Interventions for smoking cessation and reduction in individuals with schizophrenia (Review)

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[Intervention Review]

Interventions for smoking cessation and reduction in individuals with schizophrenia

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ABSTRACT

Background

Patients with schizophrenia smoke more heavily than the general population and this contributes to their higher morbidity and mortality from smoking-related illnesses. It remains unclear what interventions can help them to quit or reduce smoking.

Objectives

To evaluate the benefits and harms of different treatments for nicotine dependence in schizophrenia.

Search strategy

We searched the Cochrane Tobacco Addiction Group Specialized Register and electronic databases including MEDLINE, EMBASE and PsycINFO from inception to April 2010.

Selection criteria

We included randomized trials for smoking cessation or reduction, comparing any pharmacological or non-pharmacological intervention with placebo or with another therapeutic control in adult smokers with schizophrenia or schizoaffective disorder.

Data collection and analysis

Two reviewers independently assessed the eligibility and quality of trials and extracted data. Outcome measures included smoking abstinence, reduction in the amount smoked and any change in mental state. We extracted abstinence and reduction data at the end of treatment and at least six months after the intervention. We used the most rigorous definition of abstinence or reduction and biochemically validated data where available. Any reported adverse events were noted. Where appropriate, we pooled data using a random effects model.

Main results

We included 21 trials (11 trials of smoking cessation; four trials of smoking reduction; one trial for relapse prevention; five trials reported smoking outcomes for interventions aimed at other purposes). Seven trials compared bupropion with placebo; meta-analysis showed that smoking cessation rates after bupropion were significantly higher than placebo at the end of treatment (seven trials, N= 340; risk ratio [RR] 2.84; 95% confidence interval [CI] 1.61 to 4.99) and after six months (five trials, N=214, RR 2.78; 95% CI 1.02 to 7.58). Expired carbon monoxide (CO) level and the number of cigarettes smoked daily were significantly lower with bupropion at the end of therapy but not after six months. There were no significant differences in positive, negative and depressive symptoms between bupropion and placebo group. There was no report of major adverse event such as seizures with bupropion.

Contingent reinforcement (CR) with money may increase smoking abstinence rates and reduce the level of smoking in patients with schizophrenia. However, it is uncertain whether these benefits are maintained in the longer term. There was no evidence of benefit for the few trials of other pharmacological therapies (including nicotine replacement therapy (NRT)) and psychosocial interventions in helping smokers with schizophrenia to quit or reduce smoking.

Authors' conclusions

Bupropion increases smoking abstinence rates in smokers with schizophrenia, without jeopardising their mental state. Bupropion may also reduce the amount these patients smoke. CR may help this group of patients to quit and reduce smoking. We failed to find convincing evidence that other interventions have a beneficial effect on smoking behaviour in schizophrenia.

PLAIN LANGUAGE SUMMARY

Are there any effective interventions to help individuals with schizophrenia to quit or to reduce smoking?

People with schizophrenia are, very often, heavy smokers. It is uncertain whether treatments that have been shown to help other groups of people to quit smoking are also effective for people with schizophrenia. In this review, we found that bupropion (an antidepressant medication previously shown to be effective for smoking cessation) helps patients with schizophrenia to quit or to reduce smoking. The effect was clear at the end of the treatment and it may also be maintained after six months. Patients who used bupropion in the trials did not experience any major adverse effect and their mental state was stable during the treatment. Smokers with schizophrenia who receive money as a reward for quitting may have a higher rate of stopping smoking whilst they get payments. However, there is no evidence that they will remain abstinent after the reward stops. There was too little evidence to show whether other treatments like nicotine replacement therapy and psychosocial interventions are helpful.

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

Comparison	Smoking abstinence at the end of trial (per 100 patients)					Smoking abstinence at follow-up after 6 months (per 100 patients)				
	Number of trials	Intervention	Control	Difference *	Number needed#	Number of trials	Intervention	Control	Difference *	Number needed#
Bupropion vs. placebo	7	22	8	14 (5 to 31)	7 (3 to 20)	5	10	4	6 (0 to 24)	17 (4 to 1350)
TNP vs. placebo	Data not combined because of heterogeneity of studies					No trial found				
CR + TNP vs. minimal	1	50	10	40	3	No follow-up data available				

* calculated as absolute risk reduction/increase per 100 people treated, using the rate in control (comparator) arms of trials, with the summary RR applied to calculate the expected absolute risk reduction/ increase for the investigative arms of trials (95% confidence intervals in bracket)

' ns' = difference not statistically significant (i.e. summary risk ratio confidence intervals cross 1.00).

Number needed to be treated with the intervention to cause one person to experience difference in the direction noted. Number needed not given where difference between the intervention and the comparator arm was not significantly different (95% confidence intervals in bracket)

BACKGROUND

Schizophrenia is a chronic and severe mental illness affecting approximately one per cent of the general population (American Psychiatric Association 1994). A meta-analysis of 42 epidemiological studies across 20 different countries shows that people with schizophrenia have more than five times the odds of current smoking than the general population, and smoking cessation rates are much lower in smokers with schizophrenia compared with the general population (de Leon 2005a). In addition, smokers with schizophrenia smoke more heavily and extract more nicotine from each cigarette (Olincy 1997; Kelly 1999; de Leon 2005a; Williams 2005). People with schizophrenia have a shorter life expectancy than the general population, and chronic cigarette smoking has been suggested as a major contributing factor to higher morbidity and mortality from malignancy and, cardiovascular and respiratory diseases in this group of patients (Brown 2000; Lichtermann 2001). Tobacco use among individuals with schizophrenia is financially costly; a study has shown that it consumed 27% of the monthly income of those residing in a high tobacco tax state (Steinberg 2004).

Heavy smoking in patients with schizophrenia has been reported to be associated with more positive symptoms, increased substance misuse, more frequent psychiatric hospitalisation and a higher suicide risk (Goff 1992; Ziedonis 1994; Workgroup on Substance Use Disorders 2006). Tobacco smoking also increases the metabolism of some antipsychotic medications (Desai 2001) and some patients may use tobacco to alleviate the side effects of neuroleptic medications. Indviduals with schizophrenia often have impairment in their cognitive function including difficulty in filtering out unnecessary information (Kumari 2002), secondary to abnormalities in the sensorimotor gating. Cigarette smoking appears to improve sensory gating in patients with schizophrenia (Adler 1998). Hence, patients with schizophrenia may use cigarette smoking to improve their cognitive function. In addition to the cognitive deficits of frontal executive function and in attention among individuals with schizophrenia, depressive symptoms, drug misuse, disorganized thinking and poor task persistence may also explain their lower motivation and greater difficulty for smoking cessation (Culhane 2008; Moss 2009). Patients with schizophrenia may be ambivalent about giving up smoking, as there are few role models of ex-smokers and less specific support available for quitting smoking. Furthermore, smoking is sometimes condoned in mental health setting and in the past cigarettes were used in token economies to reinforce positive patient behaviour (Gustafson 1992s).

Tobacco control specialists and healthcare providers previously have not offered tobacco dependence treatment to patients with schizophrenia, probably secondary to stigma, lack of information, or perceived hopelessness regarding abstinence (Williams 2006). More recent initiatives have aimed to improve the physical health of those with schizophrenia, and guidelines for smoking cessation interventions for smokers with schizophrenia have now been published (Zwar 2007; Fiore 2008; Dixon 2009; Buchanan 2009).

Smokers with schizophrenia have a more severe nicotine dependence compared to smokers without schizophrenia (de Leon 2005a). Hence, interventions may not be as effective as they have shown to be in the general population. We also considered the safety of these interventions, in particular those that involve drug therapy. Some of the pharmacological treatments for nicotine dependence act on neurotransmission. For example, previous smoking cessation guidelines do not recommend the use of bupropion in smokers with schizophrenia because there may be a theoretical risk of psychotic relapse if bupropion, a dopamine agonist, is used among patients with schizophrenia (Strasser 2001). Moreover, drug treatment for smoking cessation and reduction may interact with and alter the effectiveness of the antipsychotic medications, which are commonly used among patients with schizophrenia for their illness. In addition, nicotine withdrawal can cause symptoms like depression, anxiety, irritability. All these factors may contribute to changes in the mental state of these patients, and the extent of the change in the mental state remains unclear. The aim of this review is to summarise existing evidence for different interventions in smoking cessation and reduction for patients with schizophrenia.

OBJECTIVES

This review addressed the following objectives:

1. To examine the efficacy of different interventions (alone or in combination with other interventions) on smoking cessation in individuals with schizophrenia.

2. To examine the efficacy of different interventions (alone or in combination with other interventions) on smoking reduction in individuals with schizophrenia.

3. To assess any harmful effect of different interventions for smoking cessation on the mental state of patients with schizophrenia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCT) or quasi-randomized controlled trials.

Types of participants

We included adult smokers with a current diagnosis of schizophrenia according to the criteria of the International Classification of Diseases (ICD) (World Health Organisation 2003) or Diagnostic and Satistical Manual of Mental Disorders (DSM) (American Psychiatric Association 1994). Smokers with a diagnosis of schizoaffective disorder were also included, because certain core symptoms are the same as in schizophrenia. Patients with a diagnosis of schizophrenia or schizoaffective disorder who had other substance misuse disorder or additional psychiatric disorders were not excluded, as individuals with schizophrenia have high prevalence of substance misuse disorders (Dixon 1999). If a study was conducted in a group of participants with mixed psychiatric diagnoses, that trial was included only when separate data for subjects with schizophrenia or schizoaffective disorder were available. We included subjects who may or may not have expressed an interest to stop or reduce smoking. We reported whether or not participants in a study wanted to stop or reduce smoking.

Types of interventions

We included both pharmacological and non-pharmacological interventions (alone or in combination) specific to smoking cessation or reduction. Interventions intended for another purpose (e.g. antipsychotics for treating schizophrenia) were included if smoking abstinence or reduction outcomes were reported. We reported the results of these trials separately and they did not contribute to any meta-analysis, since they were not designed to test the efficacy of the intervention for smoking cessation or reduction. The control condition could be another intervention (pharmacological or non-pharmacological), placebo, or usual care.

Types of outcome measures

Primary outcomes

Smoking abstinence at longest follow up

The primary outcome was abstinence from smoking assessed at least six months from the start of the intervention, according to the "Russell Standard" (a common standard for outcome criteria in smoking cessation trials) (West 2005). The United States Department of Health and Human Services (USDHHS) Tobacco Use and Dependence Guideline Panel also suggested a minimum of a six-month period as an adequate period of abstinence to assess treatment differences in the longer term (Fiore 2008). Abstinence could be assessed by self report or with biochemical verification. For data synthesis, we chose the strictest definition of abstinence in each trial, preferring sustained abstinence over point prevalence if both were reported. In studies that used biochemical validation of abstinence, only people whose self-reports could be validated were classified as abstinent.

Change in mental state

Change in mental state was measured by change in positive symptoms (e.g. hallucinations, delusions), negative symptoms (e.g. anhedonia, avolition), and depressive symptoms.

Secondary outcomes

Smoking abstinence at the end of the intervention

This was measured as for the primary abstinence outcome.

