was defined as a continuous measure - such as the amount of medication consumed over a given treatment period - or as a dichotomous outcome, indicating whether the treatment is being used to a specified degree (e.g. adherence for *x* number of days, or *x* amount of medication consumed). This is in contrast to a single binary measure without nuance (i.e. any amount of medication at any time vs. non-use), which was not considered an appropriate measure.

Adherence could be measured by means of a behavioural endpoint using an electronic measure, pill counts by a third party, or through a self-report or questionnaire measure (or combinations thereof).

#### Primary outcomes

Primary outcome:

- Adherence to medication for tobacco dependence

Where treatment periods were assessed at multiple timepoints, the longest timepoint reported was used. Where multiple measures of adherence were reported, we have used the most stringent measure that is available.

#### Secondary outcomes

- Abstinence from smoking measured near or at a time point relevant to the measure of adherence

Where multiple measures of abstinence were reported, we used the most stringent. If there were data from multiple timepoints, we report data measured near or at a timepoint relevant to the measure of adherence. In addition, we also report abstinence at the longest available timepoint should that differ, in order to assess the long-term benefit of the intervention on cessation rates.

- Factors plausibly associated with increases in adherence such as, but not limited to:

- intention or motivation to change health behaviour
- attitudes towards treatment, or understanding of the treatment

- Adverse events

Any adverse events or harms reported in included trials were noted, including clinical levels of depression or anxiety.

## Search methods for identification of studies

### Electronic searches

We searched the following databases on 25th July 2014:

- Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*),
- MEDLINE (OVID SP) (1946 to July Week 3 2014),
- EMBASE (OVID SP) (1980 to Week 29 2014),
- PsycINFO (OVID SP) (1806 to July Week 4 2014).

In addition, the Cochrane Tobacco Addiction Group Specialized Register was searched on 9th July 2014. The search strategies were developed to comprise searches both for keywords and medical subject headings under existing database organisational schemes. Those used are presented in Appendix 2.

We searched databases in the metaRegister of Controlled Trials to identify ongoing studies. Ongoing studies are presented in 'Characteristics of ongoing studies'. We also searched published Cochrane reviews of behavioural support for smoking cessation (Lancaster 2008, Stead 2005, Stead 2012b) for relevant studies.


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Searching other resources

We conducted forwards and backwards citation searches from included studies. We did not handsearch journals.

## Data collection and analysis

### Selection of studies

Two review authors independently screened all search results (titles and abstracts) for possible inclusion, and those selected by either or both authors were subject to full-text assessment. Two review authors independently assessed the selected articles for inclusion. Any discrepancies were resolved by consensus, overseen by a third review author acting as arbiter as necessary. We list excluded studies after full-text assessment in the table 'Characteristics of Excluded Studies', giving reasons for exclusion.

### Data extraction and management

We developed a data extraction form, which was piloted and amended as necessary. We extracted the following main sets of data from each included study:

- lead author;
- date;
- study participant inclusion criteria;
- participants (participant condition(s) and demographics: race/ethnicity, gender, religion/culture, socioeconomic status, age);
- study design and timetable; randomisation; allocation concealment;
- interventions (content and format of interventions, including details of information provided; intervention setting and delivery provider; delivery of any co-interventions, theoretical basis of intervention if stated);
- numbers of participants in each trial arm;
- outcome measures; time(s) at which outcomes assessed;
- results;
- balance of baseline characteristics;
- analysis;
- additional comments.

Two review authors independently extracted data. Data extraction was checked by a third review author and any errors or inconsistencies resolved. The first review author entered the data into RevMan, with another review author checking the accuracy of the data entry.

### Assessment of risk of bias in included studies

We assessed and report on the risk of bias of included studies by outcome, in accordance with the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We report on the following individual domains:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias) (assessed for each main outcome or class of outcome);
- incomplete outcome data (attrition bias) (assessed for each main outcome or class of outcome);
- selective reporting (reporting bias);
- other sources of bias (validity and reliability of outcome measures; comparability of baseline characteristics; consistency in intervention delivery (i.e. was the information standardised/scripted; was fidelity to protocol monitored)).

Two review authors independently assessed the risk of bias in included studies, with any disagreements resolved by discussion and consensus, and with a third review author acting as arbiter as necessary. We present our assessment in Risk of Bias tables for each included study.

A summary risk of bias judgement was derived for each study from those domains judged to be most critical in this intervention context, informed by criteria outlined in another recent Cochrane review of interventions to increase adherence to medications (Nieuwlaat 2014) and additionally including assessment of incomplete outcome data. These key domains were as follows: random sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data and validity and reliability of outcome measures. We applied an algorithm suggested in Section 8.7 (Table 8.7a) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Specifically, if the judgement in at least one of these domains was 'high risk of bias' then summary risk of bias was determined to be high. If no judgements of 'high' risk were made, but the judgement in at least one domain was 'unclear risk of bias' then the summary risk of bias was determined to be unclear. Summary risk of bias was only judged 'low' if judgements in all domains were 'low risk of bias'.

The GRADE system was used to assess the quality of the evidence for the primary and secondary outcomes across studies and a Summary of Findings table produced (Higgins 2011).

### Measures of treatment effect

For continuous outcomes where the precise nature of the measures used differ but the outcomes were regarded as comparable, they were integrated and standardised to have common effect sizes, defined as the standardised mean difference (SMD). The effect measure for comparable dichotomous outcomes is the risk ratio (RR). We obtained a pooled effect size with 95% confidence interval (CI) using the fixed-effects model, in line with our protocol. We do, however, also report effects using the random-effects model due to observed clinical heterogeneity in study characteristics.


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Unit of analysis issues

There were no cluster-randomised trials included and no unit of analysis errors were observed.

### Dealing with missing data

We suggest elsewhere (Hollands 2013) that, in the context of smoking cessation medications, it would be informative for measures of adherence to include only those participants who continue a quit attempt and not all those allocated to receive a given intervention. Including those people who abandon a quit attempt is less appropriate because first, treatment such as NRT is not indicated when a person has ceased trying to quit smoking, and second, it potentially confounds adherence with initial uptake (which may be influenced by different factors). As such, we are most interested in adherence to medication in those individuals who continue to engage with a treatment programme and do not drop out from the intervention and hence invariably remain in the study. We therefore intended to analyse data for our primary outcome in this way where available. In practice, primary outcomes for included studies were more often presented as intention-to-treat, with three exceptions where it was clear that adherence was assessed for only those who remained engaged with treatment or at least with the study (Mooney 2005; Nollen 2011; Smith 2013). We conducted a sensitivity analysis to examine if this affected the results for the primary adherence outcome, providing this was not prevented by missing data or continuous outcome data (for which imputation is problematic). Results were not found to be affected by these three studies not using ITT data. For smoking cessation outcomes, ITT data were provided in all cases, with a conservative approach being taken that assumed that drop-out implies abstinence was not achieved.

### Assessment of heterogeneity

We tested for heterogeneity by inspecting overlapping confidence intervals and further quantified this using the $I^2$ statistic (which describes the percentage of the variability in effect estimates due to heterogeneity rather than sampling error). A value greater than 50% was considered to represent substantial heterogeneity (Higgins 2011).

### Assessment of reporting biases

We did not assess likelihood of publication bias using funnel plots (Sutton 2000) as there were insufficient studies to do so.

### Data synthesis

We conducted a narrative synthesis of the included studies, presenting studies' major characteristics and results. If studies were sufficiently similar in terms of setting, population, interventions and outcomes (including the time(s) at which these are assessed), we pooled the data statistically. In line with our protocol, a fixed-effects model for meta-analysis was selected to obtain a pooled effect size with 95% CIs, as we grouped substantially similar studies. We do, however, also report effects using the random-effects model due to observed clinical heterogeneity in study characteristics, such as differences in the outcome measures used.
Mantel-Haenszel meta-analytic methods (Mantel 1959) were used for analysis of dichotomous outcomes. These are the default methods in the Review Manager software, and are considered the most appropriate when data are sparse, either in terms of event rates being low or study size being small (Higgins 2011). In such cases, the estimates of the standard errors of the effect that are used in inverse variance methods may be poor. Inverse variance methods were used for analysis of continuous outcomes and as the measures varied between studies, we used standardised mean differences.

### Subgroup analysis and investigation of heterogeneity

In all trials, smokers were motivated to quit or reduce smoking and in both arms received counselling or support to help them do so, whilst the intervention groups were given special interventions to enhance adherence. The interventions used to enhance adherence comprised a combination of two intervention strategies outlined within the taxonomy of interventions to increase adherence that is included in Appendix 1 (Haynes 2008). These were either: a) instruction for patients or b) counselling about the patients' target condition, the importance of therapy and compliance with therapy. Given this, we did not feel there were sufficient differences between intervention approaches to justify subgroup analysis. We also proposed to conduct a subgroup analysis looking at differential effects on adherence by the type of prescribed medication but there were insufficient studies to meaningfully examine this.

### Sensitivity analysis

We assessed the impact of missing ITT data in a sensitivity analysis as previously described. We also proposed to remove studies at higher risk of bias (those not considered to be at low risk of bias) from the analysis to check the robustness of the results. However, no studies were assessed as being at low risk of bias.

## RESULTS

### Description of studies

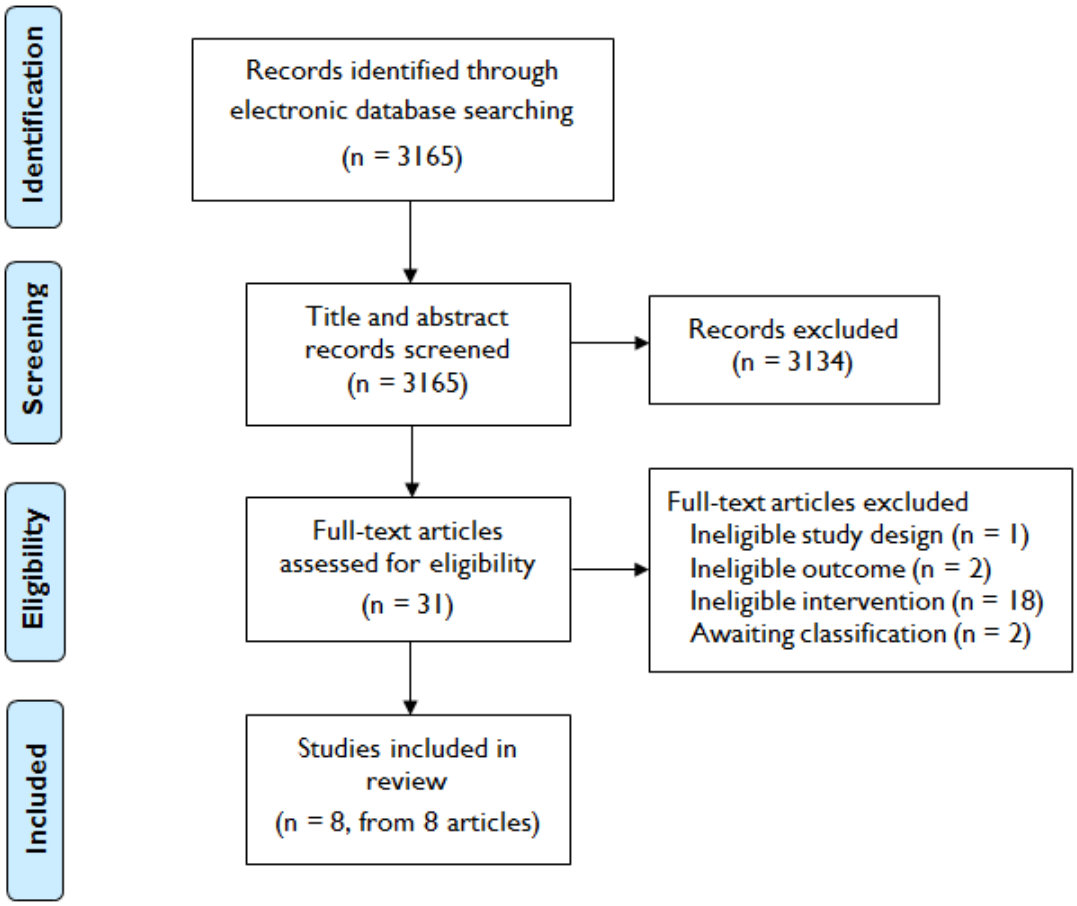
See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies for additional details of studies. An additional Table 1 provides a brief overview of the nature of adherence interventions used in the included studies.


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Results of the search

Our search strategy retrieved 3165 unique references. 31 studies were identified as potentially eligible for inclusion. Of these, 23 studies were excluded at full-text screening stage or identified as studies awaiting classification subject to further information. The flow of studies through the systematic review process is shown in Figure 1.

**Figure 1. Study flow diagram**




### Included studies

We included eight studies involving 3336 randomised participants (Chan 2010; Chan 2011; Marteau 2012; Mooney 2005; Mooney 2007; Schmitz 2005; Nollen 2011; Smith 2013).

#### Types of studies

All trials were randomised controlled trials with parallel groups. Four trials involved randomisation into two groups which were both included in our analysis (Marteau 2012;Mooney 2007; Schmitz 2005; Nollen 2011) and three trials involved randomisation into three groups, but where only two of these groups were


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

eligible for this review (Chan 2010; Chan 2011; Mooney 2005). One trial involved a 2 x 2 x 2 factorial design with eight randomised groups, but these groups were collapsed into a two-group comparison relevant to this review by the study authors (Smith 2013).

### Types of participants and settings

Participants were typically healthy general population samples of smokers. Only one study included participants with a specific clinical condition which was erectile dysfunction (Chan 2010). The mean ages of participants in trials ranged from 34.6 (Mooney 2005) to 49 (Schmitz 2005). In two trials, all participants were female (Mooney 2007; Schmitz 2005). In one trial, all participants were male (Chan 2010). In the remaining trials, % female ranged from 19.4 (Chan 2011) to 62.5 (Nollen 2011). Five trials took place in the USA (Mooney 2005; Mooney 2007; Schmitz 2005; Nollen 2011; Smith 2013), two in Hong Kong, China (Chan 2010; Chan 2011) and one was conducted in the UK (Marteau 2012). Regarding setting, all but one of the included studies featured interventions that were delivered in-person, with the other delivering the intervention by phone (Smith 2013). The interventions were delivered in clinic settings apart from one that was delivered by phone (Smith 2013) and two where the setting was unclear (Chan 2010; Chan 2011). Those delivering the intervention were trained counsellors (Chan 2010; Chan 2011; Mooney 2005; Nollen 2011; Smith 2013), nurses (Marteau 2012; Schmitz 2005) or CBT therapists (Mooney 2007).

### Types of interventions

The trials all provided some behavioural support to participants in the control arm - its form at minimum comprising dosing instructions and weekly checks of side effects (Schmitz 2005). Support for the control arm varied from a single session of twenty minutes (Mooney 2005) to seven weekly sessions (Mooney 2007; Schmitz 2005; Marteau 2012). In the main, the intervention consisted of an additional component to the standard behavioural support, with additional contact time for those in the intervention arm being provided in six studies (Chan 2010; Chan 2011; Mooney 2007; Schmitz 2005; Nollen 2011; Smith 2013). In the other two studies (Marteau 2012; Mooney 2005), the nature of the contact changed but its duration did not significantly differ. The interventions typically provided information on the rationale for, and emphasised the importance of, adherence to medication, and aided participants in developing strategies to overcome problems and barriers to maintaining adherence. As such, they included a combination of two intervention strategies outlined within the taxonomy of interventions to increase adherence (Haynes 2008) that is included in Appendix 1. These are: a) instruction for patients on medication use or b) counselling about smoking, and the value of medication in overcoming addiction. In terms of specific components, two interventions included personalised feedback of externally validated medication adherence (Schmitz 2005; Mooney 2007), one study included an additional component of personalised feedback of questionnaire responses regarding medication (Mooney 2005); one study tailored and communicated about NRT dosage using a different rationale (genotype versus phenotype) (Marteau 2012) and four studies added additional counselling contact time to standard behavioural support, focusing specifically on medication adherence (Chan 2010; Chan 2011; Nollen 2011; Smith 2013). Medications that were being used by participants in the trials were NRT in five studies (Chan 2010; Chan 2011; Marteau 2012; Mooney 2005; Smith 2013), bupropion in two studies (Mooney 2007; Schmitz 2005) and varenicline in one study (Nollen 2011).

### Types of outcome measures

Measures of adherence varied but four studies used a dichotomous outcome, meaning people were either classified as achieving or not achieving a level of adherence that represented multiple weeks of what was deemed adequate adherence (Chan 2010; Chan 2011; Mooney 2007; Schmitz 2005). Three studies used a continuous outcome, measured as the percentage of prescribed medication that was consumed (Marteau 2012; Nollen 2011) or number of days on which it was used (Smith 2013). One study presented both a dichotomous and a continuous outcome (Mooney 2005). The definitions of adequate adherence naturally varied by medication type and because there may not be agreed standards for what constitutes desirable levels of adherence. Furthermore, the operationalisation of this was not always clear. In assessing adherence, five studies used pill counts (Marteau 2012; Mooney 2005; Nollen 2011) or electronic monitoring systems (Schmitz 2005; Mooney 2007). One study clearly used self-report (Smith 2013), whilst this was probable but not clearly the case in two others (Chan 2010; Chan 2011). The period for which the primary adherence outcome was being assessed ranged from approximately two weeks (Mooney 2005; Smith 2013) to three months (Nollen 2011). Six studies reported biochemically validated abstinence outcomes, although only five provide useable data in study reports (Chan 2010; Chan 2011; Marteau 2012; Mooney 2005; Nollen 2011; but not Mooney 2007). One study provided self-reported abstinence data (Smith 2013) and Schmitz 2005 did not report abstinence. Time of abstinence outcome measurement ranged from two weeks (Mooney 2005) to six months (Chan 2010; Chan 2011; Marteau 2012; Smith 2013).

## Excluded studies

We excluded 20 studies (see Characteristics of excluded studies). Two were excluded because they did not include an eligible adherence outcome (Shaughnessy 1987; Willemsen 2006), one was not an eligible study design (Raupach 2010), whilst the other 17 studies did not include an eligible intervention.

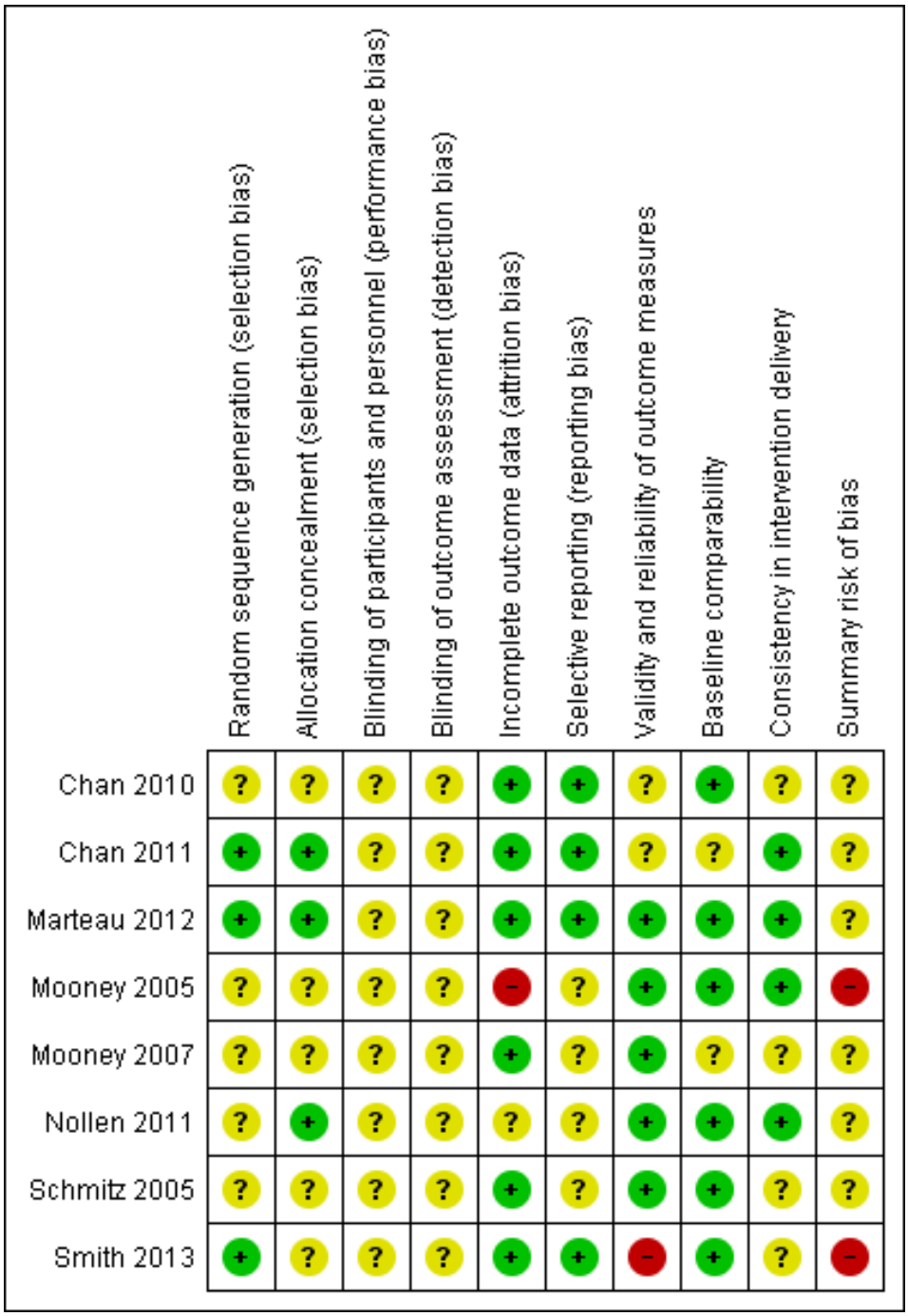

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Risk of bias in included studies

It is clear from the risk of bias summary (Figure 2) that the included studies were often difficult to assess for bias on our criteria because insufficient information was given in published reports. For two studies, we were able to judge that at least five of nine assessment domains were at low risk of bias (Chan 2011; Marteau 2012). Very few judgements were made suggesting a high risk of bias for any domain, with the only two examples being risk of bias due to validity and reliability of outcome measures for Smith 2013 and due to incomplete outcome data for Mooney 2005. For summary risk of bias judgements, as described in Assessment of risk of bias in included studies, two studies were assessed as at high risk of bias (Mooney 2005; Smith 2013) with all others were assessed as at unclear risk of bias.


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**





Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Allocation

Two studies (Chan 2011; Marteau 2012) were judged to be at low risk of selection bias with details being provided of an adequate sequence generation process and steps to ensure allocation concealment. One study (Nollen 2011) provided details of adequate allocation concealment but not sequence generation. In the other studies, insufficient detail was provided to permit a judgement of high or low risk of selection bias (Chan 2010; Mooney 2005; Mooney 2007; Schmitz 2005; Smith 2013).

### Blinding

None of the included studies were regarded as being at low risk of bias in relation to blinding. In all cases, those delivering the intervention were not blind to it. However, the nature of the intervention means that it would be impractical to blind those delivering the intervention and attempts to do so may introduce additional limitations (such as reducing potency of the intervention by impairing its delivery and introducing further systematic differences between the intervention exposures by group). Furthermore, it is unclear as to the degree of risk of bias this places on the outcome data, particularly given the typical use of objective measures of adherence in the included studies. Efforts were made to blind outcome assessors to the secondary abstinence outcome in some cases (Chan 2010; Marteau 2012), although only clearly in one example to the primary adherence outcome (Chan 2011). Where attempts to blind outcome assessors were not apparent (Mooney 2005; Mooney 2007; Schmitz 2005; Nollen 2011; Smith 2013), the use of objective outcome measures, for all other than Smith 2013, may mitigate the risk of bias impacting on the primary adherence outcome.

### Incomplete outcome data

We deemed six studies to have been sufficiently explicit in using intention to treat analysis or addressing substantial and/or differential attrition to be considered as at low risk of bias (Chan 2010; Chan 2011; Marteau 2012; Mooney 2007; Schmitz 2005; Smith 2013). One study was determined to be at unclear risk of bias (Nollen 2011) with one judged to be at high risk of bias (Mooney 2005).

### Selective reporting

Four trials were pre-registered on a clinical trials register enabling us to corroborate that specified outcomes remained consistent (Chan 2010; Chan 2011; Marteau 2012; Nollen 2011). One of these also published a protocol (Marteau 2012). The other four studies were to our knowledge not registered and so selective reporting within the final report could not reasonably be ruled out (Mooney 2005; Mooney 2007; Schmitz 2005; Nollen 2011).

### Other potential sources of bias

We regarded other potential sources of bias that were highly relevant to this review to be validity and reliability of outcome measures, comparability of baseline characteristics, and consistency in intervention delivery. Three studies were assessed as at low risk of bias for all of these criteria (Marteau 2012; Mooney 2005; Nollen 2011). Regarding validity and reliability of outcome measures, one study was assessed to be at high risk of bias, clearly using self-report to assess the primary adherence outcome (Smith 2013), two were assessed as at unclear risk of bias (Chan 2010; Chan 2011) and the remaining five studies were judged to be at low risk of bias. For comparability of baseline characteristics, two studies were determined to be at unclear risk of bias (Chan 2011; Mooney 2007) with the remainder at low risk of bias. Regarding consistency in intervention delivery, four studies were assessed as at unclear risk of bias (Chan 2010; Mooney 2007; Schmitz 2005; Smith 2013) and the remaining four at low risk of bias (Chan 2011; Marteau 2012; Mooney 2005; Nollen 2011).

## Effects of interventions

See: **Summary of findings for the main comparison** Interventions to increase adherence compared to standard care for improving adherence to medications for tobacco dependence and abstinence from smoking

#### Primary adherence outcomes

**Analysis 1.1 Adherence - dichotomous outcomes**

For dichotomous data, analysis comprises data from five studies (Chan 2010; Chan 2011; Mooney 2005; Mooney 2007; Schmitz 2005). Chan 2010 and Chan 2011 assessed whether or not there had been continuous use of NRT, for 4 weeks and 8 weeks respectively. Mooney 2005 assessed whether or not people were using 12 pieces of nicotine gum per day for every day for the first 15 days of a quit attempt. Mooney 2007 and Schmitz 2005 both assessed whether or not participants had taken two daily doses in an optimal schedule over the 7-week treatment period. A pooled analysis of these data show that these interventions increased the proportion of participants achieving a specified satisfactory level of adherence, with a Relative Risk (RR) of 1.14 (95% confidence interval (CI) 1.02 to 1.28, n = 1630, $I^2$ = 46% Analysis 1.1, that is statistically significant (P = 0.02). In other words, adherence was


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

14% higher in the intervention group than in the control group. Whilst we specified use of a fixed-effect model in our protocol, we also conducted a pooled analysis using the random-effects model due to clinical heterogeneity in study characteristics, such as differences in the outcome measures used. This analysis resulted in an RR of 1.30 (95% CI 0.99 to 1.72, $I^2$ = 46%), indicating a larger magnitude of effect but one that is no longer statistically significant (P = 0.06).

#### Analysis 1.2 Adherence - continuous outcomes

Data were available in four studies that expressed adherence as a continuous outcome (Marteau 2012; Mooney 2005; Nollen 2011; Smith 2013). Marteau 2012 assessed the proportion of prescribed NRT consumed over the four week treatment period and gave a group mean, whilst Nollen 2011 assessed the proportion of prescribed varenicline doses taken over three months, for those remaining engaged to provide data. Mooney 2005 reported the mean number of nicotine gums used during the first 15 days of a quit attempt in those who completed the treatment period only. Smith 2013 assessed self-reported number of days of nicotine patch use in the first 2 weeks, for those remaining engaged to provide data. Pooled analysis of these data showed a small and not statistically significant improvement in adherence with a standardised mean difference (SMD) of 0.07 (95% CI -0.03 to 0.17, n = 1529, $I^2$ = 0%, Analysis 1.2). No significant statistical heterogeneity was observed.