Reduction of smoking behaviour or dependence

This was assessed at the end of the intervention and during the follow-up period after the end of the intervention, if data was available. Measures could include any of the following: percentage change in cigarettes per day (CPD) from baseline level; absolute number of cigarettes foregone; incidence of achieving at least a 50% reduction in CPD; reduction of expired CO level; or reduction of scores on scale measures of nicotine dependence (e.g. Fagerstrom Test for Nicotine Dependence (FTND)).

Other adverse events

Any other adverse events reported were also recorded and assessed.

Search methods for identification of studies

Electronic searches

The specialized register of the Cochrane Tobacco Addiction group was searched in June 2009 and again in March 2010 using the topic related free-text term 'schiz*'. See the Specialized Register section of the Tobacco Addiction Group Module in the Cochrane Library for search strategies for CENTRAL (the Cochrane Central Register of Controlled Trials), MEDLINE, EMBASE, PsycINFO and Web of Science and dates of searches. CENTRAL was searched in the Cochrane Library 2009 Issue 2 using the strategy ((SR-SCHIZ) and (smoking):ti,ab,kw) AND NOT (SR-TOBACCO). In addition, we searched the following electronic databases in May 2009 and again in April 2010:

1. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations via OVID (1950 onwards)
2. EMBASE via OVID (1980 onwards)
3. PsycINFO via OVID (1806 onwards)
4. CINAHL (1979 onwards)
5. ISI Web of Science with Conference Proceedings (1900 onwards)
6. BIOSIS Previews (1969 onwards)

We included all data available up to the last date of search and in any language. We included search terms for schizophrenia, smoking and randomized trials. For schizophrenia, we used the search

terms used by the Cochrane Schizophrenia Group. For smoking cessation and reduction, we used search terms defined by the Cochrane Tobacco Addiction Group, with some modification to focus on interventions for both smoking cessation and reduction. To identify randomized trials, we used the search strategies suggested in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). Full search strategies for databases are listed in the appendix of this review (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We checked the reference lists of retrieved studies for additional relevant information. We also searched the following online clinical trials registers to identify potential ongoing and unpublished trials: (1) World Health Organisation International Clinical Trials Registry Platform Search Portal (http://apps.who.int/trialsearch); (2) ClinicalTrials.gov register (www.clinicaltrials.gov); (3) The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); (4) International Standard Randomised Controlled Trial Number Register (www.controlled-trials.com/isrctn/) and (5) UK Clinical Trials Gateway (www.controlled-trials.com/ukctg/). Where duplicate reporting of the same trial was suspected, we attempted to contact authors for clarification. If duplication was confirmed, we used the full publication together with any other related publications for additional information.

Data collection and analysis

Selection of studies

Two authors (DTT & ACW) screened the titles and abstracts identified by the search independently, and decided on the possible reports to be included. Full text reports of all potentially relevant trials were obtained and examined by both authors to decide whether the studies fulfilled the inclusion criteria. Any disagreement between the authors was resolved through discussion. All studies excluded at this stage were reported in the characteristics of excluded studies section.

Data extraction and management

Two authors (DTT & MP) independently extracted data from all included trials with a specifically designed data extraction form. Information extracted included the following:

1. Methodology - including the inclusion and exclusion criteria, method of randomization and other design features and setting of the trial.
2. Demographics of participants - including severity of tobacco dependency, concurrent medication used and severity of schizophrenic illness.
3. Details of the interventions - including any target quit date set.
4. Outcome measures - including the definition of abstinence and length of follow up and measurements used, including any biochemical verification.

We attempted to contact the authors of the reports if there were any uncertainties or possible duplicate reporting of the same patient group, or for clarification of the study design and results. We sought separate data for participants with schizophrenia or schizoaffective disorder in trials that recruited people with a wider range of psychiatric diagnoses. Any disagreement between the authors was resolved through discussions or consultation with author ACW.

We categorised trials according to the primary aim of the study (i.e. smoking cessation, smoking reduction, or intervention with other aims). To group trials by category in the Characteristics of included studies we used the prefixes *, + , and ^ as part of the study identifiers. For each category, we grouped the trials according to the specifics of the intervention.

Assessment of risk of bias in included studies

During data extraction, two authors (DTT & MP) also independently assessed each trial for risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008). We recorded sequence generation during randomization, concealment of allocation, blinding, completeness of outcome data (including use of intention-to-treat (ITT) analysis) and selective outcome reporting for each trial. Other potential sources of bias were also identified. Each trial was categorised as low, uncertain or high risk of bias of each domain, based on the standards described in the Cochrane Handbook.

Measures of treatment effect

We calculated summary estimates for the extracted data. Results for dichotomous outcomes were expressed as risk ratios (RR). RR was calculated as: (number of subjects with the outcome in intervention group / number of subjects randomized to intervention group) / (number of subjects with the outcome in the control group / number of subjects randomized to the control group). An RR greater than one favoured the intervention group. Results for continuous outcomes were expressed as mean difference (MD) where measured with the same scale, or standardised mean difference (SMD) where measured with different scales. A summary MD or SMD below zero favoured the intervention group in all continuous outcome measures.

Dealing with missing data

We attempted to contact trial authors for any missing data. For data synthesis, where no additional information was forthcoming, we assumed any missing data as failure to achieve the outcome.

The potential impact of the missing data was also addressed in the risk of bias table for each study. We did not include trials for meta-analysis of continuous outcomes if there was no standard deviation (SD) or other estimate of variability available.

Assessment of heterogeneity

We examined statistical heterogeneity among trials with the Cochran *Q* test and by calculating the I^2 statistic. The I^2 statistic describes the percentage of the variability in the summary estimate due to heterogeneity rather than chance (Higgins 2003). Values over 50% suggested moderate heterogeneity and values over 75% suggest substantial heterogeneity.

Assessment of reporting biases

Where appropriate, potential publication bias was assessed with funnel plots of the log risk ratio, mean difference or standardised mean difference.

Data synthesis

Where appropriate, we performed meta-analysis of the trial data. For abstinence and reduction, we conducted analyses with data from six-month follow up (primary outcome) and from the end of the intervention (secondary outcome). For change in mental state we conducted separate analyses for positive, negative, and depressive symptoms, using data available at the end of the intervention. For dichotomous outcomes, we calculated the summary estimates using the Mantel-Haenszel method and reported the 95% confidence intervals (CI) of the risk ratios. We calculated the summary estimates for continuous outcomes using the inverse variance approach, also with 95% CI. Change-from-baseline measurements and final measurements were combined for continuous outcomes if the MD was used to express the summary results, following the Cochrane Handbook (Higgins 2008).

Data were pooled using the random-effects model, although the fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers.

Sensitivity analysis

We conducted sensitivity analysis to assess whether the estimate of treatment effect was influenced by the publication type (i.e. full journal paper versus other reports such as conference proceedings).

RESULTS

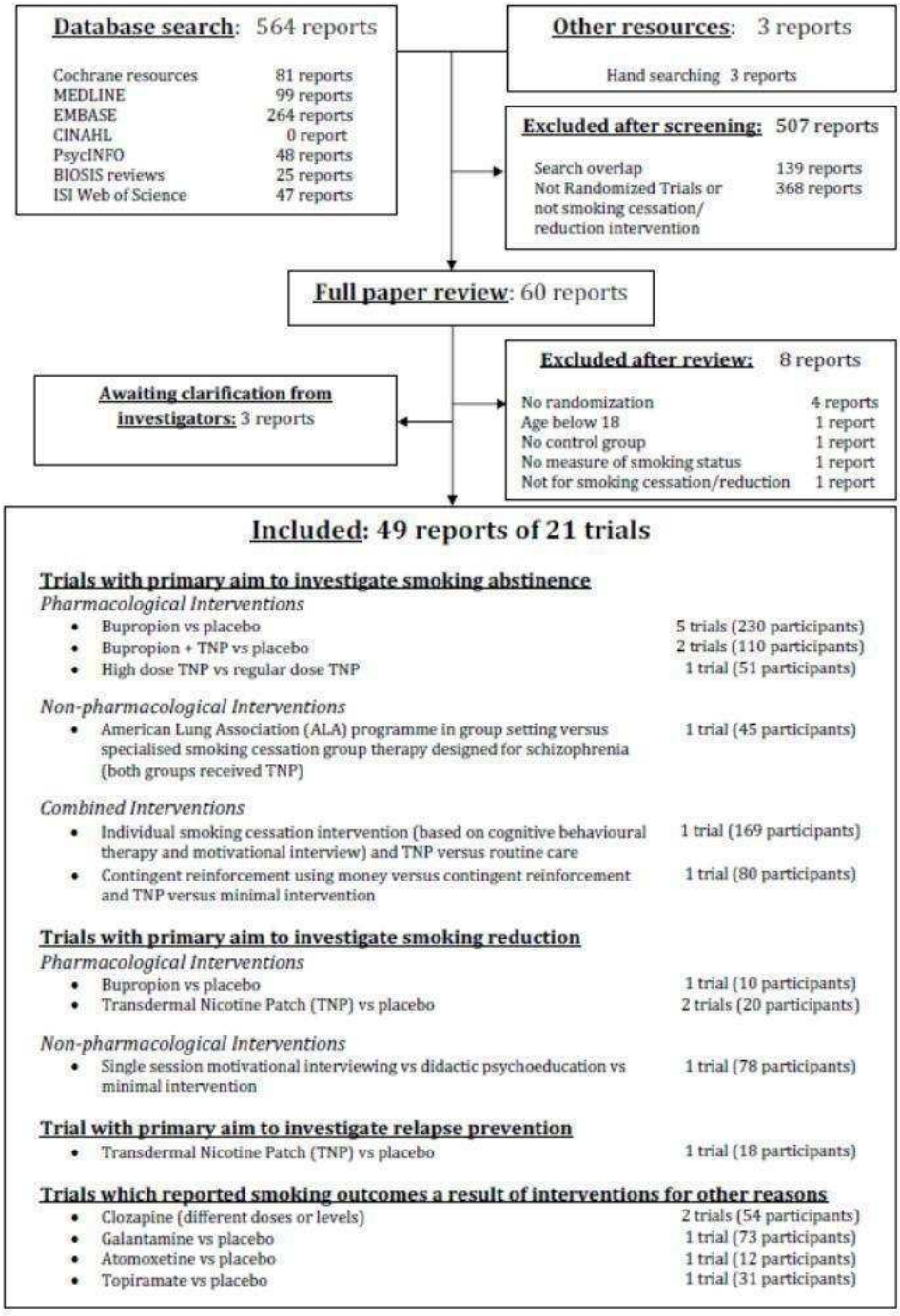
Description of studies

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

Results of the search

We identified 564 reports from the electronic search of the databases (99 reports from MEDLINE, 264 from EMBASE, 48 from PsycINFO, none from CINAHL, 25 from BIOSIS reviews, 47 from ISI Web of Science with Conference Proceedings, and 81 reports from CENTRAL and the specialized register of the Cochrane Tobacco Addiction group) (Figure 1). We identified three further trial reports from hand searching and 12 ongoing studies from the online clinical trials registers and another ongoing study from hand searching (See Characteristics of ongoing studies). After screening, we reviewed the full text of 60 reports which were considered potentially eligible. Eight trials were excluded after reviewing the full text (See Characteristics of excluded studies). We also contacted the investigators of two trials to clarify the method of treatment allocation, as we had concerns that these two trials were not randomized because of the uneven number of subjects among the treatment groups. We have not received any response; see Characteristics of studies awaiting classification.

Figure 1. Summary of the process of identifying randomized trials for inclusion



The final review includes 21 trials; see the Characteristics of included studies table. The primary aim of 11 trials was to investigate an intervention for smoking cessation (studies prefixed with an asterisk; *George 2000; *Evins 2001; *George 2002; *Evins 2005; *Baker 2006; *Evins 2007; *Gallagher 2007; *Weiner 2007; *Williams 2007; *George 2008; *Li 2009). Four studies focused on smoking reduction (studies prefixed with a cross; +Hartman 1991; +Dalack 1999; +Steinberg 2003; +Fatemi 2005). One trial investigated the use of nicotine patch for relapse prevention after smoking cessation (^Horst 2005). The remaining five studies reported outcomes related to smoking abstinence or reduction but their main aims were to evaluate the effectiveness of interventions for other purposes. These studies are reported separately, and do not contribute data to any meta-analysis (McEvoy 1995; de Leon 2005b; Kelly 2008; Weinberger 2008; Sacco 2009).

Included studies

1. Trials of interventions for smoking cessation, reduction or relapse prevention

Study and participant characteristics

There were sixteen trials in this category; most were conducted in the United States and reported in English apart from *Baker 2006, conducted in Australia; and *Li 2009, conducted in China and reported in Chinese. Most of the reports were published in journals, except three trials which were only reported as letters to editors or conference proceedings (+Fatemi 2005; *Weiner 2007; *Williams 2007). There were three cross-over studies (+Hartman 1991; +Dalack 1999; +Fatemi 2005) with washout periods from five days to two weeks. The relapse prevention study, ^Horst 2005, involved an open label phase followed by a randomized controlled trial; we only considered data from the randomized trial phase in this review.

Most trials recruited participants from the community. *Li 2009 recruited from an in-patient unit, and +Hartman 1991 recruited from hospitals and the community. Two studies did not report details of recruitment (*George 2000; +Steinberg 2003).

Three trials (+Hartman 1991; *Baker 2006; *Gallagher 2007) recruited subjects with mixed psychiatric diagnoses but data for participants with schizophrenia or schizoaffective disorder were available for separate analysis. Some studies explicitly excluded participants with any active substance misuse other than nicotine (+Dalack 1999; *Evins 2001; *George 2002; *Evins 2005; *Evins 2007; *George 2008).

Nine trials explicitly stated that participants had expressed interest in quitting smoking (*George 2000; *Evins 2001; *George 2002; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *Williams 2007; *George 2008;). +Steinberg 2003 measured changes in quitting motivation after motivational interviewing and the participants had different levels of interest in quitting smoking at the baseline. Target quit dates were set in nine studies (*George 2000; *Evins 2001; *George 2002; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *Weiner 2007; *George 2008).

Interventions

A range of interventions were evaluated. Of the studies comparing pharmacotherapy with placebo the commonest interventions were bupropion (*Evins 2001; *George 2002; *Evins 2005; +Fatemi 2005; *Weiner 2007; *Li 2009) and transdermal nicotine patch (TNP) (+Hartman 1991; +Dalack 1999; ^Horst 2005). Two studies compared the combination of bupropion and TNP with TNP and placebo (*Evins 2007; *George 2008). One study compared the efficacy of different dosages of TNP (*Williams 2007). Some of the drug therapy studies provided psychosocial interventions to all participants. These psychosocial interventions included group cognitive behavioural therapy (CBT) (*Evins 2001; *Evins 2005; *Evins 2007); group therapy for motivational enhancement, psychoeducation and relapse prevention (*George 2002); group behavioural therapy (*George 2008); smoking cessation educational classes along with discussions with health educators (^Horst 2005); and group therapy using the American Cancer Society Fresh Start Programme (*Weiner 2007). The duration of drug treatment varied from seven hours (+Hartman 1991) to six months (^Horst 2005).

Two trials predominantly examined the effect of non-pharmacological interventions. +Steinberg 2003 examined the effect of a single session of motivational interview and compared this with didactic psychoeducation and minimal control intervention. *George 2000 compared the American Lung Association programme in a group setting with a specialised group therapy designed for schizophrenia which had more focus on motivational enhancement, psychoeducation, social skills training and relapse prevention strategy; participants in both groups also received TNP. Two other trials investigated the combined effect of pharmacological and psychosocial interventions. In *Baker 2006, a combination of individually administered motivational interviewing and CBT and TNP was compared with routine care. In a three arm study, *Gallagher 2007 compared CR using money, with and without additional TNP, and a self quit control without TNP.

Outcomes

Abstinence was defined and measured in 11 trials (*George 2000; *Evins 2001; *George 2002; *Evins 2005; *Baker 2006; *Evins 2007; *Gallagher 2007; *Weiner 2007; *Williams 2007; *George

2008; *Li 2009). Two of these studies did not explicitly report whether participants expressed any interest in quitting smoking and we were not able to clarify this with the authors (*Li 2009; *Weiner 2007). Three trials did not report any continuation of follow up beyond the end of the intervention; *Williams 2007 and *Li 2009 reported abstinence at eight weeks; *Weiner 2007 after 14 weeks. The other eight studies provided results after longer follow up, of at least six months after the start of treatment. All trials except *Li 2009 validated abstinence biochemically. One study reported the rate of relapse to smoking after abstinence (^Horst 2005).

Four trials only reported smoking reduction as the main outcome measure (+Hartman 1991; +Dalack 1999; +Steinberg 2003; +Fatemi 2005). Most of the studies which measured smoking abstinence also reported some measures of smoking reduction. Self-report of reduction in CPD was commonly reported as a measure of reduction (+Hartman 1991; +Dalack 1999; *Evins 2001; *George 2002; +Steinberg 2003; *Evins 2005; +Fatemi 2005; *Baker 2006; *Evins 2007; *Gallagher 2007; *Li 2009). These outcomes were reported after a range of follow-up periods which varied from two days (+Hartman 1991) to 12 months (*Baker 2006). Expired CO level reduction was also frequently reported as an outcome measure of smoking reduction (+Dalack 1999; *George 2000; *George 2002; +Steinberg 2003; *Evins 2005; ^Horst 2005; *Gallagher 2007; *Weiner 2007). Other measures of smoking reduction included plasma cotinine level (*Evins 2001), scale measure of nicotine dependence (e.g. FTND) (+Fatemi 2005; +Steinberg 2003; *Gallagher 2007; *Weiner 2007; *Li 2009), urine cotinine level (+Fatemi 2005; *Weiner 2007) and salivary cotinine level (*Gallagher 2007).

Ten studies reported measures of mental state of the participants (+Dalack 1999;*George 2000; *Evins 2001; *George 2002; *Evins 2005; +Fatemi 2005; *Baker 2006; *Evins 2007; *George 2008; *Li 2009).

2. Trials of interventions with primary aim other than smoking cessation, reduction or relapse prevention

Five trials reported outcomes of smoking behaviour change, but were not originally designed to investigate smoking cessation or reduction (McEvoy 1995; de Leon 2005b; Kelly 2008; Weinberger 2008; Sacco 2009). One study only included participants with schizoaffective disorder, bipolar type (Weinberger 2008). Three studies included non-smokers as participants and performed separate analyses for those who smoked, in relation to their smoking behaviours (de Leon 2005b; Kelly 2008; Weinberger 2008). Two trials investigated the effect of clozapine in patients with treatment resistant schizophrenia (McEvoy 1995; de Leon 2005b). Other interventions included galantamine (Kelly 2008), atomoxetine (Sacco 2009) and topiramate (Weinberger 2008). None of these five trials included smoking abstinence as an outcome, but used various methods to measure smoking reduction.

Risk of bias in included studies

1. Trials of interventions for smoking cessation, reduction or relapse prevention

We judged eight trials to have used an adequate method for generating the randomization sequence (+Dalack 1999; *Evins 2001; +Steinberg 2003; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *Gallagher 2007). Most of the other studies were classified as unclear because there was no description of the randomization process and we could not clarify details with the investigators. We obtained additional information on *Li 2009 (see details in Characteristics of included studies) and judged it as having a high risk of bias (ROB).

We judged four studies to have used an adequate method of allocation concealment (+Dalack 1999; *Evins 2001; *Evins 2005; *Evins 2007). Other studies did not clearly report the method of allocation concealment and we could not clarify this with the investigators, so the risk of bias was unclear. From the correspondence with *Li 2009, there was definitely no concealment of allocation sequence and hence we judged the study as having a high risk of bias. We had some clarification from *Gallagher 2007 regarding allocation concealment. In their study, allocation was not done centrally and there was a possibility that research staff might know which group the subsequent participant would be assigned to. Hence, we judged that study as having a high risk of bias in allocation concealment.

Adequate blinding to treatment allocation in assessment of outcomes was observed in seven trials (+Hartman 1991; +Dalack 1999; *Evins 2001; *George 2002; *Evins 2005; +Fatemi 2005; *Evins 2007). Some studies reported double-blinding but their reports did not explicitly state who was blinded and we were not able to clarify with the investigators (*Weiner 2007; *Williams 2007; *George 2008; *Li 2009). We judged that double-blinding implied that it was likely participants and investigators were blinded, but declared all these studies as having an unclear risk of bias; although it was likely that the possible bias introduced to these studies was minimal. Some studies were assessed to have inadequate blinding. Significant bias could be introduced in these studies without adequate blinding, as self-report measures (e.g. self-report reduction of cigarettes used) and subjective assessment (e.g. assessment of psychiatric symptoms) were used for outcome assessments. Two studies did not report any blinding (*George 2000; *Gallagher 2007). Only the outcome assessor was blinded in another two studies (+Steinberg 2003; *Baker 2006). ^Horst 2005 blinded participants but not the outcome assessor.

There were wide-ranging variations in how missing outcome data were handled among trials. We judged four studies as low risk of bias secondary to incomplete outcome data (+Dalack 1999; *George 2002; *Baker 2006; *Evins 2007). These studies included all participants who were randomized and used proper ITT analysis. Missing data were classified either as non-abstinent or

as a failure to achieve smoking reduction in these studies (*Baker 2006; *Evins 2007). Some trials used the "last observation carried forward" approach to handle missing data (+Steinberg 2003; *Gallagher 2007). We had concern whether this approach was appropriate, as those who lost to follow up may be more likely to relapse and the "last observation carried forward" approach probably would have overestimated the intervention effect by assuming these participants had maintained abstinence. Hence, we categorised these trials as having a high risk of bias for incomplete outcome data. In other trials, participants who were randomized were excluded from the analysis for various other reasons. These reasons included drop-out before start of intervention (*Evins 2001; *Evins 2005; *George 2008), the need for dose change for symptom stabilization or side effects of medications (*George 2000), stopping the intervention during the trial (^Horst 2005; *Li 2009) and lost to follow up (+Hartman 1991). We judged all these studies to have a high risk of bias for incomplete outcome data. Three trials did not clearly state how they handled missing outcome data and we classified them as having an unclear risk of bias (+Fatemi 2005; *Weiner 2007; *Williams 2007).

Four studies did not report all outcome results as suggested in the methods section or in their protocol, and these trials were classified as having a high risk of selective reporting (+Dalack 1999; +Fatemi 2005; *Gallagher 2007; *Weiner 2007).