### Secondary abstinence outcomes

We report assessments at the timepoint that most closely concords with the assessment of adherence, plus the longest timepoint available should there be additional timepoints reported.

#### Analysis 2.1 Short-term abstinence (< 6 months)

This analysis comprised data from four studies (Marteau 2012; Mooney 2005; Nollen 2011; Smith 2013). Additional data have been requested for Mooney 2007 which will be added to this analysis should we receive them.

Marteau 2012 assessed biochemically validated prolonged abstinence at 28 days, Mooney 2005 assessed biochemically validated point-prevalent abstinence at 2 weeks and Nollen 2011 assessed biochemically validated point-prevalent abstinence at 3 months. Smith 2013 measured self-reported 30-day point-prevalent abstinence at 6 weeks.

A pooled analysis of these data gave an RR of 1.07 (95% CI 0.95 to 1.21, n = 1755, $I^2$ = 0%, Analysis 2.1). This shows a small and not statistically significant effect of adherence interventions on short-term abstinence from smoking.

#### Analysis 2.2 Long-term abstinence (≥ 6 months)

We extracted data on abstinence at the longest follow-up reported. This analysis comprised data from four studies (Chan 2010; Chan 2011; Marteau 2012; Smith 2013). All four studies assessed abstinence at 6 months, this being biochemically validated in all cases apart from Smith 2013. A pooled analysis of these studies gave a statistically significant effect of adherence interventions on longer-term abstinence (RR = 1.16, 95% CI 1.01 to 1.34, n = 3049, P = 0.03, $I^2$ = 72%). Participants given information to improve adherence were 16% more likely to be abstinent at 6 months than those given standard behavioural support for smoking cessation.

The substantial heterogeneity observed is attributed primarily to Smith 2013, being the only study where the direction of effect slightly favours the control. To illustrate its impact on statistical heterogeneity, its removal from this analysis resulted in no observed heterogeneity ($I^2$ = 0%) and a stronger effect of the intervention (RR = 1.63, 95% CI 1.24 to 2.14, n = 2062). This post-hoc exploratory finding is, however, presented as a sensitivity analysis, as we did not pre-specify such an exclusion on this basis and we cannot explain the contrary effect in Smith 2013 by reference to differences between the clinical characteristics of this and other studies. Whilst there were such differences, in that the intervention is delivered by telephone and because abstinence is assessed only by self-report, cessation support delivered by telephone has been shown to increase quitting (Stead 2013) and the use of a self-report measure is more likely to bias the results towards favouring the intervention arm as participants may feel more pressure to falsely report abstinence. Whilst we specified use of a fixed-effects model in our protocol, we also conducted a pooled analysis using the random-effects model due to observed heterogeneity in study characteristics, such as differences in the outcome measures used. This analysis resulted in a RR of 1.36 (95% CI 0.96 to 1.94, $I^2$ = 72%), indicating a larger magnitude of effect but one that is no longer statistically significant.

### Other secondary outcomes

No studies reported any further relevant secondary outcomes that did not relate to adherence or cessation, other than adverse events.

### Adverse events

Adverse events are reported by trial arm in Marteau 2012; Mooney 2005; and Smith 2013. In Marteau 2012, no adverse events occurred that were plausibly related to the intervention or its effect on participants' exposure to medication. There were also no differences between groups in levels of anxiety at either one week or six month assessment times. In Mooney 2005, there was no difference in adverse events between groups and in Smith 2013 there were no serious adverse events during the study.


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

# DISCUSSION

## Summary of main results

There was some evidence that interventions that devote special attention to improving adherence through providing information and facilitating problem-solving can lead to modest increases in adherence, when added to behavioural support for smoking cessation. In turn there was some evidence that such interventions may lead to modest increases in abstinence. However, the limited nature of the available evidence - as a result of the small number of studies, clinical heterogeneity, and impaired study quality - precludes strong statements about the effects of interventions. Lack of data produced imprecise estimates of effect and overall the results are suggestive but inconclusive that adherence interventions may enhance adherence and abstinence.

### Primary outcome

The extant evidence suggests that adherence interventions may lead to a modest increase in the proportion of participants achieving a specified satisfactory level of adherence (as reflected in dichotomous outcomes), but at best a small effect on aggregate levels of adherence (as reflected in continuous outcomes). Both outcomes are important, with evidence, at least as far as NRT is concerned, suggesting that the more medication that is consumed the better, and that high levels are inevitably better than low levels. But because there is unlikely to be clear guidance as to what should be regarded as an adequate or effective level of adherence to a given medication, dichotomous measures may be subject to greater variation, arbitrariness and be less directly comparable and interpretable. Applying the GRADE system, the quality of evidence for the effect estimates for dichotomous and continuous adherence outcomes was assessed as moderate and low, respectively (see Summary of findings for the main comparison). This suggests that further research is at the least likely to have an important impact on the confidence we can have in the estimates, and may change the estimates.

Should this pattern of results - with a larger effect on levels of adequate rather than aggregate adherence, but drawn from few studies - represent a true effect, it may reflect the potential of adherence interventions to work mainly by changing the distribution of adherence, i.e. by shifting those who would always be relatively adherent over a threshold, rather than systematically increasing use in all exposed to it. This may mean that such interventions would most efficiently be targeted at those with a realistic chance of attaining adequate levels of adherence, possibly determined by assessing factors shown to predict adherence. Characteristics of the treatment could also be shaped to attempt to increase the overall background levels of adherence - in essence meaning that there would be less work for the intervention to do to facilitate adequate levels to be reached. For example, characteristics of the medication (Hollands 2013) and its delivery (Hajek 1999) have been shown to impact on adherence.

### Secondary outcomes

There is some evidence that adherence interventions lead to improved rates of cessation, with the estimated effect being more convincing for the effect on long-term abstinence at six months or more. This is consistent with evidence that suggests that increasing adherence will benefit subsequent cessation and that a wide variety of behavioural support interventions have a small effect on long-term smoking cessation, although it may also be due to effects on other potential precursors. Applying the GRADE system, the quality of evidence for the effect estimates for short-term and long-term abstinence outcomes was assessed as low for both (see Summary of findings for the main comparison). This suggests that further research is very likely to have an important impact on the confidence we can have in the estimates, and is likely to change the results. There was also no evidence of adverse unintended effects on behaviour (with all pooled estimates being in the direction of effect of improving health outcomes) and no evidence of adverse clinical or psychological consequences.

There were not enough studies to examine whether specific types of intervention were more effective than others. Furthermore, much of the content of the included interventions appeared relatively homogenous. It is of course possible that this may in part be a function of either the lack of detail in reporting or the lack of consistency in terminology used to describe interventions, rather than reflecting true homogeneity. Ongoing initiatives to improve the reporting of behavioural interventions (e.g. Michie 2013), in combination with a larger and more varied set of included studies and intervention components therein, may allow a meaningful and nuanced analysis of the effects of specific components to be conducted in future.

Although there is a perception that adherence is often suboptimal, the studies in this review that have quantified it show high adherence on the whole. One problem assessing the degree of adherence is that almost all studies used different measures of adherence. Two studies (Marteau 2012; Nollen 2011) reported the mean percentage of prescribed doses taken, and used objective rather than self-report measures. Both of these studies demonstrated high adherence, being over 82% in both arms for Nollen 2011 study and over 63% in both arms for Marteau 2012 (despite reflecting an ITT analysis in which no response at follow-up was taken as zero adherence). Dichotomous measures of adequate adherence were less obviously comparable because their criteria varied more, but in three studies over 50% of participants achieved adequate levels of adherence (Chan 2011; Mooney 2007; Schmitz 2005). Levels of adherence were much lower in one study (Chan 2010), with only 14% of the intervention arm being classified as having adhered adequately. The authors attribute this in part to cost, as only one week of free medication was provided to participants, with cost


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

being given as the main reason for not continuing with medication.

## Overall completeness and applicability of evidence

Whilst the included studies do encompass a reasonable range of participants and intervention and treatment characteristics, the small number of studies mean that the depth of evidence relating to any given characteristic and thus completeness is lacking. In terms of the applicability of the evidence, all trials in this review featured participants who were motivated to quit or reduce smoking and who had agreed to receive medication and behavioural support to assist them in doing so. Furthermore, none of the included studies reported specifically targeting participants who were more likely to be non-adherent, such as those who had previously been unable to adhere to medication regimens. In these contexts, there is evidence that medication use is quite high but also that special interventions to enhance adherence may increase this further. However, improving on levels of adherence that are already high may be challenging and this may help explain why the interventions in this review achieved only modest effects. These characteristics are shared by, for example, smoking cessation services delivered in primary care, suggesting that the findings should be generalisable to these settings. Most people who stop smoking, however, either do not use medication or use it without behavioural support, and typically any medication must be purchased at considerable cost. It is likely that adherence is much lower in this context and that interventions to improve adherence may be particularly helpful. These will have to be delivered by media other than the in-person consultation - typically by trained counsellors or clinical staff - that was examined in all but one of these trials (Smith 2013, which featured an intervention delivered over the phone). At the moment, we know little about what to do to increase adherence outside of in-person, clinic settings, though it is plausible that the same kinds of approaches that look like they may be effective in clinical contexts may also prove to be outside these. In order to address applicability to settings and populations in which there is low adherence to medications, researchers will be required to specifically target contexts in which low adherence is known to be prevalent or where participants are specifically identified as having previously been non-adherent to medication regimens.

## Quality of the evidence

At the level of individual studies included in this review, most gave inadequate information to allow us to evaluate whether or not they were at risk of bias. This is reflected in the majority of summary risk of bias assessments being judged as unclear. Despite being published in the era of the CONSORT statement, descriptions of attempts to address selection bias through adequate randomisation and allocation concealment were often inadequate. Only two of the included studies clearly did so (Chan 2011; Marteau 2012). It is possible that this led to bias, but unlikely. In the context of smoking cessation clinics, trial participants are usually unknown to the therapists and there is therefore no clear incentive or basis for therapists to assign particular participants to particular arms and subvert the randomisation. That said, inadequate procedures or description of these should be easy to address and future trials should do so clearly. One potential source of bias that is common throughout the studies is the involvement of the practitioners providing the adherence intervention in collecting data on the degree to which people were adhering and the related issue of the lack of blinding of separate outcome assessors. This may provide an incentive to falsely inflate adherence for people who have received an adherence intervention. This concern is mitigated somewhat by the use of 'pill counts', common to all but one of these trials (Smith 2013). It is encouraging that the use of such more objective measures appears commonplace in this intervention context, meaning that measurement issues were not considered to confer particular risk of bias. This is contrary to what was found in a recent Cochrane review focusing on adherence to prescription medications, where most studies used self report measures (Nieuwlaat 2014). Furthermore, whilst in the past, electronic monitoring approaches have been applied primarily to the opening and closing of pill bottles, making them suitable for certain types of medications only, technology has been developed that will enable this to be used for other types of medication storage. A final key risk of bias domain concerned incomplete outcome data, as, in adherence studies, participants lost to follow-up are likely to be non-adherent, thus inflating adherence levels when this is not adequately accounted for. This was not determined to be a major issue for the included studies as either analysis was conducted as randomised, or dropout was neither differential by arm or considered substantial in proportion. A global assessment of the evidence for each outcome in the review, through applying the GRADE system, incorporates concerns about the limitations of the included studies and finds that the evidence for our results ranges from low to moderate. This suggests that further research will be valuable in increasing the reliability and precision of effect estimates and the confidence we can place in them.

## Potential biases in the review process

Key possible limitations of the review are that first, we failed to identify all relevant research for inclusion in the review. We did take steps to minimise this possibility such as backward and forward citation searching and searching the Tobacco Addiction Group's specialised register in addition to electronic database searches, but this remains possible and will be addressed if necessary when the review is updated. Second, there is the possibility of publication bias, particularly given that all included studies were journal publications. Although this is difficult to examine with small numbers


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

of included studies, we did ultimately include trials that showed effects that did not favour the adherence intervention.

### Agreements and disagreements with other studies or reviews

We are not aware of other reviews of this specific literature. Cochrane reviews show that behavioural support increases smoking cessation and, typically, such studies include people using medication, and adherence advice is included in standard smoking cessation support (Lancaster 2008; Stead 2012b). However, it is not possible within these reviews to identify the specific impact of intervention components focused on increasing adherence, as these were combined with other types of behavioural support for participants. In terms of reviews of interventions to increase adherence, Haynes 2008 (recently updated in Nieuwlaat 2014) produced a Cochrane review but excluded tobacco dependence medications. Consistent with what we found, they reported that information and counselling approaches improved adherence and patient outcomes.

## AUTHORS' CONCLUSIONS

### Implications for practice

There is limited evidence that interventions that devote special attention to improving adherence to smoking cessation medication through providing information and facilitating problem-solving may enhance adherence and no evidence that it does harm when this is added to standard behavioural support for smoking cessation. Given this, it seems reasonable to recommend this as an option for therapists in smoking cessation clinics. It is unclear whether it may be similarly effective in less clinical contexts and such interventions cannot be recommended for those who are not seeking behavioural support to quit or reduce smoking because evidence for this context is lacking.

What remains unresolved is a disentangling of the specific characteristics and active components within adherence interventions that are likely to confer effectiveness, needed to enable practitioners to design maximally effective interventions. This will require a greater depth of evidence, perhaps accompanied by advances in the science and reporting of behavioural interventions to aid in its interrogation. Even if these interventions demonstrate effect sizes of the small magnitudes seen here, the potential for aggregate impact is substantial given the extent to which medications for tobacco dependence are currently used, at least in the developed world. The degree to which this ultimately applies globally is dependent on increasing the uptake of effective pharmacotherapies, in part via increasing their availability and reducing their cost (Reda 2012).