There were large differences in contact time between the intervention group and the control group in three out of the four trials which examined the effect of non-pharmacological interventions. *Baker 2006 compared an intervention involving eight hours of individual contact over eight weeks with routine care, which had no extra contact time. *Gallagher 2007 compared three groups; CR with TNP, CR only; and self quit without any active intervention. The self quit group had only three visits but the other two groups had 12 visits for each group. +Steinberg 2003 compared three groups: motivational interview for 40 minutes; didactic psychoeducation for 40 minutes; and minimal intervention for five minutes.

There were some other possible biases. Despite randomization, two studies had statistically significant differences in some characteristics between the intervention and the control groups (*George 2000; *Evins 2005). In ^Horst 2005,where the RCT followed an earlier open label phase, the report did not clearly state whether the two comparison groups were similar in terms of their baseline characteristics. Two trials lacked biochemical validation of smoking status (+Hartman 1991; *Li 2009). Two of the three cross-over studies had a relatively short washout period: five days (+Dalack 1999) and one week (+Hartman 1991). In the other cross-over study (+Fatemi 2005), individual data were not available in the report and it was unclear whether paired analyses were used in the analysis. In those studies which were reported either as 'letters to editors' or as conference proceedings (*Weiner 2007; *Williams 2007), there was insufficient information to assess whether any other important bias existed and we judged them as unclear.

2. Trials of interventions with primary aim other than smoking cessation, reduction or relapse prevention

We could only judge one study to have a low risk of bias in sequence generation and allocation concealment (Kelly 2008). Other trials did not explicitly describe the way in which the randomization sequence was generated and we could not clarify this with the investigators, so the risk of bias in sequence generation and allocation concealment was unclear. Two trials reported double-blinding but their reports did not explicitly state who were blinded and we were not able to clarify this with the investigators (McEvoy 1995; Sacco 2009). The study by de Leon 2005b excluded four subjects from the analysis without stating the reason. Another study used the last observation carried forward method for missing data (Weinberger 2008). We judged these two trials as having a high risk of bias for the incomplete outcome data.

In two studies, the results in the reports were subgroup analyses of larger related trials and some people who smoked were not included in the analysis (Kelly 2008; Weinberger 2008). The reason for not including these people was uncertain and selection bias might have been introduced. The study by de Leon 2005b reported unequal numbers among the intervention groups and there was no information as to whether these groups were comparable in characteristics and in their baseline cotinine level. There was also baseline difference between comparison groups in the study by McEvoy 1995. As a result, we judged all these trials as having a high risk for other bias.

Effects of interventions

See: **Summary of findings for the main comparison** Applicability in clinical practice - projected numbers of people with schizophrenia per hundred patients treated with smoking cessation therapies (smoking abstinence at the end of the trial and at follow-up after 6 months); **Summary of findings 2** Applicability in clinical practice - smoking reduction at the end of the trial and at follow-up after 6 months among people with schizophrenia treated with smoking cessation therapies

Trials are grouped under the following categories: (1) trials in which the primary aim was smoking abstinence; (2) trials in which the primary aim was smoking reduction; (3) trials in which the primary aim was relapse prevention; (4) trials of other interventions which reported smoking outcomes. Within each category, if appropriate, trials were grouped according the principal intervention comparison in each study. For instance, if the main comparison of a study was a drug therapy (even if there was any additional psychosocial intervention to both treatment and placebo group), the study was grouped under pharmacological interventions. Similarly, if the main comparison of a study was a psychosocial intervention (even if there was any additional drug treatment to all the comparison groups), this was grouped under non-pharmacological interventions.

1. Trials with a primary aim of smoking abstinence

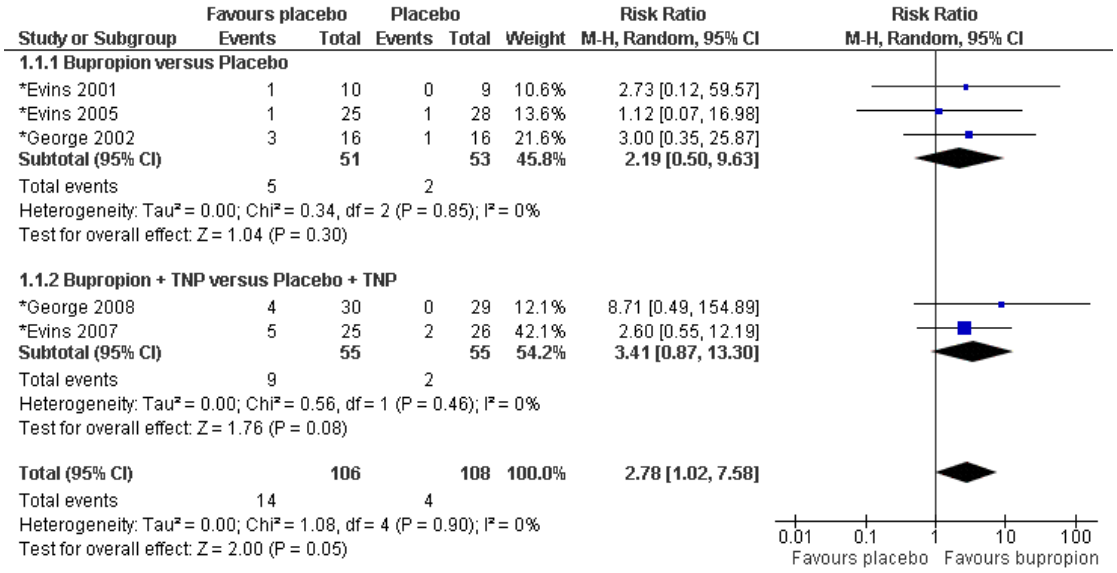
1.1 Pharmacological intervention - Bupropion

Intervention rationale: Bupropion is an atypical antidepressant with both dopaminergic and adrenergic actions. There is robust evidence that bupropion is a safe and effective treatment for nicotine dependence in the general population (Hughes 2007). There is however a theoretical concern about the safety of using bupropion in patients with schizophrenia, as bupropion may precipitate or exacerbate psychosis because of its pharmacodynamic and pharmacokinetic properties. Bupropion and its metabolite inhibit the cytochrome P450 CYP2D6 isoenzyme, and co-administration of bupropion with drugs that are metabolised by this isoenzyme (including antipsychotic medications such as risperidone, haloperidol) may cause significant drug interactions (GlaxoSmithKline 2008). This, as well as bupropion's dopaminergic action, may adversely affect the mental state of individuals with schizophrenia. In addition, seizure is a recognised adverse effect of bupropion in the general population, with a rate of between 0.1% and 0.4% (GlaxoSmithKline 2008).

Abstinence outcomes

Seven trials with a total of 340 participants investigated bupropion as an aid for smoking cessation. Five trials (*Evins 2001; *George 2002; *Evins 2005; *Evins 2007; *George 2008) had six-months follow up from the start of bupropion treatment, recruited participants who were interested in quitting smoking, and set a target quit date. Neither of the shorter-term trials (*Weiner 2007; *Li 2009) reported whether participants had any interest in quitting. At six-month follow up, participants who took bupropion were nearly three times more likely to be abstinent compared to those allocated to placebo, with a lower confidence interval that just excluded one (5 trials, N=214, RR 2.78, 95% CI 1.02 to 7.58, I^2 = 0%; Analysis 1.1; Figure 2). There was no strong evidence for a difference in relative effect between the three trials using bupropion as the sole pharmacotherapy and the two trials using bupropion as an adjunct to TNP (*Evins 2007; *George 2008); confidence intervals were wide in both subgroups. The number of successful quitters was small in all studies. Two trials (*Evins 2001; *Evins 2007) reported data of smoking cessation from follow up of longer than six months: In the two-year follow up report for *Evins 2001, 4 of 18 participants were abstinent including the only one subject who was abstinent at the end of the trial. The investigators reported that three of the four abstinent after two years received bupropion SR during the trial or during the follow-up period and the fourth quit during an extended medical hospitalisation. By the 12-month follow up for *Evins 2007, two more intervention group participants had relapsed. Had the outcome at this point been used in the meta-analysis the estimated effect would have been smaller and the confidence intervals for the pooled estimate would have included one.

Figure 2. Bupropion versus placebo: Abstinence at 6-month follow-up (primary outcome)

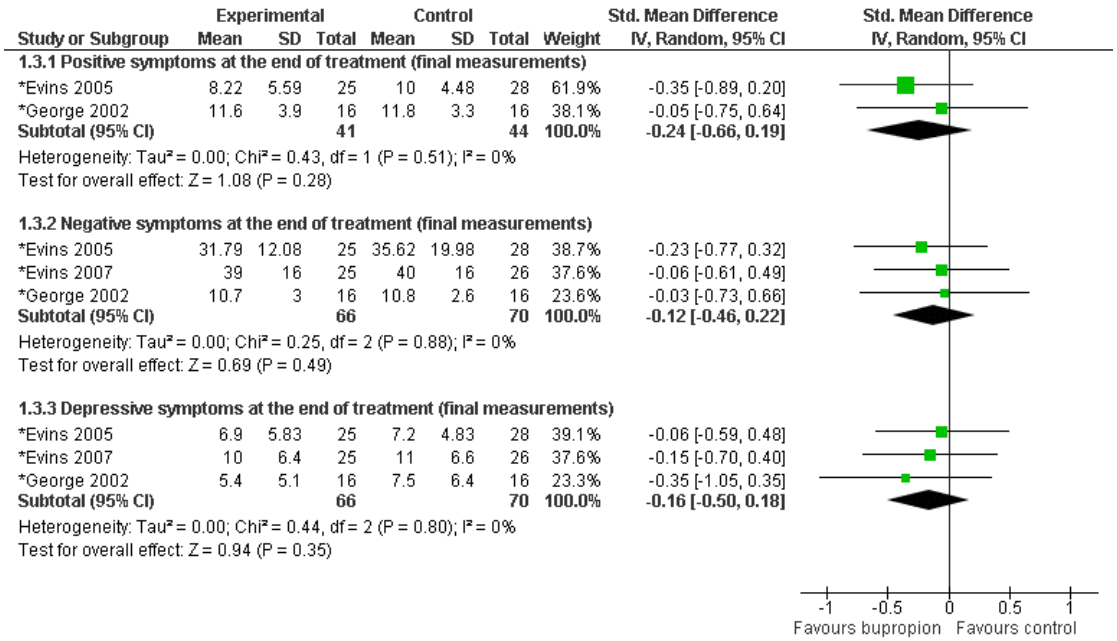


The effect size was similar for the secondary outcome of abstinence at the end of treatment, but the confidence intervals were narrower reflecting the two additional trials and the larger number of successful short term quitters (7 trials, N=340; RR 2.84, 95% CI 1.61 to 4.99, I² = 0%; Analysis 1.2). Sensitivity analyses detected no important difference in effect from omitting any of the following; one trial was reported only as a conference abstract (*Weiner 2007); two trials in which the participants' interest in quitting smoking were uncertain (*Weiner 2007; *Li 2009); or one trial using the lower dose of 150 mg bupropion daily, compared with 300 mg daily in other trials (*Evins 2001).

Mental state outcomes

All trials reported the effect of bupropion on the mental state of the participants. Compared with placebo, there was no evidence that bupropion caused any significant deterioration of positive, negative or depressive symptoms in patients with schizophrenia during smoking cessation. Two studies provided sufficient final measurement data for estimation of change of positive symptoms and one additional study also provided sufficient data to estimate the effect of bupropion on negative and depressive symptoms. There was no evidence that bupropion, compared to control, caused a significant difference in positive symptoms (2 trials, N=85; SMD -0.24, 95% CI -0.66 to 0.19; I^2 = 0%), negative symptoms (3 trials, N=136; SMD -0.12, 95% CI -0.46 to 0.22; I^2 = 0%) or depressive symptoms (3 trials, N=136; SMD -0.16, 95% CI -0.50 to 0.18; I^2 = 0%) (Analysis 1.3; Figure 3). Other trials also consistently reported that there was no significant difference in these symptoms between the bupropion group and the placebo group after bupropion treatment, but without reporting full data (*Weiner 2007; *George 2008; *Li 2009). In another study, bupropion treatment was associated with improvement in negative symptoms and greater stability of psychotic and depressive symptoms, compared to the placebo, during the quit attempt (*Evins 2001). Three studies also reported the effect of abstinence on the mental state of the subjects and there were no effects of smoking abstinence on positive, negative or depressive symptoms (*Evins 2005; *Evins 2007; *George 2008).

Figure 3. Bupropion versus placebo: Mental state outcomes



Other adverse effects

Regarding other adverse effects of bupropion, no trials reported any seizures. The prevalence of dry mouth was significantly higher in the bupropion group compared to the control group in one study (p<0.05) (*George 2002). The same research group, in a second study, reported significant differences on concentration,

jitteriness, light-headedness, muscle stiffness and frequent nocturnal awakening in the bupropion group (*George 2008). Three patients out of 59 participants (two in the placebo group and one in the bupropion group) had psychotic breakdown during that trial, but the authors concluded this was unrelated to bupropion. *Li 2009 reported significantly higher prevalence of insomnia, dry mouth and sweatiness in the bupropion group compared to the control group. Two subjects from this trial had recurrence of psychotic symptoms but the author did not report which group these two subjects were allocated to. One participant in *Evins 2005 randomized to bupropion had an allergic reaction to the medication. Two participants in *Evins 2007 using bupropion and TNP dropped out from the trial because of insomnia and dizziness. One trial did not mention any adverse effects in the reports (*Weiner 2007) and the remaining trial reported "no serious adverse events" (*Evins 2001).

Smoking reduction

Most trials also reported some outcome measures for smoking reduction. However, the data reported for these outcome measures were likely from the entire sample (i.e. including both participants who successfully abstained from smoking and participants who continued to smoke). Three trials reported data for smoking reduction measured by expired CO level. At the end of treatment, there was a significant reduction of expired CO level in the bupropion group compared to the control group (3 trials, N=123; MD -7.03ppm, 95% CI -11.38 to -2.67ppm, I^2 = 0%; Analysis 1.4). Two trials reported incomplete data for expired CO level and did not contribute in the meta-analysis, but both favoured bupropion at the end of the treatment (*Evins 2001; *Weiner 2007). At six months after start of treatment, there was no significant difference in expired CO level (3 trials, N=123; MD -5.55ppm, 95% CI -17.89 to 6.78ppm; Analysis 1.5) but there was substantial heterogeneity among trials (I^2 = 83%), largely due to one trial in which the average CO level was higher in the bupropion group than the placebo group (*Evins 2005).

Three trials provided data from the entire sample to contribute to a meta-analysis for smoking reduction measured by CPD. At the end of bupropion treatment, there was a significant reduction of number of CPD in the bupropion group compared to controls (3 trials, N=184; MD -10.77, 95% CI -16.52 to -5.01, I^2 = 40%; Analysis 1.6). One study reported a separate analysis for participants who had not quit smoking; those who received bupropion had a significant reduction in CPD compared to those received placebo (*Evins 2005). Another trial which did not provide raw data for meta-analysis also reported a significant reduction in self-reported CPD in the bupropion group versus the placebo group (*George 2002). At six months after start of bupropion, two studies provided sufficient data for meta-analysis. At this point there was no significant difference in the number of CPD between the bupropion group and the placebo group (2 trials, N=104; MD 0.40, 95% CI -5.72 to 6.53, I^2= 0%; Analysis 1.7).

1.2 Pharmacological intervention - Transdermal nicotine patch (TNP)

One trial compared the use of high dose (42mg) TNP with regular dose (21mg) TNP in 51 patients with schizophrenia who wanted to quit smoking (*Williams 2007). There was no placebo control group. Seven-day point prevalence abstinence rates at eight weeks were not significantly different between the high dose group (32%) and the regular dose group (23%). Survival analysis examining time to first relapse back to smoking also did not differ between two groups. However, the author reported that tolerability and compliance was good for both groups.

Two other studies examined the effect of TNP together with non-pharmacological interventions (*Baker 2006; *Gallagher 2007). In *Gallagher 2007, the smoking abstinence rate at the end of the trial (36 weeks) were significantly higher in participants who used TNP when compared to those without TNP; both groups also received money as CR. Results of these two studies were summarised in the following section of "combined interventions".

1.3 Non-pharmacological intervention

American Lung Association (ALA) programme in group setting versus specialised smoking cessation group therapy designed for schizophrenia (both groups received TNP)

*George 2000 investigated the efficacy of specialised smoking cessation group therapy among patients with schizophrenia who were interested in quitting. There was a borderline significant difference in smoking abstinence rate at the end of the trial (based on continuous abstinence in the last 4 weeks of treatment) between the ALA programme group (23.5%) and the specialised group therapy group (32.1%, p = 0.06). However, at the six-month follow up, smoking abstinence rate was significantly higher in the ALA programme group (17.6%) than the specialised group therapy group (10.7%, p<0.03). There was no statistically significant difference in the expired CO level between the two therapy groups during the course of the trial. There were also no significant differences in psychiatric symptoms or medication side effects between the ALA group and the specialised group therapy group. The authors also performed a secondary analysis based on whether the subject received atypical or typical antipsychotic medications. Smoking abstinence rates at the end of the trial and at six-month follow up were significantly higher in the group of patients who receive atypical antipsychotic medications.There was also a significant reduction in expired CO level with TNP in patients treated with atypical antipsychotic medications, compared to those treated with typical antipsychotics.

1.4 Combined interventions

Individual smoking cessation intervention (based on cognitive behavioural therapy and motivational interview) and TNP versus routine care

*Baker 2006 compared the effect of individual smoking cessation intervention (based on CBT and motivational interview) and TNP with routine care in a group of patients with psychotic disorder of mixed diagnoses. All the participants expressed interest in quitting smoking. The authors provided a subgroup analysis of subjects with diagnosis of schizophrenia and schizoaffective disorder (N=169). There were no overall statistically significant differences between the treatment group and the control group in either continuous abstinence or point prevalence abstinence rate at three months, six months and twelve months after the initial assessment (the authors had set the threshold for statistical significance at $p<0.01$ to control for multiple comparisons). In terms of smoking reduction, there was a significant difference in smoking reduction at three months after the initial assessment, with 42.5% of the treatment group reducing their cigarette consumption by at least 50% relative to baseline; compared to only 15.7% of the control group (odds ratio 3.96, 99% CI 1.53 to 10.23, $p<0.001$). However, the differences in smoking reduction between the treatment group and the control group were not statistically significant at the subsequent follow up sessions at six months and at 12 months after the initial assessment.

Contingent reinforcement using money versus contingent reinforcement and TNP versus minimal intervention

*Gallagher 2007, evaluated the effects of CR using money (with and without additional TNP) compared with minimal intervention in a group of patients with serious mental illnesses. We conducted a subgroup analysis for participants with diagnosis of schizophrenia or schizoaffective disorder (N=80). About 32.5% of participants expressed interest in quitting smoking. The abstinence rates at week 20 and at week 36 (the end of the trial) were significant higher in CR with TNP group compared to the CR group without TNP (week 20: 56.3% versus 27.8%; week 36: 50% versus 27.8%) and also versus the minimal intervention group (week 20: 10%; week 36: 10%). There was also a significantly larger reduction in FTND scores in the CR with TNP group at both week 24 and week 36, compared to the CR group without TNP and the minimal intervention group. The CR with TNP group had a significantly lower expired CO level at both week 20 and week 36 compared to the minimal intervention group. However, there was no significant difference in the expired CO level at either week 20 or week 36 between the CR with TNP group and the CR group. CPD was lower at week 36 in the CR with TNP group compared to the minimal intervention group but there was no statistically significant difference at week 20. There was no significant difference in the number of CPD at either week 20 or week 36 between the CR group and the minimal intervention group, nor between the CR with TNP group and the CR group.

2. Trials with a primary aim of smoking reduction

2.1 Pharmacological intervention - Bupropion

+Fatemi 2005 investigated the efficacy of bupropion for smoking reduction among patients with schizophrenia, using a cross-over study design. These participants were encouraged to reduce the amount they smoked, rather than to quit entirely. The investigators reported that at the end of the 21-day active bupropion phase, participants showed a non-significant trend for reductions in exhaled CO, urine cotinine and urine nicotine and metabolites, as compared to the placebo phase. Their results also showed that during the trial, bupropion did not exacerbate positive and negative symptoms in these patients.

2.2 Pharmacological intervention - Transdermal nicotine patch

Two cross-over trials investigated the efficacy of transdermal nicotine patch (TNP) as a single pharmacotherapy for smoking reduction in schizophrenia. +Dalack 1999 examined the effect of TNP on smoking reduction over 32 hours in 10 participants with schizophrenia who did not express interest in quitting smoking. The expired CO level and CPD were not significantly different when the subjects were using the TNP or the placebo. Subgroup analysis suggested that the heaviest smokers (identified by placebo phase nicotine plasma level or expired CO level above group median, i.e. nicotine plasma level >20.4 ng/ml or expired CO level >42.5 ppm) had a statistically significant decrease in expired CO level of at least 20%. The author reported that although nicotine levels increased with the TNP, there was no evidence of nicotine toxicity or significant side effects. Psychiatric symptoms did not differ significantly between the TNP phase and the placebo phase. However, there was a statistically significant increase in abnormal involuntary movements with TNP plus smoking and six out 10 subjects had more abnormal involuntary movement when using the TNP.

+Hartman 1991 investigated the effect of TNP for seven hours on smoking reduction in a group of 14 people who did not try to stop smoking. We re-analysed the data for 10 patients with schizophrenia and schizoaffective disorder. These patients smoked significantly fewer cigarettes while receiving nicotine than while receiving placebo (N=10, mean number of cigarettes with nicotine = 10.5, mean number of cigarettes with placebo = 13.5, t = -3.21, df = 9, p <0.05). There was no biochemical measurement in this trial. The report also noted that only patients who smoked at least 12 cigarettes (approximately 1.8/hour) while wearing the placebo patch achieved benefit from the nicotine patch. No participants reported any difference in subjective experience while wearing the

two patches, nor did they or the observers notice any changes in their mental status.