### Implications for research

There is a lack of high-quality randomised controlled trials to allow us to reliably estimate and interpret effects of interventions to increase adherence to tobacco dependence medications. Furthermore, the specific active components that may increase medication use remain to be delineated. This highlights the value of the current drive in the behavioural sciences towards developing an improved conceptual understanding of the active components of interventions in order to better test, evaluate, and describe them (Michie 2013; Davis 2014; Hollands 2013b). This requires more systematic research but also more detailed and consistent reporting by researchers. In combination with increasing numbers of studies, this then opens up the potential for more detailed analysis of the moderating effects of specific intervention characteristics or components.

A further implication for research is that it would benefit from greater consistency of outcomes and a more tightly defined meaning of adherence. It is rare for clear information to be provided about why a given adherence outcome has been selected and how it has been operationalised. We suggest elsewhere (Hollands 2013) that our understanding of adherence to tobacco dependence medications would benefit from considering the following. First, a distinction should be made between overall consumption and adherence to a prescribed regimen and both outcomes reported, because a prescribed regimen may not be optimal. Second, a continuous outcome, such as percentage of prescribed medication or milligrams of medication consumed, is preferable as opposed to a dichotomous outcome of a specified satisfactory level of adherence. Third, study authors should report intention-to-treat data for the entire sample that is randomised, but also for the subset of randomised participants who are continuing a quit attempt at the time of assessment. The latter is ultimately more meaningful because NRT is not indicated when a person has given up a quit attempt.

Finally, where possible, researchers should conduct trials in settings and populations in which there is low adherence (or an increased probability thereof), in order to aid understanding of approaches to increase adherence beyond relatively adherent patients treated in supportive clinical contexts. This will enable us to better determine whether the modest intervention effects observed are due to these interventions being no more than modestly effective across all contexts, or instead are due to the interventions being directed to where there is less potential for benefit.

## ACKNOWLEDGEMENTS

The authors would like to thank Monaz Mehta (Managing Editor), Lindsay Stead (Managing Editor, who ran searches of the Tobacco Addiction Group Specialized Register), and all at the Cochrane


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Tobacco Addiction Group. We also greatly appreciate the input of the peer reviewers who have commented on this review throughout its development.

## REFERENCES

### References to studies included in this review

**Chan 2010** *{published data only}*
Chan SSC, Leung DYP, Abdullah ASM, Lo SST, Yip AWC, Kok W-M, Ho S-Y, Lam T-H. Smoking-Cessation and Adherence Intervention Among Chinese Patients with Erectile Dysfunction. *American Journal of Preventive Medicine* 2010;**39**(3):251–258.

**Chan 2011** *{published data only}*
Chan SSC, Leung DYP, Abdullah ASM, Wong VT, Hedley AJ, Lam T-H. A randomized controlled trial of a smoking reduction plus nicotine replacement therapy intervention for smokers not willing to quit smoking. *Addiction* 2011; **106**:1155–1163.

**Marteau 2012** *{published data only}*
Hollands GJ, Sutton S, McDermott M, Marteau TM, Aveyard P. Adherence to and consumption of nicotine replacement therapy and the relationship with abstinence within a smoking cessation trial in primary care. *Nicotine & Tobacco Research* 2013;**15**(9):1537-1544.
* Marteau TM, Aveyard P, Munafò MR, Prevost AT, Hollands GJ, Armstrong D, et al. Effect on adherence to nicotine replacement therapy of informing smokers their dose is determined by their genotype: a randomised controlled trial. *PLoS ONE* 2012;**7**(4):e35249.
Marteau TM, Munafò MR, Aveyard P, Hill C, Whitwell S, Willis TA, Crockett RA, Hollands GJ, Johnstone EC, Wright AJ, Prevost AT, Armstrong D, Sutton S, Kinmonth AL. Trial Protocol: Using genotype to tailor prescribing of nicotine replacement therapy: a randomised controlled trial assessing impact of communication upon adherence. *BMC Public Health* 2010;**10**(1):680.

**Mooney 2005** *{published data only}*
* Mooney M, Babb D, Jensen J, Hatsukami D. Interventions to increase use of nicotine gum: A randomized, controlled, single-blind trial. *Nicotine & Tobacco Research* 2004;**7**(4): 565–579.
Mooney M, Green C, Hatsukami D. Nicotine self-administration: cigarette versus nicotine gum diurnal topography. *Human Psychopharmacology* 2006;**21**(8): 539–548.

**Mooney 2007** *{published data only}*
Mooney ME, Sayre SL, Hokanson PS, Stotts AL, Schmitz JM. Adding MEMS feedback to behavioral smoking cessation therapy increases compliance with bupropion: A replication and extension study. *Addictive Behaviors* 2007; **32**:875–880.

**Nollen 2011** *{published data only}*
Nollen NL, Sanderson Cox L, Nazir N, Ellerbeck EF, Owen A, Pankey S, Thompson N, Ahluwalia JS. A Pilot Clinical Trial of Varenicline for Smoking Cessation in Black Smokers. *Nicotine & Tobacco Research* 2011;**13**(9):868–873.

**Schmitz 2005** *{published data only}*
Schmitz JM, Sayre SL, Stotts AL, Rothfleisch J, Mooney ME. Medication Compliance During a Smoking Cessation Clinical Trial: A Brief Intervention Using MEMS Feedback. *Journal of Behavioral Medicine* 2005;**28**(2):139–147.

**Smith 2013** *{published data only}*
Smith SS, Keller PA, Kobinsky KH, Baker TB, Fraser DL, et al. Enhancing tobacco quitline effectiveness: identifying a superior pharmacotherapy adjuvant. *Nicotine & Tobacco Research* 2013;**15**(3):718–28.

### References to studies excluded from this review

**Aveyard 2007** *{published data only}*
Aveyard P, Brown K, Saunders C, Alexander A, Johnstone E, Munafo MR, Murphy M. Weekly versus basic smoking cessation support in primary care: a randomised controlled trial. *Thorax* 2007;**62**:898–903.

**Bansal-Travers 2010** *{published data only}*
Bansal-Travers M, Cummings KM, Hyland A, Brown A, Celestino P. Educating smokers about their cigarettes and nicotine medications. *Health Education Research* 2010;**25** (4):678–686.

**Berlin 2011** *{published data only}*
Berlin I, Jacob N, Coudert M, Perriot J, Schultz L, Rodon N. Adjustment of nicotine replacement therapies according to saliva cotinine concentration: the ADONIS* trial-a randomized study in smokers with medical comorbidities. *Addiction* 2011;**106**(4):833–843.

**Bock 2014** *{published data only}*
Bock BC, Papandonatos GD, de Dios MA, Abrams DB, Azam MM, Fagan M, Sweeney PJ, Stein MD, Niaura R. Tobacco Cessation Among Low-Income Smokers: Motivational Enhancement and Nicotine Patch Treatment. *Nicotine & Tobacco Research* 2014;**16**(4):413–422.

**Brendryen 2008** *{published data only}*
Brendryen H, Kraft P. Happy Ending: a randomized controlled trial of a digital multi-media smoking cessation intervention. *Addiction* 2008;**103**:478–484.

**Buchanan 2004** *{published data only}*
Buchanan LM, El-Banna M, White A, Moses S, Siedlik C, Wood M. An exploratory study of multicomponent treatment intervention for tobacco dependency. *Journal of Nursing Scholarship* 2004;**36**(4):324–330.


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Gariti 2009** *{published data only}*
Gariti P, Lynch K, Alterman A, Kampman K, Xie H, Varillo K. Comparing smoking treatment programs for lighter smokers with and without a history of heavier smoking. *Journal of Substance Abuse Treatment* 2009;**37**(3):247–255.

**ICRFGPRG 199** *{published data only}*
* ICRFGPRG. Effectiveness of a nicotine patch in helping people stop smoking: results of a randomised trial in general practice. *BMJ* 1993;**306**:1304–1308.
ICRFGPRG. Randomised trial of nicotine patches in general practice: results at one year. *BMJ* 1994;**308**: 1476–7.

**Ingersoll 2009** *{published data only}*
Ingersoll KS, Cropsey KL, Heckman CJ. A test of motivational plus nicotine replacement interventions for HIV positive smokers. *AIDS & Behavior* 2009;**13**(3): 545–554.

**Lando 1988** *{published data only}*
Lando HA, Kalb EA, McGovern PG. Behavioral self-help materials as an adjunct to nicotine gum. *Addictive Behaviors* 1988;**13**(2):181–184.

**Lifrak 1997** *{published data only}*
Lifrak P, Gariti P, Alterman A, McKay J, Volpicelli J, Sparkman T, O'Brien C. Results of two levels of adjunctive treatment used with the nicotine patch. *The American Journal on Addictions* 1997;**6**(2):93–98.

**Okuyemi 2006** *{published data only}*
Okuyemi KS, Thomas JL, Hall S, Nollen NL, Richter KP, Jeffries SK Caldwell AR, Ahluwalia JS. Smoking cessation in homeless populations: a pilot clinical trial. *Nicotine & Tobacco Research* 2006;**8**(5):689–699.

**Okuyemi 2013** *{published data only}*
Okuyemi KS, Goldade K, Whembolua GL, Thomas JL, Eischen S, Sewali B, Guo H, Connett JE, Grant J, Ahluwalia JS, Resnicow K, Owen G, Gelberg L, Des Jarlais D. Motivational Interviewing to Enhance Nicotine Patch Treatment for Smoking Cessation among Homeless Smokers: A Randomized Controlled Trial. *Addiction* 2013; **108**:1136–1144.

**Raupach 2010** *{published data only}*
Raupach T, Shahab L, Eimer S, Puls M, Hasenfuss G, Andreas S. Increasing the use of nicotine replacement therapy by a simple intervention: an exploratory trial. *Substance Use & Misuse* 2010;**45**(3):403–413.

**Rigotti 2013** *{published data only}*
Rigotti NA, Japuntich S, Regan S, Kelley JH, Chang Y, Reyen M, Viana JC, Park ER. Levy D, Korotkin M, Streck J, Singer DE. Promoting smoking cessation after hospital discharge: The helping hand randomized controlled comparative effectiveness trial. *Journal of General Internal Medicine* 2013;**28**:S160.

**Shaughnessy 1987** *{published data only}*
Shaughnessy AF, Davis RE, Reeder CE. Nicotine Chewing Gum: Effectiveness and theInfluence of Patient Education in a Family Practice. *The Journal of Family Practice* 1987;**25** (3):266–9.

**Shiffman 2000** *{published data only}*
Shiffman S, Paty JA, Rohay JM, Di Marino ME, Gitchell J. The Efficacy of Computer-Tailored Smoking Cessation Material as a Supplement to Nicotine Polacrilex Gum Therapy. *Archives of Internal Medicine* 2000;**160**: 1675–1681.

**Strecher 2005** *{published data only}*
Strecher VJ, Shiffman S, West R. Randomized controlled trial of a web-based computer-tailored smoking cessation program as a supplement to nicotine patch therapy. *Addiction* 2005;**100**(5):682–8.

**Swan 2010** *{published data only}*
Swan GE, McClure JB, Jack LM Zbikowski SM, Javitz HS, Catz SL, Deprey M, Richards J, McAfee TA. Behavioral counseling and varenicline treatment for smoking cessation. *American Journal of Preventive Medicine* 2010;**38**(5): 482–490.

**Tønnessen 2006** *{published data only}*
Tønnessen P, Mikkelsen K, Bremann L. Nurse-Conducted Smoking Cessation in Patients With COPD Using Nicotine Sublingual Tablets and Behavioral Support. *Chest* 2006; **130**:334–342.

**Willemsen 2006** *{published data only}*
Willemsen MC, Wiebing M, Van Emst A, Zeeman G. Helping smokers to decide on the use of efficacious smoking cessation methods: a randomized controlled trial of a decision aid. *Addiction* 2006;**101**(3):441–449.

## References to studies awaiting assessment

**Applegate 2007** *{published data only}*
Applegate BW, Raymond C, Collado-Rodriguez A, Riley WT, Schneider NG. Improving adherence to nicotine gum by SMS text messaging: a pilot study. Society for Research on Nicotine and Tobacco 13th Annual Meeting February 21-24, Austin, Texas. 2007.

**Yuhongxia 2011** *{published data only}*
Yuhongxia L. The compliance of varenicline usage and the smoking abstinence rate via mobile phone text messaging combine with varenicline: A single-blind, randomised control trial.. *Respirology. Conference publication: 16th Congress of the Asian Pacific Society of Respirology Shanghai China.* 2011;**16**:46–7.

## References to ongoing studies

**Fiore** *{unpublished data only}*
Evaluation of Treatments to Improve Smoking Cessation Medication Adherence. Ongoing study June 2010.

**Shelley** *{unpublished data only}*
Improving Adherence to Smoking Cessation Medication Among PLWHA (HIV). Ongoing study March 2013.

## Additional references

**Burns 2008**
Burns EK, Levinson AH. Discontinuation of Nicotine Replacement Therapy Among Smoking-Cessation


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

Attempters. *American Journal of Preventive Medicine* 2008; **34**:212–215.

**Cahill 2012**
Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 4. [DOI: 10.1002/14651858.CD006103.pub6]

**Cheong 2010**
Cheong YS, Ahn SH. Effect of Multi-modal Interventions for Smoking Cessation in a University Setting: A Short Course of Varenicline, Financial Incentives, E-mail and Short Message Service. *Korean Journal of Family Medicine* 2010;**31**:355–360.

**Davis 2014**
Davis R, Campbell R, Hildon Z, Hobbs L, Michie S. Theories of behaviour and behaviour change across the social and behavioural sciences: a scoping review. *Health Psychology Review* 2014. [DOI: DOI:10.1080/17437199.2014.941722]

**Hajek 1999**
Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, a transdermal patch, nasal spray, and an inhaler. *Archives of Internal Medicine* 1999;**159**:2033-2038.

**Hammond 2004**
Hammond D, McDonald PW, Fong GT, Borland R. Do smokers know how to quit? Knowledge and perceived effectiveness of cessation assistance as predictors of cessation behaviour. *Addiction* 2004;**99**:1042–1048.