2.3 Non-pharmacological intervention

Single session motivational interviewing versus didactic psychoeducation versus minimal intervention

+Steinberg 2003 did not detect a significant reduction in CPD or changes in expired CO level among the three groups at one week and at one month after the psychosocial intervention. However, a greater proportion of participants receiving the motivational interviewing intervention followed through on a referral for tobacco dependence treatment within one week and one month post intervention, although there was no statistically significant difference among the groups in their motivation to quit smoking. The participants of this trial showed different levels of interest in quitting smoking.

3. Trials with a primary aim of preventing relapse to smoking

Transdermal nicotine patch

^Horst 2005 reported the relapse rate of recent quitters with schizophrenia who were randomized to either active or placebo TNP for six months. Participants had quit smoking by the end of an open label phase during which they had received group support and TNP. A significantly higher proportion of those on placebo (eight out of eight) compared with those on active TNP (three out of nine) relapsed prior to completion of the six-month period (p<0.01). There was no report of skin rash for any subjects. In addition, the authors did not report any dropouts due to adverse events.

4. Trials of other interventions reporting smoking outcomes

Clozapine

Intervention rationale: Clozapine is an atypical antipsychotic medication and it carries a significant risk of agranulocytosis and seizure. Hence, it is reserved to be used in patients with treatment resistant schizophrenia. Previous literature (mainly naturalistic studies or case reports) has suggested that clozapine treatment may be associated with a reduction of smoking in schizophrenia. We identified two RCTs that examined the effect of different doses or blood levels of clozapine on the mental state in patients with treatment resistant schizophrenia. These two trials measured smoking behaviours of the participants; it was uncertain whether participants had any interest in quitting smoking. One trial investigated the number of cigarettes used and expired CO level in patients with different blood levels of clozapine (McEvoy 1995). Subjects with a therapeutic plasma level of clozapine (>200ng/ml) showed a significant decline of number of cigarettes used and expired CO level at a range of 25-35%. Patients treated at sub-therapeutic clozapine plasma levels (50-150 ng/ml) did not show any change with respect to these measures of smoking. However, the author also suggested a cautious interpretation of the results, as those patients assigned to the sub-therapeutic clozapine also had lower CO levels at baseline.

de Leon 2005b used a number of different ways to re-analyse the data on smoking status from an RCT of different doses of clozapine for 16 weeks. They did not find any evidence in any of their five different analyses to support clozapine for reducing smoking. However, the author suggested that their study could not rule out a small decrease in smoking in some subjects, which did not yield significant changes in total sample mean values.

Galantamine

Intervention rationale: Galantamine is an acetylcholinesterase inhibitor. It has been used as a cognitive enhancing medication for dementia. Recent literature suggests its effect of cognitive enhancement may extend to other mental illness like schizophrenia. It also acts as a positive allosteric modulator of nicotine acetylcholine receptors (nAchR) and some research has suggested that drugs that modulate nAchR may help in the management of nicotine dependence.

Kelly 2008 investigated the effect of galantamine on cognitive function among patients with schizophrenia. In a secondary analysis of data from smokers, they did not detect any statistically significant difference in expired CO level before and after 12-week galantamine treatment between participants who received galantamine and placebo. On the contrary, there was a significant and moderate increase in the mean score of FTND in subjects with galantamine compared to placebo (effect size of 0.4). These participants did not express interest in quitting smoking.

Atomoxetine

Intervention rationale: Atomoxetine is a norepinephrine (noradrenaline) reuptake inhibitor and it is approved for the treatment of attention deficit hyperactivity disorder (ADHD). Atomoxetine is thought to increase extracellular levels of both norepinephrine and dopamine in the prefrontal cortex and this may help to improve the neurocognitive deficits in patients with schizophrenia. Nicotine may improve selected cognitive deficits in these patients and one of the theories for the high rates of smoking in schizophrenia is that patients with schizophrenia may remediate their neurocognitive deficits by smoking. Hence, there is a suggestion that

atomoxetine may help in nicotine dependence by improving the cognitive function of patients with schizophrenia.

Sacco 2009 investigated the effects of atomoxetine on cognitive function and cigarette smoking among patients with schizophrenia. They did not detect any statistically significant changes in smoking behaviours as measured by cigarette consumption or expired CO levels in smokers with schizophrenia taking atomoxetine for two weeks, when compared to those who took placebo. The authors did not report whether the participants had any interest in quitting smoking. Atomoxetine was well-tolerated and there was no evidence of changes in positive or negative symptoms during the trial.

Topiramate

Intervention rationale: Topiramate is a novel anticonvulsant which may have clinical benefits as an adjunctive treatment for bipolar disorder. It has been suggested that topiramate may help in treating addictions including nicotine dependence due to its modulation of dopaminergic activity in the cortico-mesolimbic axis through actions on GABAergic and glutamatergic systems.

Weinberger 2008 was a secondary analysis of a trial of the efficacy of topiramate as a treatment for schizoaffective disorder (bipolar type). The investigators did not detect any significant change in the expired CO level in a subgroup of 24 smokers treated with topiramate or placebo, for eight weeks. There were also no significant differences in the reduction of psychiatric symptoms between the topiramate and the placebo group.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Comparison	Expired CO level at the end of trial (ppm)				Expired CO level at follow-up after 6 months (ppm)			
	Number of trials	intervention	control	Difference	Number of trials	Intervention	Control	Difference
Bupropion vs. placebo	3	12.9	20.3	7.0 (2.7 to 11.4)	3	18.8	22.7	ns
TNP vs. placebo	Data not combined because of heterogeneity of studies				No trial found			
CR + TNP vs. minimal	1	17.7	27.5	9.8	No follow-up data available			

' ns' = difference not statistically significant

DISCUSSION

Summary of main results

Interventions used in trials to help smokers with schizophrenia to stop or to reduce smoking are heterogeneous. Summary of findings for the main comparison and Summary of findings 2 summarises the main results of this review for the most important outcomes. Smokers with schizophrenia who used bupropion to aid smoking cessation had nearly three times higher likelihood of abstinence at the end of the drug therapy, compared with those who did not. Although there were fewer trials with six-month or longer follow up, the relative effect on abstinence seemed to be sustained at six months, and the results appeared consistent among trials. However, the evidence of sustained abstinence was based on five small trials from just two research groups.

At the end of treatment, smokers with schizophrenia who received bupropion smoked about 11 fewer CPD, than those who did not take bupropion. A reduction of expired CO level also occurred in the bupropion group, when it was compared to the placebo group. However, the reduction was not sustained at six months. The findings for smoking reduction should be interpreted cautiously, as these data included the entire sample which consisted of participants who had successfully abstained from smoking, as well as those who continued to smoke after bupropion. Hence, the reduction could be due to smoking abstinence, rather than reduction in those who did not manage to stop smoking.

There was no evidence from the meta-analysis to suggest that smokers with schizophrenia had significant deterioration in positive, negative or depressive symptoms of schizophrenia due to bupropion. Although some adverse effects of treatment which may be important to patients were noted, there were no significant adverse clinical events such as seizure or suicide. However, the total number of subjects on bupropion was small (N = 170), so there was not adequate power to test differences in risk of low event rates, such as seizure (risk of seizure for bupropion in the general population is between 0.1% and 0.4%).

It was unclear whether TNP helped smoking cessation in this group of patients, as it was tested only in a small number of trials with small sample sizes. There was some indirect evidence that the abstinence rate was higher in the group with contingency reinforcement with TNP, compared to the group with contingency reinforcement alone (*Gallagher 2007). Some studies showed that TNP may reduce the number of CPD (+Hartman 1991) or the FTND score (*Gallagher 2007) but the evidence available did not show that TNP reduced the expired CO level (+Dalack 1999, *Gallagher 2007). One study showed that TNP may reduce the relapse rate of smoking after smoking abstinence in schizophrenia. Higher doses of TNP did not show any additional benefit in smoking abstinence or preventing relapse after smoking cessation in schizophrenia.

From trials using interventions for reasons other than smoking cessation, there were inconclusive findings that the antipsychotic clozapine helped in smoking reduction in schizophrenia. There was no evidence to support the use of galantamine, atomoxetine or topiramate as an aid in smoking cessation or reduction in individuals with schizophrenia.

Regarding non-pharmacological interventions, one trial showed evidence to support the use of CR with money for smoking cessation in schizophrenia. There was also some evidence that CR with and without TNP significantly reduces the FTND scores, expired CO level and CPD. However, there was no evidence that CR produced sustained results for these outcomes in the longer term. As the evidence only came from a single study, these findings should be treated with caution. There was no evidence that a single session of motivational interviewing reduced smoking in patients with schizophrenia. There was no evidence that specialised smoking cessation group therapy specifically designed for patients with schizophrenia was more effective for either smoking cessation or reduction, when compared to a standard smoking cessation programme.

There were design limitations in most of the included trials. For example, most studies had small numbers of participants and only a few studies had outcomes after at least the six-month follow up. These factors have limited the validity and precision of the evidence.

Overall completeness and applicability of evidence

In this review, the participants of the included studies were recruited from in-patient units, the community, or from outpatient psychiatric treatment sites. Hence, they represented a range of patients with schizophrenia. The interest in quitting smoking varied across sites and studies. As a result, there was significant heterogeneity of the included trials. Because of this, we considered it was only appropriate to perform a meta-analysis and report the pooled estimate among studies which examined bupropion, because these studies were relatively more homogenous.

Our review included both pharmacological and non-pharmacological interventions. For medication treatments, the U.S. Food and Drug Administration (FDA) has approved nicotine replacement therapies (gum, patch, nasal spray, inhaler and lozenge), bupropion, and varenicline as first-line medications for the treatment of nicotine dependence in the general public. For this review, we found several studies that examined the use of nicotine patch and bupropion for smoking cessation and reduction in schizophrenia. There are also a number of ongoing studies which investigate the use of varenicline (Meszaros (NCT00727103); Evins (NCT00621777); Pfizer (NCT00644969); Smith (NCT00802919); Weiner (NCT00554840)) but no results from these studies are available at present . We did not find any studies that examined the effect of other forms of nicotine replacement, such as gum, nasal spray, inhaler and lozenge in people with schizophrenia, but there is an ongoing study which investigates the use of nicotine nasal spray for

smoking cessation in schizophrenia (Williams (NCT01010477)). We also did not find any trials of other medications that have been investigated for possible efficacy for smoking cessation in the general public, such as clonidine, nortriptyline, selegiline and naltrexone. We also examined the effects of antipsychotics (in particular clozapine) in smoking reduction in schizophrenia, as there have been a number of reports about the possible link between antipsychotic use and nicotine dependence in schizophrenia (Ereshefsky 1985; McEvoy 1995). In addition, smokers with schizophrenia may use nicotine to improve their cognitive function (Adler 1998, Sacco 2004). Thus, we found studies which examined the effects of medications such as galantamine and atomoxetine in smoking reduction in individuals with schizophrenia. Finally, topiramate modulates dopaminergic activity in the brain through its action on GABAergic and glutamatergic systems and it has been suggested that topiramate may have an effect in addiction (Johnson 2005). We identified one study which examined its effects on smoking in patients with schizoaffective disorder.

Previous reviews have shown that individual behavioural counselling, group behavioural therapy and telephone counselling were effective interventions to help smokers in the general public to quit smoking (Lancaster 2005a; Stead 2005; Stead 2006). Simple advice from a physician and self-help material may also have some effect on increasing smoking cessation rate in the general public (Lancaster 2005b; Stead 2008). The one study which examined the effect of individual smoking cessation based on CBT and motivational interviewing among smokers with schizophrenia did not show any benefit in increasing abstinence. In another study, there was no evidence that single session motivational interviewing reduced the severity of smoking. There was no study comparing group therapy with individual therapy in schizophrenia. There was no evidence to support specialised smoking cessation group therapy designed for patients with schizophrenia as being superior to non-specialised group therapy. We also did not find any studies on the effect of telephone counselling, simple advice from a physician, or self-help interventions in smoking cessation or reduction in schizophrenia. Interestingly, we found some evidence to support the use of incentives to increase the rate of abstinence and to reduce the severity of smoking in the group of patients with schizophrenia at the end of the trial, but this study did not have any longer term follow up after the 36-week trial and a previous review has shown that incentives do not enhance long-term cessation rates and early success may not be maintained when the rewards are no longer offered (Cahill 2008).

In this review, we reported smoking reduction as one of the secondary outcomes. Smoking cessation is the recommended method to reduce the harm of smoking to smokers (US Department of Health and Human Services 2000). However, the majority of smokers never quit smoking, even those in countries with the most effective cessation activities such as the United States (Giovino 2002; West 2006). As a result, smoking reduction has been proposed as one of the non-cessation methods to reduce harm from tobacco. There is evidence to support that smokers who are not interested in quitting can make significant reductions in their smoking when they receive appropriate treatment and these reductions can be maintained over time (Hughes 2005). One of the concerns over smoking reduction is that it may undermine smokers' motivation to quit smoking, as they may see reduction as an easier alternative to abstinence; and that reduction may be all they desire to, or can, accomplish. Nevertheless, recent literature has shown that smoking reduction actually increases the probability of future cessation (Hughes 2006). Individuals with schizophrenia have much lower smoking cessation rates compared with the general population (de Leon 2005a) and smoking reduction may be able to be a step for them toward cessation. We hypothesise that this step toward accomplishing the difficult task of smoking cessation might increase their self-efficacy and make subsequent success more likely. Smoking reduction may also make it easier to quit smoking by reducing the level of nicotine dependence, as dependence is a major barrier to smoking cessation (Shadel 2000). Most of the trials also provided some information about any potential harmful effects of interventions, in particular on the mental state of the participants. Some medications for smoking cessation are psychotropic themselves (e.g. bupropion) and it is important to monitor whether these medications have a major impact on mental stability in these patients. In addition, nicotine withdrawal can cause changes in the mental state, including depression and anxiety (Zwar 2007).

There is some literature reporting interventions which address tobacco addiction at an organisation or system level (Lawn 2005; Shmueli 2008; Wye 2009). These interventions may include training of staff to manage tobacco addiction among patients with schizophrenia and changing the psychiatric facilities into smoke-free settings (Ziedonis 2007). This is particularly important as a number of countries including the UK and the USA have enforced smoking bans in mental health units. However, we did not find any RCTs for these interventions in our search.

Quality of the evidence

In this review, we found the largest amount of evidence for bupropion, which included seven studies and a total of 340 participants in the meta-analysis. Even though the number of studies was still relatively small, there was no significant heterogeneity among these studies. The amount of evidence for the other interventions including NRT, individual counselling and group therapy was limited, even though there is good evidence of their benefit in other populations of smokers. Hence, the lack of efficacy for treatments other than bupropion for patients with schizophrenia is likely due to the lack of evidence, rather than negative trials.

The main aim of some included studies was to examine the efficacy of an intervention for other purposes, rather than primarily for smoking cessation or reduction (de Leon 2005b and McEvoy 1995 for clozapine; Kelly 2008 for galantamine; Weinberger 2008 for

topiramate; Sacco 2009 for atomoxetine). These trials all included smokers who were not trying to quit and smoking status was a secondary outcome; subgroup analyses were used to investigate the effects of the interventions for a group of smokers. In three trials, some of the smokers were excluded from the subgroup analyses without justification. As a result, the results of these studies should be viewed with caution.

Potential biases in the review process

This systematic review used comprehensive search strategies and widely inclusive criteria. This improved the chance of identifying all relevant trials. Reports in any language and unpublished data such as conference abstracts were obtained to reduce potential selection and publication biases. We included outcomes at least six months after the intervention and at the end of the intervention, so that the immediate effect and longer term sustained abstinence could be compared. Sensitivity analyses were performed in the meta-analysis and the robustness of the findings was also evaluated.
There are two issues to consider in this review. Firstly, the number of studies which were included in the meta-analysis for bupropion is relatively small, so we did not use a funnel plot to examine potential publication bias. We could not exclude the possibility that studies with negative results and small sample size may not have been published. Publication bias may significantly distort the results from the meta-analysis especially when the number of studies is relatively small. Secondly, the findings may not apply to all smokers with schizophrenia, as some of the included trials (in particular those which examine the effect of bupropion) explicitly excluded patients who had a diagnosis of both schizophrenia and a co-morbid substance misuse other than nicotine.
There is more emphasis recently on the importance of evaluating the potential harms associated with interventions in both clinical trials and systematic review (Cuervo 2003; Tunis 2003). This review also examines the effect of different interventions on the mental state of smokers with schizophrenia as one of the outcome measures. This allows us to answer the question whether different interventions can be safely used in patients with schizophrenia for smoking cessation and reduction.

Agreements and disagreements with other studies or reviews

In the Cochrane review of antidepressants for smoking cessation in the general population, Hughes 2007 estimated that bupropion approximately doubled the odds of quitting smoking after at least six months, when used as the sole pharmacotherapy (OR 1.94, 95% CI 1.72 to 2.19, 31 trials, 9940 participants). It did not detect a significant effect from combining bupropion and NRT, compared to NRT alone (OR 1.37, 95% CI 0.65 to 2.91, 4 trials, 990 participants) after six months. Although our pooled estimates suggest that bupropion may have a significant beneficial effect on smoking abstinence in schizophrenia when we combine all the trials together, neither the subgroup analysis for bupropion alone, or bupropion and TNP, individually reached statistical significance.
The results of this review largely concur with treatment guidelines which make some recommendations about treatment of nicotine dependence in schizophrenia. The Clinical Practice Guideline published by the United States Department of Health and Human Services (Fiore 2008) suggests that bupropion and nicotine replacement therapies may be effective for treating smoking in individuals with schizophrenia. Zwar 2007 also gives a similar suggestion for individuals with schizophrenia in the non-systematic reviewed Australian guidelines regarding pharmacotherapy of tobacco addiction.
The Schizophrenia Patient Outcomes Research Team (PORT) has also recently published some treatment recommendations (Kreyenbuhl 2009). The team recommends that people with schizophrenia who want to quit or reduce cigarette smoking should be offered treatment with bupropion SR, 150 mg twice daily, for 10 to 12 weeks, with or without NRT to achieve short-term abstinence. They also suggest that this pharmacological treatment should be accompanied by a smoking cessation education or support group, although they do not think there is sufficient evidence to recommend a particular psychosocial approach.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the best currently available evidence, the results of this systematic review support the effectiveness of bupropion in smoking cessation, as well as smoking reduction in patients with schizophrenia. The strength of the evidence is relatively weak with wide confidence intervals, especially for longer term benefit, because of the small number of participants. There is no evidence to support any significant deterioration of mental state secondary to use of bupropion in schizophrenia. Bupropion use in individuals with schizophrenia did not increase risk of seizure.

For other drug treatment (including NRT) and psychosocial interventions, we did not find sufficient and convincing evidence in this review to support use in clinical practice.

Implications for research

Evidence for the effectiveness of interventions for smoking cessation and reduction in schizophrenia is limited to a small number of small studies without adequate power to detect reasonable treatment effect. Further trials with adequate sample size would be informative. Moreover, the report for future studies should include more detailed and specific information. Some of the included reports do not specify whether subjects had the intention to quit

smoking and the intention to quit can significantly affect the abstinence rate. It will also be useful to be more explicit whether the reduction rates in the reports for trials with a primary aim to investigate smoking abstinence include the entire sample, or only subjects who do not quit.

In addition, the following areas should be considered for future research:

1. the effectiveness of NRT for smoking cessation and reduction, especially with forms other than nicotine patches;

2. the interaction of antipsychotic medication treatment, and smoking behaviour and cessation in schizophrenia;

3. the effectiveness of different forms of psychosocial interventions, and the essential component(s) for the effectiveness of the intervention;

4. any sustained effect on smoking cessation and reduction in CR and other treatments;

5. the level of concordance of treatment for smoking cessation among patients with schizophrenia;

6. the effect of interventions at systematic and policies level on smoking behaviours in patients with schizophrenia;

7. how to integrate treatment for smoking cessation into routine psychiatric care;

8. economic analysis to address the cost-effectiveness of different interventions. This would allow the construction of a decision analysis algorithm, which would aid clinicians, patients and policy-makers in making evidence-based treatment decisions.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

***Baker 2006**

Methods	RCT, Australia. Subjects recruited in the community.
Participants	298 smokers (at least 15 CPD) with ICD-10 diagnosis of psychotic disorder. Subjects who were acutely psychotic, had acquired cognitive impairment and any medical conditions that would preclude the use of nicotine patch were excluded. All participants interested in quitting; TQD set at week 3. 156 male, mean age of all 298: 37.2, average CPD 30. 126 had a diagnosis of schizophrenia and 43 a diagnosis of schizoaffective disorder.
Interventions	1. Individually administered smoking cessation intervention (6 weekly sessions and 2 boosters at week 8 and 10, 1 hour each): based on motivational interviewing and cognitive behavioural therapy (CBT) + Transdermal nicotine patch (TNP) (21 mg from week 3 to 8; 14 mg from week 9 to 10; 7 mg from week 11 to 12) 2. Routine care Both groups received booklets regarding smoking cessation.
Outcomes	Abstinence measured at 3 m, 6 m and 12 m by continuous abstinence (from TQD to point of assessment) and point-prevalence abstinence (from 7 days before the point of assessment). Both were from subjects' self-report and confirmed with expired CO level < 10 ppm. Reduction of smoking measured at 3 m, 6 m and 12 m by incidence of achieving at least 50% reduction of daily consumption of cigarettes. Effects on mental state were measured by BPRS, BDI and STAI.
Notes	Results in the current review only included subjects with diagnosis of schizophrenia or schizoaffective disorder. Data supplied by authors.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Subjects drew a sealed envelope from a set of envelopes in which there was initially an equal distribution of the treatment or control allocations at each site.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	No	Outcome assessors were blinded. However, the experimental design did not allow participants to be blinded and self-report were used in both primary and secondary outcome measures.

***Baker 2006** (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	Missing data were classified either as non-abstinent or as a failure to achieve smoking reduction.
Free of selective reporting?	Yes	
Free of other bias?	No	The control group were not comparable to the smoking cessation intervention group as they differed in terms of therapy time. In addition, bias may be introduced in definition of abstinence; if the participant reported abstinence but their expired CO level was greater than 10ppm, the participant was still classified as abstinent.