**Haynes 2008**
Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD000011.pub3]

**Hays 2010**
Hays JT, Leischow SJ, Lawrence D, Lee TC. Adherence to treatment for tobacco dependence: Association with smoking abstinence and predictors of adherence. *Nicotine & Tobacco Research* 2010;**12**(6):574–81.

**Higgins 2011**
Higgins JPT, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.10 [updated March 2011]*. The Cochrane Collaboration, 2011.

**Hollands 2013**
Hollands GJ, Sutton S, McDermott M, Marteau TM, Aveyard P. Adherence to and consumption of nicotine replacement therapy and the relationship with abstinence within a smoking cessation trial in primary care. *Nicotine & Tobacco Research* 2013;**15**(9):1537-44.

**Hollands 2013b**
Hollands GJ, Shemilt I, Marteau TM, Jebb SA, Kelly MP, Nakamura R, Suhrcke M, Ogilvie D. Altering micro-environments to change population health behaviour: towards an evidence base for choice architecture interventions. *BMC Public Health* 2013;**13**:1218.

**Hughes 2014**
Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2014, Issue 1. [DOI: 10.1002/14651858.CD000031.pub4]

**Lancaster 2008**
Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD001292.pub2]

**Mantel 1959**
Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *Journal of the National Cancer Institute* 1959;**22**:719–748.

**Michie 2013**
Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions. *Annals of Behavioral Medicine* 2013;**46**(1):81–95.

**Nieuwlaat 2014**
Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, CotoiC, Haynes RB. Interventions for enhancing medication adherence. *Cochrane Database of Systematic Reviews* 2014, Issue 11. [DOI: 10.1002/14651858.CD000011.pub4.]

**Raupach 2014**
Raupach T, Brown J, Herbec A, Brose L, West R. A systematic review of studies assessing the association between adherence to smoking cessation medication and treatment success. *Addiction* 2014;**109**(1):35–43.

**Reda 2012**
Reda AA, Kotz D, Evers SM, van Schayck CP. Healthcare financing systems for increasing the use of tobacco dependence treatment. *Cochrane Database of Systematic Reviews* 2012, Issue 6. [DOI: 10.1002/14651858.CD004305.pub4]

**Shiffman 2007**
Shiffman S. Use of more nicotine lozenges leads to better success in quitting smoking. *Addiction* 2007;**102**:809–814.

**Shiffman 2008**
Shiffman S, Sweeney ST, et al. Relationship between adherence to daily nicotine patch use and treatment efficacy: Secondary analysis of a 10 week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics* 2008; **30**:1852–1858.

**Stead 2005**
Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database of Systematic Reviews* 2005, Issue 2. [DOI: 10.1002/14651858.CD001007.pub2]


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Stead 2012a**

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 11. [DOI: 10.1002/14651858.CD000146.pub4]

**Stead 2012b**

Stead LF, Lancaster T. Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD009670.pub2]

**Stead 2013**

Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews* 2013, Issue 8.

**Sutton 2000**

Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000;**320**:1574–7.

* *Indicates the major publication for the study*


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

## CHARACTERISTICS OF STUDIES

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

**Chan 2010**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: Hong Kong, China<br>Recruitment methods: Mass media publicity and referrals from hospitals/clinics and physicians<br>Setting: No information other than a non-clinical setting |
| Participants | Inclusion criteria: Male; Chinese; 18+ years old; Self-reported erectile dysfunction; Smoked at least 1 cigarette per day; Intended to quit smoking within 7 days of first contact; Willing to use NRT; Not following any other smoking cessation regime<br>Exclusion criteria: Psychologically or physically unable to communicate; Taking regular psychotropic medications; Serious health problems preventing use of NRT<br>Participants randomised: 501 participants in eligible groups (mean age = 48.8 years (s. d.=11.5); 0% female; 100% Chinese) |
| Interventions | Aim of intervention: To increase adherence to NRT and smoking cessation<br>Nature of intervention: Additional counselling component focused on medication adherence, delivered by trained male counsellor. Patient centred approach, utilising motivational interviewing techniques and the 4R approach. The NRT adherence intervention was developed from WHO guidelines on adherence interventions which emphasize the importance of adhering to the prescribed dosage, assessed and discussed ways to overcome barriers and delivered problem-oriented interventions to improve adherence<br>Participants received 15 minutes face-to-face smoking cessation counselling and 3 minutes NRT adherence counselling, plus 1 week of free NRT (gum or patch) at first contact. They were tested for carbon monoxide (CO) and given a self-help quitting pamphlet. They also received a telephone hotline number of a counsellor. There was further counselling and CO testing at 1 week and 4 weeks, plus 1 week of NRT at 1 week. At 1 week, NRT usage was checked and additional adherence counselling was given. At 4 weeks NRT usage was checked and additional counselling given as needed<br>Nature of control: The control group received the same content apart from the NRT adherence counselling at baseline and the NRT checking and adherence counselling at week 1 |
| Outcomes | Primary adherence outcome (dichotomous data): Continuous use of NRT for 4 weeks, assessed at 3 months (ITT data). Checked by self-report via telephone contact and possibly pill counts of medication also used, although procedure unclear<br>Other adherence outcomes: 8-week NRT adherence rate at 3 months. Checked by telephone call at 3 months. This outcome relates to adherence beyond the treatment period with no NRT being supplied<br>Secondary outcomes: Self-reported 7-day point prevalent abstinence, assessed at 6 months; Biochemically validated quit rate, assessed at 6 months (selected as abstinence outcome by review authors); Self-reported reduction (≥50%) in cigarette consumption, assessed at 6 months |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

| | |
|---|---|
| Notes | An additional 218 participants were randomised to a third arm which was ineligible for this review. Abstinence outcome not reported by arm and so not useable data in report. Study authors were contacted and supplied data 4/2014, confirming that the biochemically validated quit rate for group A1 and group A2 was 13.3% (33/249) and 9.5% (24/252), respectively |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No details given to enable judgement beyond stating that it was randomised (pg252, para 7) |
| Allocation concealment (selection bias) | Unclear risk | No details given to enable judgement. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No details given to enable judgement. |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Insufficient details of procedure to enable judgement although longer-term follow-up by telephone was conducted by staff blinded to assignment (pg253, para 2) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis was used and reported (pg253, para 7). There were no differences in attrition between arms (pg253, paragraph 8) |
| Selective reporting (reporting bias) | Low risk | Trial was pre-registered ISRCTN13070778 with specified outcomes remaining consistent for the study report |
| Validity and reliability of outcome measures | Unclear risk | Adherence outcomes may have included pill counts of medication used as well as self-report by telephone but procedure unclear (pg253, para 1). Abstinence outcome was biochemically validated (pg253, para 3) |
| Baseline comparability | Low risk | No reported differences between arms in baseline demographic and smoking characteristics (pg253, para 7) |
| Consistency in intervention delivery | Unclear risk | No details given to enable judgement. |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Chan 2011**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: Hong Kong, China<br>Recruitment methods: Local media publicity and by contacting previous cohorts of smokers who had cessation counselling but failed to quit<br>Setting: No information but appears to be smoking cessation clinic |
| Participants | Inclusion criteria: 18+ years old; Chinese; Smoked at least 2 cigarettes per day; No intention to quit in the next 4 weeks but interested in reducing smoking; Not following any other smoking cessation regime; No contraindication to NRT<br>Exclusion criteria: Psychologically or physically unable to communicate; Taking regular psychotropic medications; Serious health problems preventing use of NRT; Pregnant / intending to become pregnant in next 6 months<br>Participants randomised: 928 participants in eligible groups (mean age = 41.9 years (s. d.=10.3); 19.4% female; 100% Chinese) |
| Interventions | Aim of intervention: To increase adherence to NRT, and smoking reduction and cessation<br>Nature of intervention: Additional counselling component focused on medication adherence, delivered by trained smoking cessation counsellor. Patient centred approach, utilising motivational interviewing techniques and the 5R approach. The NRT adherence intervention was developed from WHO guidelines on adherence interventions which emphasise the importance of adhering to the prescribed dosage, assessed and discussed ways to overcome barriers and delivered problem-oriented interventions to improve adherence<br>Participants received 15 minutes face-to-face smoking reduction intervention, including information on the health consequences of smoking and counselling emphasising achieving the goal of cessation by focusing on reduction before quitting, highlighting how reduction is effective when quitting is difficult and how to reduce their smoking. They also received 3 minutes NRT adherence counselling plus 1 week of free NRT (gum or patch) at first contact. They were tested for carbon monoxide (CO) and given a self-help quitting pamphlet. There was further smoking reduction and adherence counselling and CO testing at 1 week, plus administration of a further 3 weeks of NRT. NRT usage was also checked. At 4 weeks, participants received a similar intervention as at 1 week<br>Nature of control: The control group received the same content apart from the NRT adherence counselling at baseline, week 1 and week 4 |
| Outcomes | Primary adherence outcome (dichotomous data): Continuous use of NRT over 8 weeks, assessed at 3 months (ITT data). Checked by self-report via telephone contact but possibly also by pill counts and procedure not clear<br>Other adherence outcomes: Continuous use of NRT over 4 weeks, assessed at 3 months<br>Secondary outcomes: Self-reported 7-day point prevalent abstinence, assessed at 6 months; Biochemically validated quit rate, assessed at 6 months (selected as abstinence outcome by review authors); Self-reported 7-day point prevalent abstinence, assessed at 3 months; Self-reported reduction (≥50%) in cigarette consumption, assessed at 6 months |
| Notes | An additional 226 participants were randomised to a third arm which was ineligible for this review |
| ***Risk of bias*** | |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Chan 2011** (*Continued*)

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Used random numbers generated by a computer prior to participant recruitment (pg1156, para 6) |
| Allocation concealment (selection bias) | Low risk | Allocation sequence was determined by a research assistant not conducting the intervention. Assignment was by opening sealed, opaque envelopes and followed informed consent (pg1156, para 6) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Counsellors were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Research assistants contacting participants at follow-up were blinded to arm allocation (pg1157, para 2) but it is not clear that this was the only means by which the primary outcome was assessed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis was used and reported with non-respondents at follow-up treated conservatively as non-adherent and continuing smokers (pg1158, para 1). There were no differences in attrition between arms (pg1158, para 2) |
| Selective reporting (reporting bias) | Low risk | Trial was pre-registered ISRCTN05172176 with specified outcomes remaining consistent for the study report |
| Validity and reliability of outcome measures | Unclear risk | Adherence outcome was seemingly checked by self-report but combination of pill counts of medication used and self-report may have been used and procedure not clear (pg1156, paragraph 6; pg1157 para 2). Abstinence outcome was biochemically validated (pg1157, para 5) |
| Baseline comparability | Unclear risk | Reported difference between arms in baseline CO level and it is not mentioned if this is adjusted for in the analysis (pg253, para 7) |
| Consistency in intervention delivery | Low risk | Some sessions conducted by each of the counsellors were recorded and validated by |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Chan 2011** (*Continued*)

| | | |
|---|---|---|
| | | an experienced nurse supervisor |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |

**Marteau 2012**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: UK<br>Recruitment methods: Participants were recruited through NHS primary care practices. Smokers were identified through practice registers and sent a letter offering assistance to quit and an invitation to participate in the trial<br>Setting: Smoking cessation clinics in primary care |
| Participants | Inclusion criteria: Smoking at least 10 cigarettes per day; Wanting to quit smoking; 18+ years old<br>Exclusion criteria: None stated<br>Participants randomised: 633 participants (mean age = 47.3 years (s.d.=13.3); 54.3% female; 90.2% white |
| Interventions | Aim of intervention: To increase adherence to NRT by informing participants that their oral dose is tailored based on an analysis of their genotype, rather than their phenotype (FTND score)<br>Nature of intervention: Communicating different means of tailoring prescribed medication, delivered by trained research nurses. Behavioural support (based on withdrawal orientated therapy) and nicotine patches were provided (with the patch dose tailored in relation to cigarettes per day) to all participants. Participants were also prescribed an oral NRT product of their choice. The dose of oral NRT in the intervention arm was tailored based on gene variant. Participants were given both forms of NRT one day pre-quit and told the basis for their dosage. They were also provided with a personalised booklet and an appointment card documenting the dose of NRT to use daily and giving the reason for the dose. The rationale for the dose was reiterated at each subsequent clinic. Behavioural support was offered twice prior to quit day, weekly afterwards for 4 weeks and then at 8 weeks. The quit day was set two weeks and a day after baseline. Support sessions lasted 10-30 minutes, depending on progress and stage of quit attempt<br>Nature of control: The control group received the same content apart from the dose of oral NRT and the corresponding communication of the rationale was tailored based on FTND score |
| Outcomes | Primary adherence outcome (continuous data): Proportion of all prescribed NRT taken over 28 days, assessed at 28 days of treatment period (ITT data). Checked by pill counts of medication used<br>Other adherence outcomes: Proportion of all prescribed NRT taken over 7 days; Proportion of participants showing no use of NRT; Proportion of participants showing use of NRT beyond 28 days<br>Secondary outcomes: Biochemically validated prolonged abstinence at 28 days; Biochemically validated prolonged abstinence at 6 months; Anxiety assessed using the short-form Spielberger State-Trait Anxiety Inventory (STAI-6) |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| | |
|---|---|
| Notes | Phenotype arm is regarded as control arm as it is more similar to standard care |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Random sequence was computer generated (pg4, para 2) |
| Allocation concealment (selection bias) | Low risk | Allocation was conducted from a central isolated location, separate from trial co-ordination and participant recruitment (pg4, para 2). The randomisation sequence was revealed sequentially and concealed from the trial team, nurses and participants (pg4, para 3) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | After assignment, nurses were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment (pg4, para 3) |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Outcome assessors for primary outcome were not blinded, but because pill counts were used it is unclear if this constitutes a clear risk of bias. Outcome assessors for longer-term follow-up were blinded to allocation (pg4, para 3) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | ITT analysis was used and reported with non-respondents at follow-up treated conservatively as non-adherent and continuing smokers (pg4, para 11). There were no differences in attrition between arms (pg7, para 3) |
| Selective reporting (reporting bias) | Low risk | Study was pre-registered including specified outcomes and these were unchanged in study report (ISRCTN14352545). This is also clear in a published protocol |
| Validity and reliability of outcome measures | Low risk | Primary adherence outcome was checked by pill counts of medication used (pg3, para 5). Abstinence outcomes were biochemically validated (pg3, para 13) |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Marteau 2012** (*Continued*)

| | | |
|---|---|---|
| Baseline comparability | Low risk | No reported differences between arms in baseline demographic and smoking characteristics (pg6, Table 1) |
| Consistency in intervention delivery | Low risk | A standardised script was used, detailed in the published protocol (pg3, para 3) |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |

**Mooney 2005**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: USA<br>Recruitment methods: Recruited from community via radio, newspaper and handbill advertisements<br>Setting: Research clinic at tobacco research centre |
| Participants | Inclusion criteria: Aged 18-65; Physically healthy; Smoking 15-50 cigarettes per day for at least one year; No untreated major mental illness; No contraindications for nicotine gum use; No concurrent use of other nicotine or tobacco products; Have experienced past nicotine withdrawal syndrome according to DSM<br>Exclusion criteria: Pregnancy<br>Participants randomised: 63 participants (mean age = 34.6 years (s.d.=10.9); 55.6% female; 87.3% Caucasian) |
| Interventions | Aim of intervention: A brief low-cost intervention to increase compliance to NRT<br>Nature of intervention: Additional personalised feedback component focused on medication use / adherence, delivered by smoking cessation counsellors. Participants initially received a presentation on the benefits of quitting, a review of coping skills and support and encouragement. Personalised feedback was then delivered that addressed the effectiveness, safety and necessity of nicotine replacement. First, facts were presented about NRT followed by personalised feedback based on responses to three questionnaires completed at visit 1- the beliefs about medicines questionnaire, the attitudes about nicotine replacement questionnaire, and the perceived risks of nicotine replacement questionnaire. Tailored scripts were used to reinforce correct knowledge and pro-medication beliefs. In contrast incorrect knowledge, negative or ambivalent positions were raised using nonconfrontational language that allowed for engagement, reflection and clarification. A clarifying statement would then be offered. The broader goal was to define the pros and cons of treatment and shift the decisional balance toward adequate use of gum. The intervention was a single session of approximately 20 minutes<br>Nature of control: Participants received a presentation on the benefits of quitting, a review of coping skills and support and encouragement. A smoking history section reviewed general smoking experiences. This section was intended as a 'placebo' topic with some face relevance but little probable influence on gum use |
| Outcomes | Primary adherence outcomes (dichotomous and continuous data): Rates of gum compliance of 12 pieces per day (for those who received medication and started the treatment phase, not ITT); Total gum use (in participants completing the treatment phase, not |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| | |
|---|---|
| | ITT). These two outcomes were selected as primary outcomes by review authors as most stringent dichotomous data and continuous data, respectively. Checked by pill counts of medication used. Assessed for days 1-15<br>Other adherence outcomes: Daily gum use<br>Secondary outcomes: Biochemically validated point-prevalent abstinence at 1 week; Biochemically validated point-prevalent abstinence at 2 weeks (selected by the review authors as most stringent and consistent with adherence outcome timepoint); Self-reported point-prevalent abstinence at 4,5,6 and 7 weeks; NHLBI defined abstinence at 3 and 6 weeks;<br>Additional secondary outcome measures for which the data are not reported were as follows: Three measures of attitudes and knowledge about nicotine replacement therapy at weeks 1, 6 and 7 - BMQ, ANRT-12, PRNR; The Minnesota Nicotine Withdrawal Scale<br>Adverse events relating to nicotine toxicity and nicotine gum were also assessed |
| Notes | An additional 34 participants were randomised to an additional arm not eligible for inclusion in this review |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No details given to enable judgement. |
| Allocation concealment (selection bias) | Unclear risk | No details given to enable judgement. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Counsellors were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not clear that outcome assessors were blinded, but because pill counts were used it is unclear if this constitutes a clear risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | There were no significant differences in attrition over time across all three arms (pg571, para 4), but the two arms of interest had substantial and differing attrition levels over the treatment period of 31% (intervention) and 55% (control). Data reported for the primary outcome does not refer to all randomised participants and reasons for dropout are not detailed |
| Selective reporting (reporting bias) | Unclear risk | Unable to find any trial registration or published protocol |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Mooney 2005** (*Continued*)

| | | |
|---|---|---|
| Validity and reliability of outcome measures | Low risk | Primary adherence outcome was checked by pill counts of medication used (pg569, para 5). Abstinence outcomes were biochemically validated (pg570, para 3) |
| Baseline comparability | Low risk | No differences were observed at baseline (pg571, para 3). |
| Consistency in intervention delivery | Low risk | A standardised script and checklist was used (pg568 para 7) |
| Summary risk of bias | High risk | Summary risk of bias assessed as high. |

**Mooney 2007**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: USA<br>Recruitment methods: Not reported.<br>Setting: Outpatient research clinic, located at a university medical centre |
| Participants | Inclusion criteria: Female; Aged 20-65; Physically healthy; Smoking a minimum of 10 cigarettes per day; No current DSM-IV Axis 1 disorder<br>Exclusion criteria: Pregnancy / nursing; Current treatment with bupropion or other smoking cessation medication<br>Participants randomised: 55 participants (mean age = 42.1 years (s.d.=10); 100% female; 61.8% Caucasian) |
| Interventions | Aim of intervention: To provide feedback on medication use (using electronic Medication Event Monitoring Systems (MEMS) to increase bupropion compliance<br>Nature of intervention: Provision of additional feedback on adherence levels, given by a CBT therapist. Following baseline assessment all participants began 7 weeks of open-label treatment with bupropion SR (300mg) dispensed in Medication Event Monitoring bottles (containing a computer chip that records the times when bottle opening occurs) . In addition, all participants received individual weekly CBT sessions for smoking cessation, focusing on identification of high risk situation for smoking, coping skills training and lapse recovery strategies. In the intervention condition the weekly CBT was increased in duration by 10 minutes a session, during which time the MEMS feedback was given in graphical form and the treatment regimen was clarified. Problem solving techniques were used to help the participant to tailor the regime to their schedule by associating medication taking with regular activities or routines. Secondly potential barriers to compliance were identified and strategies for removing barriers discussed. Third participants were encouraged to self-monitor pill consumption on daily diaries reviewed at the next therapy session<br>Nature of control: As above but without the extra 10 minutes added to each session for enhanced therapy |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| | |
|---|---|
| Outcomes | Primary adherence outcome (dichotomous data): Rates of full compliance i.e. two doses taken per day in an optimal schedule (ITT data). Assessed daily over 7-week treatment period, objectively using Medication Event Monitoring bottles<br>Other adherence outcomes: Rates of dose compliance i.e. two doses taken per day over 7-week treatment period<br>Secondary outcomes: Biochemically validated abstinence at week 6 (selected as abstinence outcome by review authors. as most consistent with adherence outcome timepoint but there is no useable data in the report); Biochemically validated abstinence at week 3 |
| Notes | Authors contacted to attempt to obtain data for secondary abstinence outcome but no response received |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No details given to enable judgement. |
| Allocation concealment (selection bias) | Unclear risk | No details given to enable judgement. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Therapists were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not clear that outcome assessors were blinded, but because MEMS monitoring data used it is unlikely that this constitutes a clear risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There were no differences in attrition between arms (pg878, para 2). Data reported for the primary outcome appears to refer to all randomised participants |
| Selective reporting (reporting bias) | Unclear risk | Unable to find any trial registration or published protocol |
| Validity and reliability of outcome measures | Low risk | Primary adherence outcome was only measured objectively using MEMS monitoring data. Abstinence biochemically validated |
| Baseline comparability | Unclear risk | No details given to enable judgement |
| Consistency in intervention delivery | Unclear risk | No details given to enable judgement |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Nollen 2011**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: USA<br>Recruitment methods: Not detailed.<br>Setting: Community-based clinic serving a predominantly black population |
| Participants | Inclusion criteria: Black; ≥ 18 years of age; smoking >10 cpd; wanting to quit; willing to take varenicline<br>Exclusion criteria: Planning to move from the area within three months; had contraindications to the use of varenicline, including a cardiovascular event in the month prior to enrolment, renal impairment, taking insulin for diabetes but unwilling to closely monitor blood sugar, or history of clinically significant allergic reactions to varenicline; a major depressive disorder in the past year requiring treatment; history of alcohol or drug dependency in the past year; history of psychosis, panic disorder, bipolar disorder, or any eating disorders; current breast feeding, pregnancy, or plans to get pregnant in the next three months<br>Participants randomised: 72 participants (mean age = 46.8 years (SD=11.3); 62.5% female; 100% black) |
| Interventions | Aim of intervention: To improve varenicline use.<br>Nature of intervention: The intervention arm received standard components which were also received by the control arm, plus additional adherence support counselling. These were delivered by study counsellors although their disciplinary backgrounds/training are not detailed<br>The standard components comprised i) A culturally targeted quit smoking guide addressing the health consequences of smoking, benefits of quitting, and strategies to promote abstinence; ii) a one-month supply of varenicline in a monthly pill box. Participants were verbally instructed on how to take the medication. Participants were encouraged to initiate varenicline on Day 1, set a quit date on Day 8 and to not smoke cigarettes during the 3-month treatment phase. Participants returned to the clinic at the end of months 1 and 2 for medication refills; iii) Standard counselling: All participants met with a study counsellor during the randomisation visit to develop a plan for quitting on day 8. Counsellors followed semi-structured scripts to provide information about the risks of continued smoking, benefits of quitting, discuss strategies for coping with withdrawal and assist participants in developing a quit plan<br>The additional adherence support counselling comprised five additional counselling sessions on days 8, 12, 20, 30, and 60 of the treatment period. Using the Information-Motivation-Behavioural skills model of adherence behaviour change, counsellors provided information to enhance participants' motivation in their ability to take the medication as prescribed (e.g., consequences of adherence/nonadherence) and behavioural skills for managing side effects (e.g., nausea) and remembering to take their medication (e.g., timing doses with daily activities)<br>Nature of control: The control arm received the three standard components only |
| Outcomes | Primary adherence outcome (continuous data): Percentage of prescribed varenicline doses taken at three months (for those remaining engaged to provide data). Assessed during monthly medication refill clinic visits by research staff with pill counts<br>Other adherence outcomes: Percentage of prescribed varenicline doses taken at one month; Percentage of prescribed varenicline doses at two months<br>Secondary outcomes: Biochemically validated 7-day point-prevalence abstinence at three months, verified by salivary cotinine (selected as abstinence outcome by review authors |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

| | |
|---|---|
| | as most consistent with adherence outcome timepoint); biochemically validated 7-day point-prevalence abstinence at one month, verified by CO; biochemically validated 7-day point-prevalence abstinence at two months, verified by CO. Reduction in self-reported cigarettes per day from baseline, assessed at three months. Adverse events were assessed |
| Notes | Participants numbers per arm are not given for primary outcome in published paper. We contacted the authors for clarification and they confirmed that n=29 for control arm, and n=32 for intervention arm (8/2014) |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of allocation sequence not detailed. |
| Allocation concealment (selection bias) | Low risk | Allocation was determined by drawing a sealed envelope with preassigned randomisation numbers, at the randomisation visit (pg869, para 4) |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Counsellors were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not clear that outcome assessors were blinded, but because pill counts were used it is unclear if this constitutes a clear risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | The overall level of attrition is moderate across the treatment period (15-21%) but reasons for dropout are not detailed. No reported differences in attrition by arm (pg870, Results para 1). Data reported for the primary outcome does not appear to refer to all randomised participants |
| Selective reporting (reporting bias) | Unclear risk | Unable to find any trial registration or published protocol |
| Validity and reliability of outcome measures | Low risk | Primary adherence outcome was by pill counts. Abstinence was biochemically validated |
| Baseline comparability | Low risk | No significant differences at baseline were reported |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| | | |
|---|---|---|
| Consistency in intervention delivery | Low risk | Standard counselling was delivered according to semi-structured scripts. Adherence counselling was delivered based on a model of adherence behaviour change. All counselling sessions were audiotaped and integrity of protocols was checked by weekly supervision of audiotaped sessions |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |

**Schmitz 2005**

| | |
|---|---|
| Methods | Design: Randomised controlled trial<br>Country: USA<br>Recruitment methods: Advertisements in local papers and radio announcements<br>Setting: Outpatient research clinic, located at a university medical centre |
| Participants | Inclusion criteria: English-speaking; Female; Aged 30-70; Physically healthy; Smoking a minimum of 10 cigarettes per day<br>Exclusion criteria: Dependence on other substances; Evidence of psychotic, depressive or anxiety disorders; Pregnancy / nursing; Serious medical problems<br>Participants randomised: 97 participants (mean age = 49 (s.d.=9.9); 100% female; 72% Caucasian) |
| Interventions | Aim of intervention: To determine whether pill taking instructions and personalised feedback using MEMS (Medication Event Monitoring System) enhances bupropion compliance<br>Nature of intervention: Provision of additional feedback on adherence levels, given by a clinic nurse. Participants received written and verbal instructions on proper administration of bupropion. All doses were administered in MEMS bottles (containing a computer chip that records the times when bottle opening occurs) in the morning and one in the evening with at least 8hrs (but not more than 12hr) between. Participants in the intervention group were told about the recording device in the bottle cap - specifically that the cap would record the time and date that they took the medication. MEMS feedback was given in graphical form weekly with repeated instructions to increase compliance and a check of side effects. Feedback sessions lasted approximately 5-10 mins. The treatment regime was 7 weeks in duration with weekly counselling visits<br>Nature of control: Participants did not receive any particular information, direction or feedback beyond the standard dosing instructions. Participants met briefly with nurse for a weekly check of side effects. The control arm was designed to typify usual care in a medical setting |
| Outcomes | Primary adherence outcome (dichotomous data): Rates of full compliance i.e. two doses taken per day in an optimal schedule (ITT data). Assessed daily over 7-week treatment period, objectively using Medication Event Monitoring bottles<br>Other adherence outcomes: Rates of dose compliance i.e. two doses taken per day over 7-week treatment period<br>Secondary outcomes: None reported |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| Notes | | |
|---|---|---|
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | No details given to enable judgement. |
| Allocation concealment (selection bias) | Unclear risk | No details given to enable judgement. |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Nurses were inevitably not blind to the intervention but it is not clear that this is likely to influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Not clear that outcome assessors were blinded, but because MEMS monitoring data used it is unlikely that this constitutes a clear risk of bias |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | There were no differences in attrition between arms (pg142, para 7). We assume that data reported refers to all randomised participants (given wording used and consistent with reported degrees of freedom for F-tests) |
| Selective reporting (reporting bias) | Unclear risk | Unable to find any trial registration or published protocol |
| Validity and reliability of outcome measures | Low risk | Primary adherence outcome was only measured objectively using MEMS monitoring data. Abstinence biochemically validated |
| Baseline comparability | Low risk | No reported differences between arms in baseline demographic and smoking characteristics (pg142, para 5) |
| Consistency in intervention delivery | Unclear risk | No details given to enable judgement |
| Summary risk of bias | Unclear risk | Summary risk of bias assessed as unclear. |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Smith 2013**

| | |
|---|---|
| Methods | Design: Randomised controlled trial. The study was a 2 x 2 x 2 factorial design examining three manipulations, only one of which is relevant to this review<br>Country: USA<br>Recruitment methods: Participants were recruited from people who called the Wisconsin Tobacco Quit Line (WTQL), who were invited to participate in the study. There was no additional advertising or targeted recruitment<br>Setting: Counselling intervention conducted over the telephone |
| Participants | Inclusion criteria: Age ≥18 years; English speaking; smoking ≥10 cigarettes/day; willing to set a quit date within the next 30 days<br>Exclusion criteria: Pregnant or lactating; medical contraindications for study medications (e.g., past 30 days, heart attack or stroke; past 6 months, serious or worsening angina, very rapid or irregular heartbeat requiring medication); unwillingness to use study medications<br>Participants randomised: 987 participants (mean age = 41.9 years (s.d.=13.0); 57.6% female; 76.4% Caucasian) |
| Interventions | Aim of intervention: To address problematic beliefs or knowledge about NRT that might adversely affect appropriate use of the pharmacotherapies<br>Nature of intervention: All study participants received a standard quit guide in the mail, access to recorded medication information (via phone), and access to an online cessation program maintained by the quitline. They could make ad hoc calls to the quitline for additional assistance. They received standard cessation counselling. During call 1, quitline counsellors discussed smoking history, prior quit attempts, problem-solving and coping strategies, social support, and appropriate use of cessation medications; also, a target quit date was set during this first call. Call 2 occurred on or close to the quit date and focused on management of withdrawal symptoms, appropriate use of medications, strategies to maintain abstinence in high-risk situations, and early relapse prevention. Calls 3 and 4 also addressed relapse prevention but counselling was tailored to address concerns and questions raised by the participant<br>In addition, intervention participants received medication adherence counselling (MAC) during all standard counselling calls. The MAC protocol was developed by study investigators and involved the following: (a) prequit assessment of beliefs that might undermine NRT adherence, (b) ongoing medication adherence assessment by counsellors, and (c) tailored coaching based on the ongoing assessments<br>Nature of control: Control participants received the standard quit materials and standard counselling only |
| Outcomes | Primary adherence outcome (continuous data): Self-reported number of days of nicotine patch use in the first 2 weeks in those remaining engaged at this timepoint (this was the most relevant outcome given the factorial design because all participants irrespective of randomised arm received nicotine patches for at least 2 weeks)<br>Other adherence outcomes: Self-reported number of days of gum use in the first 2 weeks; Self-reported number of weeks of nicotine patch use in the first 6 weeks; Self-reported number of weeks of gum use in the first 6 weeks<br>Secondary outcomes; 30-day PPA at 6 weeks postquit (selected as timepoint most relevant to adherence outcome), 30-day PPA at 12 weeks postquit, 30-day PPA at 26 weeks postquit (selected as longest timepoint). 7-day PPA at 2 weeks postquit; 7-day PPA at 6 weeks postquit; 7-day PPA at 12 weeks postquit; 7-day PPA at 26 weeks postquit. |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

| | |
|---|---|
| | Abstinence outcomes were assessed by self-report |
| Notes | The study uses a factorial design in order to examine the effect of three different enhancements to quitline treatment: i) patch only versus combination (patch plus oral) nicotine replacement therapy (NRT); ii) shorter versus longer duration of NRT; iii) standard counselling versus counselling to increase NRT adherence. We are only interested in the effect of the latter, with data for this comparison collapsing the other factor conditions<br>Study authors contacted and responded 8/2014 in seeking exact number of participants by arm for primary outcome. Their response indicated that there were 386 participants in the standard counselling group and 413 participants in the adherence counselling group |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants were randomly assigned to the eight treatment combinations via a list of randomised numbers generated by SAS Proc Plan (SAS Institute Inc., Cary, NC) (pg719) |
| Allocation concealment (selection bias) | Unclear risk | Insufficient details to determine that allocation was adequately concealed |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Counsellors were responsible for randomisation and subsequent pre-quit counselling and so were inevitably not blinded to condition (pg719, para 7), but it is not clear that this would influence the treatment |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Outcome data were collected by university-based research staff not affiliated with the quitline, but it is unclear if they were blinded (pg720, para 5) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | The level of attrition is moderate (18-20%) and not different between arms (pg721, para 5) and reasons for dropout are given. Not intention to treat (pg720, Analysis plan and statistical methods para 1) |
| Selective reporting (reporting bias) | Low risk | Study was pre-registered including specified primary outcomes and these were unchanged in study report (NCT01087905) |
| Validity and reliability of outcome measures | High risk | Primary adherence outcome was only measured by self-report via phone. Abstinence measures were not biochemically validated |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

**Smith 2013** (*Continued*)

| | | |
|---|---|---|
| Baseline comparability | Low risk | No reported differences between arms in baseline demographic and smoking characteristics (pg721, para 4) |
| Consistency in intervention delivery | Unclear risk | No details given to enable judgement although seemed to (if not clearly stated) follow a basic protocol in terms of outlining the intended focus of each call |
| Summary risk of bias | High risk | Summary risk of bias assessed as high. |

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

| Study | Reason for exclusion |
|---|---|
| Aveyard 2007 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence - the protocol for the behavioural support interventions "did not specify the nature of the support offered". Adherence outcome was of use / not use for specific time periods - assessing "whether NRT was being used in general and not the degree of adherence" |
| Bansal-Travers 2010 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use |
| Berlin 2011 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence - it is not suggested that this is an aim for the study or that the intervention is being employed to encourage increased adherence in participants |
| Bock 2014 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence |
| Brendryen 2008 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Participants in both the intervention and control arms "recommended the use of NRT and contained information about such products and their use" |
| Buchanan 2004 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use and for the intervention arm the component focused on medication use was one of multiple elements relating to smoking cessation |
| Gariti 2009 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use |
| ICRFGPRG 199 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence |
| Ingersoll 2009 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Intervention and control conditions were two different formats both "designed to provide motivation for |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

(*Continued*)

| | |
|---|---|
| | cessation and patch use through attention to the participants' own assessment of their reasons to quit, tools needed to quit, and goal-setting around quitting or reducing smoking" |
| Lando 1988 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. For the intervention materials the adherence component was one of multiple elements - "emphasis was placed upon a range of behavioral coping mechanisms of which gum was simply one major strategy for combating urges to smoke" |
| Lifrak 1997 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use |
| Okuyemi 2006 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use |
| Okuyemi 2013 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Intervention is seemingly focused on both smoking cessation and adherence components with smoking cessation being the primary outcome |
| Raupach 2010 | Not an eligible study design - historical cohort study |
| Rigotti 2013 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Intervention is focused on both smoking cessation and adherence components with smoking cessation being the focus of the stated aim and the stated primary outcome |
| Shaughnessy 1987 | No eligible adherence outcome was assessed |
| Shiffman 2000 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. The stated aim of the intervention is to evaluate the efficacy of tailored and untailored materials as supplements to nicotine replacement therapy. The specified primary outcomes are rates of continuous abstinence. Prompts to comply with the medication are one of multiple reported elements of the intervention |
| Strecher 2005 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. Both intervention and control include a focus on medication use |
| Swan 2010 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. All arms include a focus on medication use |
| Tønnessen 2006 | Intervention is not principally focused on increasing adherence to medications for tobacco dependence. The stated aim of the intervention was "to evaluate the efficacy of the nicotine sublingual tablet or placebo combined with either low or high behavioral support for smoking cessation in COPD patients after 6 months and 12 months" with specified primary and secondary outcomes being smoking cessation, smoking reduction and quality of life. The intervention is described as "counselling on smoking cessation... and subjects were also given take-home material with tips on smoking cessation". Participants were "recommended to use study medication" as one of multiple reported elements of the counselling intervention but it is not reported that this is administered differentially to intervention and control arms |
| Willemsen 2006 | No eligible adherence outcome was assessed - includes a measure of use vs not use of medication |


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

## Characteristics of studies awaiting assessment *[ordered by study ID]*

**Applegate 2007**

| | |
|---|---|
| Methods | (from abstract) "A secure web program was created to properly dose cigarette smokers to gum strength (2 vs. 4 mg) and dosing program (# of pieces/day [PPD]). The program then sends SMS text messaging to the user's cellular telephone to prompt medication use at regular intervals. We then conducted a randomised trial examining tailored text messaging (TTM) to support text messaging (STM) in 110 cigarette smokers attempting to quit smoking while using nicotine gum." |
| Participants | The sample was 53% male, 63% White, 43 + 11 years of age, and smoked 19 + 7.6 cigarettes per day (CPD). There were no differences between groups at baseline for CPD, gum dosing, and recommended PPD." |
| Interventions | Tailored text messaging (TTM) to support text messaging (STM) |
| Outcomes | Outcome variables included self-reported seven day recalls of nicotine gum use and cigarette smoking at 7, 28, and 56 days post quit date |
| Notes | Requires assessment of full text to confirm eligibility but only an abstract is seemingly available. Lead author unable to be contacted, although member of author team who was able to be contacted (5/2013) indicated that the study was conducted by a company and had not been written up for publication. Abstract presents results as follows: On an intent-to-treat basis, independent-sample t-tests revealed that subjects in the TTM condition reported chewing more nicotine gum than subjects in the STM condition, (6.5 PPD vs. 4.5 PPD, respectively, P=.003). No significant differences were found at 4 weeks or 8 weeks, or for cigarette use variables |

**Yuhongxia 2011**

| | |
|---|---|
| Methods | Design: Randomised controlled trial.<br>Country: China. |
| Participants | Smokers willing to make a quit attempt |
| Interventions | Participants were randomly assigned to either:<br>i) varenicline combined with a mobile phone text messaging smoking cessation programme. The programme comprised motivational messages, support for behavioural change and 'medicine attention'<br>ii) a control group that received varenicline only |
| Outcomes | The primary outcomes were varenicline usage for 12 weeks and self-reported continuous smoking abstinence, biochemically verified by exhaled CO test at 3 and 6 months |
| Notes | Only an abstract is available. It is not clear from this whether the principal focus of the intervention was on increasing adherence, although this seems unlikely from the abstract content. We have been unable to contact the authors to receive more information |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

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

**Fiore**

| | |
|---|---|
| Trial name or title | Evaluation of Treatments to Improve Smoking Cessation Medication Adherence |
| Methods | Randomised trial |
| Participants | 544 smokers |
| Interventions | Medication Duration during quit attempt; Counselling; Automated Medication Adherence Calls; Electronic Medication Monitoring Device + Feedback; Cognitive Adherence Intervention |
| Outcomes | Medication Adherence assessed for 26 weeks (depending on the condition) after the target quit day |
| Starting date | June 2010 |
| Contact information | Tanya R Schlam, PhD: trschlam@ctri.medicine.wisc.edu |
| Notes | Identifier: NCT01120704 |

**Shelley**

| | |
|---|---|
| Trial name or title | Improving Adherence to Smoking Cessation Medication Among PLWHA (HIV) |
| Methods | Randomised trial |
| Participants | 190 smokers from HIV/AIDS clinics |
| Interventions | Standard Care (SC); SC + text message reminders; SC + text message reminders + cell phone-delivered adherence-focused behavioral therapy (ABT) |
| Outcomes | Adherence to varenicline and biochemically validated smoking abstinence at 12 weeks and 3-month follow-up from the time of study enrolment |
| Starting date | March 2013 |
| Contact information | Principal Investigator: Donna Shelley, NYU School of Medicine; Contact: Tuo-Yen.Tseng@nyumc.org |
| Notes | Identifier: NCT01898195 |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## DATA AND ANALYSES

### Comparison 1. Primary outcome (adherence)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Adherence - Dichotomous outcomes | 5 | 1630 | Risk Ratio (M-H, Fixed, 95% CI) | 1.14 [1.02, 1.28] |
| 2 Adherence - Continuous outcomes | 4 | 1529 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.07 [-0.03, 0.17] |

### Comparison 2. Secondary outcomes

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Short-term abstinence < 6 months | 4 | 1755 | Risk Ratio (M-H, Fixed, 95% CI) | 1.07 [0.95, 1.21] |
| 2 Long-term abstinence ≥ 6 months | 4 | 3049 | Risk Ratio (M-H, Fixed, 95% CI) | 1.16 [1.01, 1.34] |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Analysis 1.1. Comparison 1 Primary outcome (adherence), Outcome 1 Adherence - Dichotomous outcomes.

Review: Interventions to increase adherence to medications for tobacco dependence

Comparison: 1 Primary outcome (adherence)

Outcome: 1 Adherence - Dichotomous outcomes

| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Chan 2010 | 34/249 | 32/252 | | 10.6 % | 1.08 [ 0.69, 1.69 ] |
| Chan 2011 | 270/479 | 236/449 | | 80.9 % | 1.07 [ 0.95, 1.21 ] |
| Mooney 2005 | 7/27 | 3/22 | | 1.1 % | 1.90 [ 0.56, 6.50 ] |
| Mooney 2007 | 15/27 | 9/28 | | 2.9 % | 1.73 [ 0.92, 3.26 ] |
| Schmitz 2005 | 28/51 | 13/46 | | 4.5 % | 1.94 [ 1.15, 3.28 ] |
| **Total (95% CI)** | **833** | **797** | | **100.0 %** | **1.14 [ 1.02, 1.28 ]** |

Total events: 354 (Intervention), 293 (Control)

Heterogeneity: $Chi^2$ = 7.40, df = 4 (P = 0.12); $I^2$ =46%

Test for overall effect: Z = 2.31 (P = 0.021)

Test for subgroup differences: Not applicable





Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Analysis 1.2. Comparison 1 Primary outcome (adherence), Outcome 2 Adherence - Continuous outcomes.

Review: Interventions to increase adherence to medications for tobacco dependence

Comparison: 1 Primary outcome (adherence)

Outcome: 2 Adherence - Continuous outcomes

| Study or subgroup | Intervention N | Mean(SD) | Control N | Mean(SD) | Std. Mean Difference IV,Fixed,95% CI | Weight | Std. Mean Difference IV,Fixed,95% CI |
|---|---|---|---|---|---|---|---|
| Marteau 2012 | 315 | 68.5 (36.3) | 318 | 63.6 (39) | | 41.5 % | 0.13 [ -0.03, 0.29 ] |
| Mooney 2005 | 22 | 120.1 (55.3) | 14 | 102.5 (53.9) | | 2.2 % | 0.31 [ -0.36, 0.99 ] |
| Nollen 2011 | 32 | 82.1 (36.4) | 29 | 89.2 (24.4) | | 4.0 % | -0.22 [ -0.73, 0.28 ] |
| Smith 2013 | 413 | 10 (5.07) | 386 | 9.8 (4.91) | | 52.4 % | 0.04 [ -0.10, 0.18 ] |
| **Total (95% CI)** | **782** | | **747** | | | **100.0 %** | **0.07 [ -0.03, 0.17 ]** |

Heterogeneity: $Chi^2$ = 2.55, df = 3 (P = 0.47); $I^2$ =0.0%

Test for overall effect: Z = 1.42 (P = 0.15)

Test for subgroup differences: Not applicable



Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

### Analysis 2.1. Comparison 2 Secondary outcomes, Outcome 1 Short-term abstinence < 6 months.

Review: Interventions to increase adherence to medications for tobacco dependence

Comparison: 2 Secondary outcomes

Outcome: 1 Short-term abstinence < 6 months

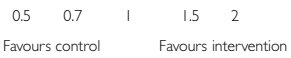
| Study or subgroup | Intervention n/N | Control n/N | Risk Ratio M-H,Fixed,95% CI | Weight | Risk Ratio M-H,Fixed,95% CI |
|---|---|---|---|---|---|
| Marteau 2012 | 151/315 | 147/318 | | 46.0 % | 1.04 [ 0.88, 1.22 ] |
| Mooney 2005 | 13/32 | 10/31 | | 3.2 % | 1.26 [ 0.65, 2.44 ] |
| Nollen 2011 | 8/36 | 9/36 | | 2.8 % | 0.89 [ 0.39, 2.04 ] |
| Smith 2013 | 172/502 | 150/485 | | 48.0 % | 1.11 [ 0.93, 1.33 ] |
| **Total (95% CI)** | **885** | **870** | | **100.0 %** | **1.07 [ 0.95, 1.21 ]** |

Total events: 344 (Intervention), 316 (Control)

Heterogeneity: $Chi^2 = 0.71$, df = 3 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 1.17 (P = 0.24)

Test for subgroup differences: Not applicable





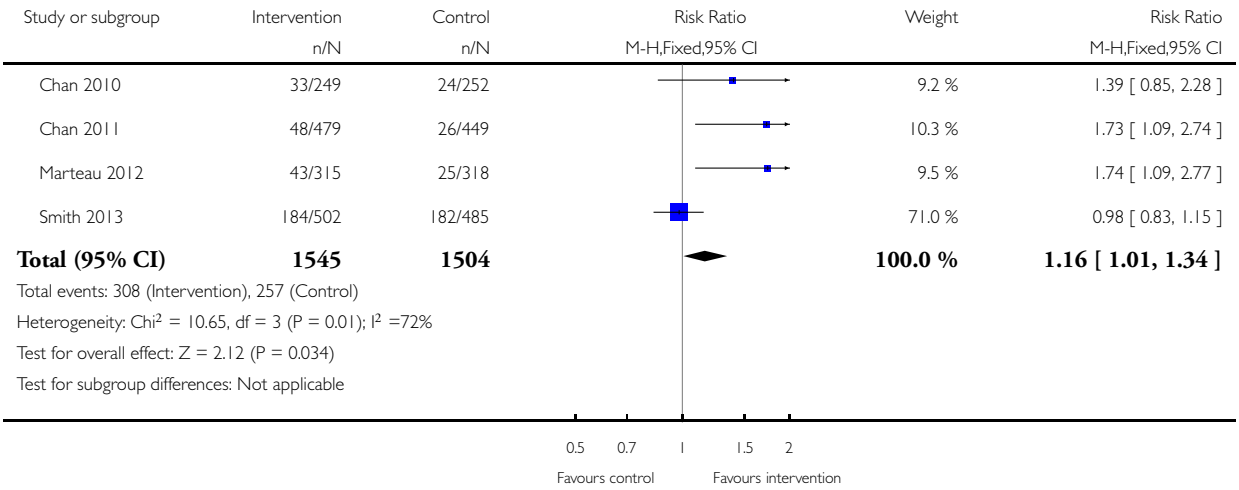
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Analysis 2.2. Comparison 2 Secondary outcomes, Outcome 2 Long-term abstinence ≥ 6 months.**

Review: Interventions to increase adherence to medications for tobacco dependence

Comparison: 2 Secondary outcomes

Outcome: 2 Long-term abstinence ≥ 6 months




## ADDITIONAL TABLES

**Table 1. Brief descriptions of adherence interventions**

| Study | Brief description of specific intervention components intended to increase adherence* | Additional contact time relative to standard care? | Medication for which adherence was targeted |
|---|---|---|---|
| Chan 2010 | Added counselling contact time to standard behavioural support, focusing specifically on medication adherence | Yes | NRT |
| Chan 2011 | Added counselling contact time to standard behavioural support, focusing specifically on medication adherence | Yes | NRT |
| Marteau 2012 | Tailored and communicated about NRT dosage using a more potent rationale (genotype versus phenotype) | No | NRT |


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

**Table 1. Brief descriptions of adherence interventions** (*Continued*)

| | | | |
|---|---|---|---|
| Mooney 2005 | Personalised feedback of questionnaire responses regarding medication | No | NRT |
| Mooney 2007 | Personalised feedback of externally validated medication adherence | Yes | Bupropion |
| Nollen 2011 | Added counselling contact time to standard behavioural support, focusing specifically on medication adherence | Yes | Varenicline |
| Schmitz 2005 | Personalised feedback of externally validated medication adherence | Yes | Bupropion |
| Smith 2013 | Added counselling contact time to standard behavioural support, focusing specifically on medication adherence | Yes | NRT |

** For further details see* ***Characteristics of Included Studies***

# APPENDICES

## Appendix 1. Taxonomy of possible interventions (adapted from Haynes 2008)

a) more instruction for patients, e.g. verbal, written, or visual material; programmed learning; and formal education sessions;
b) counselling about the patients' target condition, the importance of therapy and compliance with therapy, the possible side-effects, patient empowerment, couple-focused therapy to increase social support;
c) automated telephone, computer-assisted patient monitoring and counselling;
d) manual telephone follow-up;
e) family intervention;
f ) various ways to increase the convenience of care, e.g. provision at the worksite or at home;
g) simplified dosing;
h) involving patients more in their care through self-monitoring;
i) reminders, e.g. programmed devices, and tailoring the regimen to daily habits;
j) special 'reminder' medication packaging;
k) dose-dispensing units of medication and medication charts;
l) appointment and prescription refill reminders;
m) reinforcement or rewards for both improved adherence and treatment response, e.g. reduced frequency of visits;
n) different medication formulations, such as tablet versus syrup ;
o) crisis intervention conducted when necessary;
p) direct observation of treatments (DOTS) by health workers or family members;
q) lay health mentoring;
r) augmented pharmacy services;
s) psychological therapy, e.g. cognitive behaviour therapy, multisystemic therapy;


**Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.**

t) mailed communications;
u) group meetings.

## Appendix 2. MEDLINE (Ovid SP) search strategy

1 exp medication adherence/ 7730
2 exp smoking cessation/ 20345
3 (adhere* or complian* or concord*).tw. 222406
4 or/1-3 244332
5 (NRT or nicotine replacement therap* or bupropion or wellbutrin or zyban or voxra or budeprion or aplenzin or amfebutamone or varenicline or chantix or champix).tw. 5254
6 (nicotine adj7 (patch* or gum* or inhaler* or inhalator* or lozenge* or microtab* or tablet* or spray*)).tw. 2247
7 5 or 6 6925
8 randomised controlled trial.pt. 379042
9 controlled clinical trial.pt. 88839
10 clinical trial.pt. 489753
11 random*.tw. 656627
12 placebo.tw. 151719
13 trial.tw. 341515
14 groups.tw. 1279987
15 or/8-14 2179105
16 4 and 7 and 15 1705
17 limit 16 to humans 1700

## Appendix 3. Embase (Ovid SP) search strategy

1 exp medication adherence/ 4398
2 exp smoking cessation/ 37433
3 (adhere* or complian* or concord*).tw. 310641
4 or/1-3 348019
5 (NRT or nicotine replacement therap* or bupropion or wellbutrin or zyban or voxra or budeprion or aplenzin or amfebutamone or varenicline or chantix or champix).tw. 8998
6 (nicotine adj7 (patch* or gum* or inhaler* or inhalator* or lozenge* or microtab* or tablet* or spray*)).tw. 2677
7 5 or 6 10951
8 randomised controlled trial/ 345939
9 single blind procedure/ or double blind procedure/ 131682
10 crossover procedure/ 39531
11 random*.tw. 884924
12 placebo*.tw. 199266
13 ((singl* or doubl*) adj (blind* or mask*)).tw. 157668
14 (cross over or crossover or factorial* or latin square).tw. 93570
15 (assign* or allocat* or volunteer*).tw. 488528
16 or/8-15 1411900
17 4 and 7 and 16 1897
18 limit 17 to human 1836


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## Appendix 4. PsycINFO (Ovid SP) search strategy

1 exp medical regimen compliance/ 11128
2 exp smoking cessation/ 9156
3 (adhere* or complian* or concord*).tw. 46968
4 or/1-3 58112
5 (NRT or nicotine replacement therap* or bupropion or wellbutrin or zyban or voxra or budeprion or aplenzin or amfebutamone or varenicline or chantix or champix).tw. 2854
6 (nicotine adj7 (patch* or gum* or inhaler* or inhalator* or lozenge* or microtab* or tablet* or spray*)).tw. 1221
7 5 or 6 3739
8 random*.ti,ab,hw,id. 132134
9 trial*.ti,ab,hw,id. 123964
10 placebo*.ti,ab,hw,id. 31234
11 ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id. 22030
12 (cross over or crossover or factorial* or latin square).ti,ab,hw,id. 21908
13 (assign* or allocat* or volunteer*).ti,ab,hw,id. 119014
14 treatment effectiveness evaluation/ 16887
15 mental health program evaluation/ 1870
16 exp experimental design/ 47784
17 "2000".md. 27392
18 or/8-17 379651
19 4 and 7 and 18 1030
20 limit 19 to human 1016

## Appendix 5. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 (adhere* or complian* or concord*):ti,ab,kw 24410
#2 (NRT or nicotine replacement therap* or bupropion or wellbutrin or zyban or voxra or budeprion or aplenzin or amfebutamone or varenicline or chantix or champix):ti,ab,kw or (nicotine adj7 (patch* or gum* or inhaler* or inhalator* or lozenge* or microtab* or tablet* or spray*)):ti,ab,kw 1589
#3 (#1 AND #2) in Trials 147

## CONTRIBUTIONS OF AUTHORS

Draft the protocol: All authors

Develop the search strategy: GJH, MM

Search for trials: GJH, MM, FV, AF

Obtain copies of trials: GJH

Select which studies to include: GJH, MM

Extract data from studies: GJH, MM, FV, AF, NL

Enter data into RevMan: GJH, MM

Carry out the analysis: GJH

Interpret the analysis: All authors

Draft the final review: All authors

Update the review: GJH


Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

## DECLARATIONS OF INTEREST

Gareth Hollands and Paul Aveyard are authors of one study included in this review. All other authors declare that they have no competing interests.

## SOURCES OF SUPPORT


### Internal sources

- King's College London, UK.

Database access

- University of Cambridge, UK.

Computer use, database access

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The criteria for eligible interventions was refined between the protocol and the review. The original primary intention of the review was to examine the effect of interventions to increase adherence where this was the clearly intended focus of those intervening. However, this primary intention was not adequately reflected in the original criteria. As such, a large number of studies of interventions that could in theory alter adherence but where this was not the researchers' intention would have been relevant for inclusion. Furthermore, this lack of clarity meant that most extant studies that featured any intervention in smokers would have to be examined at the full-text screening stage because a clear focus on increasing adherence (which can typically be derived from the title and abstract screening process) was not necessary for consideration for inclusion.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Benzazepines [therapeutic use]; Bupropion [therapeutic use]; Drug Therapy, Combination [methods]; Medication Adherence [*statistics & numerical data]; Nicotinic Agonists [*therapeutic use]; Nortriptyline [therapeutic use]; Quinoxalines [therapeutic use]; Randomized Controlled Trials as Topic; Smoking Cessation [*methods]; Tobacco Use Disorder [*drug therapy]; Varenicline

### MeSH check words

Humans



Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.