***Evins 2001**

Methods	RCT, USA. Subjects recruited from the community.
Participants	19 smokers (at least half pack of cigarettes per day) with DSM-IV diagnosis of schizophrenia. All subjects were on stable dose of antipsychotic medications for at least 4 weeks. Patients with co-morbid substance abuse or bulimia, or with a history of seizure disorder or current major depressive episode were excluded. All participants interested in quitting; TQD set between weeks 3 and 4. 11 male; mean age 44.1; 16 Caucasian; average CPD 34. 8 subjects were on clozapine and 7 on typical antipsychotic. Average length of illness 12 years.
Interventions	1. Bupropion 150mg/day for 12 weeks 2. Placebo for 12 weeks Both groups received nine weekly 1-hour sessions of group CBT
Outcomes	Abstinence measured by point prevalence at weeks 12 & 24 (self-report verified by expired CO level < 9 ppm or serum cotinine < 14 ng/ml). A follow-up study also reported abstinence after 2 years. Reduction of smoking measured by serum cotinine, and incidence of achieving a $\geq$ 50% reduction in CPD verified with a 30% reduction of expired CO level. Measurements at baseline, week 12 and 24. Effects on mental state measured by BPRS, SANS and HAM-D. Parkinsonism symptoms measured by SAS and AIMS.
Notes	Two-year follow up data were also available.

Risk of bias

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

***Evins 2001** (*Continued*)

Adequate sequence generation?	Yes	Allocation sequence was generated by a computer program.
Allocation concealment?	Yes	Randomization was performed at the research pharmacy which was separated from the main research personnel.
Blinding? All outcomes	Yes	Participants, outcome assessors and investigators were blinded.
Incomplete outcome data addressed? All outcomes	No	1/19 dropped out prior to medication and was not included in the analysis.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

***Evins 2005**

Methods	RCT, USA. Subjects recruited from the community.
Participants	57 smokers (at least 10 CPD) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type. All participants were on antipsychotic medication for more than 30 days and had stable psychiatric symptoms. Patients with substance use disorder (other than nicotine or caffeine) within 6 months, or with a history of seizure disorder, bulimia, mania or current major depressive episode were excluded. All participants interested in quitting; TQD set at week 3. 39 male; mean age 45.7; average CPD 30. 12 subjects were on clozapine, 5 on typical antipsychotic.
Interventions	1. Bupropion 300 mg/day for 12 weeks (150 mg/day for first week) 2. Placebo for 12 weeks Both groups received twelve weekly 1-hour sessions of group CBT.
Outcomes	Seven-day point prevalence and 4-week continuous abstinence at week 12 and week 24 (self report verified by expired CO level < 9 ppm). Reduction of smoking measured by expired CO level and number of cigarettes smoked. Measurements at baseline, week 12, 14, 18 and 24. Effects on mental state measured by PANSS, SANS, HAM-D and HAM-A. Parkinsonism symptoms measured by SAS and AIMS.
Notes	

Risk of bias

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

***Evins 2005** (*Continued*)

Adequate sequence generation?	Yes	Allocation sequence was generated by a computer program.
Allocation concealment?	Yes	Randomization was performed at the research pharmacy which was separated from the main research personnel.
Blinding? All outcomes	Yes	Participants, outcome assessors and investigators were blinded.
Incomplete outcome data addressed? All outcomes	No	4/57 drop-out prior to medication (not included in the analysis), 10/53 drop-out at week 12, 9 more drop-outs at week 24. Subjects who were lost to follow up were included in the analysis as smokers.
Free of selective reporting?	Yes	
Free of other bias?	No	More clozapine-treated subjects were randomized to the placebo group (1/25 versus 11/28).

***Evins 2007**

Methods	RCT, USA. Subjects recruited from the community.
Participants	51 smokers (at least 10 CPD for past year) with DSM-IV diagnosis of schizophrenia. All participants were on antipsychotic medication for more than 30 days and had stable psychiatric symptoms. Patients with substance use disorder (other than nicotine or caffeine) within 6 months, or with a history of seizure disorder, bulimia, mania or current major depressive episode were excluded. All participants interested in quitting; TQD set at week 4. Sex distribution uncertain; mean age 44.2; average CPD 26. 16 subjects were on clozapine.
Interventions	1. Bupropion SR 300mg/day for 12 weeks. (150 mg/day for first 7 days) 2. Placebo for 12 weeks Both groups received: (1) twelve weekly 1-hour sessions of group CBT; (2) nicotine patch (from week 4) 21mg/day for 4 weeks, then 14 mg/day for 2 weeks, 7 mg/day for 2 weeks + up to 18 mg per day nicotine gum as required.
Outcomes	Continuous abstinence at week 8, 12, 24 & 52 (defined by meeting the seven-day point prevalence abstinence by self report every assessment after target quit date at the time point , verified by expired CO level $\leq$ 8 ppm). Reduction of smoking measured by number of cigarettes smoked. Measurement at baseline, week 12 & 24. Effects on mental state measured by PANSS, SANS, HAM-D and STAI. Parkinsonism

***Evins 2007** (*Continued*)

	symptoms measured by SAS and AIMS.
Notes	6 month abstinence used in meta-analysis for comparability with other trials. 2 participants in the intervention group relapsed by 1 year

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Allocation sequence was generated by a computer program.
Allocation concealment?	Yes	Randomization was performed at the research pharmacy which was separated from the main research personnel.
Blinding? All outcomes	Yes	Participants, investigators and outcome assessors were blinded.
Incomplete outcome data addressed? All outcomes	Yes	5/25 (bupropion) and 8/26 (control) lost in follow up. Dropouts were considered smokers.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

***Gallagher 2007**

Methods	RCT, USA. Subjects recruited from the community and study conducted in a clinic.
Participants	181 participants (60 subjects in each arm, 1 died shortly after enrolment because of lung cancer) with DSM-IV axis I diagnosis of psychotic spectrum or affective disorders. At least 10 cigarettes per day and smoked regularly for more than 3 years. CO level $\geq$ 10 ppm after at least 15 minutes smoke-free at baseline visit. Subjects with co-morbid substance misuse disorder were not excluded. No TQD set. 80 had a diagnosis of schizophrenia or schizoaffective disorder. 50 of these 80 were male; mean age 42.3; 71.2% White, 20% Hispanic, 8.8% Black; average CPD 29. 32.5% wanted to cut down or quit smoking. 47.5% had co-morbid diagnosis of substance misuse. 40% had diagnosis of schizophrenia.
Interventions	1. Contingent Reinforcement (CR) with money for 36 weeks (up to 480 US dollars) if participants abstained from smoking. Participants did not receive reinforcement at the visit if they relapsed but they would be able to resume receiving reinforcement if they abstained again. 2. CR with money for 36 weeks (as above) + TNP (dose varies from subjects) for first 16 weeks 3. Self-quit (no active intervention - just attended assessment)

***Gallagher 2007** (*Continued*)

	Significant support was provided to ensure adherence for all three groups, including reminder phone calls and outreach, provision of bus pass to attend appointments.
Outcomes	Abstinence at week 20 and week 36 (defined as expired CO level $\leq$ 10 ppm or salivary cotinine level $\leq$ 15 ng/ml). Reduction of smoking was measured by expired CO level, Fagerstrom Test for Nicotine Dependence (FTND) score, salivary cotinine level and number of CPD. Measurements were taken at baseline and various points including week 20 and week 36. Effects on mental state measured by Brief Symptoms Inventory.
Notes	Results in the current review only included subjects with diagnosis of schizophrenia or schizoaffective disorder.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	The sequence was generated by a computer random number generator.
Allocation concealment?	No	A list of random numbers was used to allocate the participants by the research staff.
Blinding? All outcomes	No	Participants, investigators and outcome assessors were not blinded for the allocation of intervention group.
Incomplete outcome data addressed? All outcomes	No	29 subjects were lost during follow up at week 20 and another 6 subjects were lost at week 36. Intention-to-treat analyses were conducted where data from the last observation of participants lost to follow up were used. However, we do not think the "last observation carried forward" approach was appropriate for missing data.
Free of selective reporting?	No	Only a few outcome measures were reported in the report.
Free of other bias?	No	The interventions were not comparable: the self-quit group had only 3 visits, compared to 12 visits in the other two groups.

***George 2000**

Methods	RCT, USA. Setting unclear.
Participants	45 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. FTND score at least 5. All participants interested in quitting; TQD set at week 3. 30 males; mean age 39.7; 28 participants were White, 13 Black, 4 Hispanic; average CPD 30. 19 had a diagnosis of schizophrenia. Mean daily dose of antipsychotics (chlorpromazine equivalence) 612.3 mg. 18 subjects were on atypical antipsychotics.
Interventions	1. American Lung Association (ALA) programme weekly for 10 weeks (60 minutes each session): first 7 weeks behavioural group therapy + final 3 weeks supportive group counselling 2. Specialised group therapy designed for schizophrenia, weekly for 10 weeks (60 minutes each session): first 3 weeks motivational enhancement therapy + last 7 weeks psychoeducation, social skills training and relapse prevention strategy Both groups also received TNP (21 mg/day for first 6 weeks then 14 mg/day for another 2 weeks and 7 mg/day for final 2 weeks)
Outcomes	Abstinence at week 10 (end of therapy) and at 6 months follow up (defined as continuous abstinence for last 4 weeks - by self report of cigarette use and verified by expired CO level <10 ppm) Reduction of smoking measured by expired CO level; measurements at baseline and weekly for 12 weeks. Effects on mental state measured by PANSS and BDI. Parkinsonism symptoms measured by Webster Extrapyramidal symptoms scale and AIMS.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Mentioned block randomization but unclear how the allocation sequence was generated.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	No	Participants were not blinded and unclear whether investigators or outcome assessors were blinded.
Incomplete outcome data addressed? All outcomes	No	Subjects who were lost follow up were counted as smokers (number of subjects lost to follow up was not reported). However, subjects who required a dose change for symptom stabilisation or antipsychotic side effects were excluded from the analysis.
Free of selective reporting?	Yes	

***George 2000** (*Continued*)

Free of other bias?	No	Baseline difference between two groups: specialised group therapy had significantly more subjects with schizoaffective disorder and subjects in that group also had a significantly lower negative syndrome score; the ALA group had significantly more subjects prescribed atypical antipsychotics.

***George 2002**

Methods	RCT, USA. Subjects recruited from the community.
Participants	32 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects were clinically stable on psychotic or affective symptoms. They also fulfilled the following criteria: (1) FTND score $\geq$ 5; (2) expired CO level $\geq$10ppm; (3) plasma cotinine level $\geq$150ng/ml. Subjects were excluded if they had (1) history of epilepsy or seizure; (2) history of alcohol or drug abuse 6 months before the study; (3) a change of dose of antipsychotic for symptom control or side effect in the past 6 months. All participants interested in quitting; TQD set at week 3. 18 males; mean age 43.2; 20 White, 11 Black; average CPD 24. 20 had a diagnosis of schizophrenia. 22 were on atypical antipsychotics. Mean daily dose of antipsychotics (chlorpromazine equivalence) 757 mg
Interventions	1. Bupropion 300 mg/day for 10 weeks (150 mg/day for first 3 days) 2. Placebo for 10 weeks Both groups received ten, weekly, 1-hour sessions of group therapy for motivational enhancement, psychoeducation and relapse prevention.
Outcomes	Abstinence at week 10 and 6 month follow up (defined as seven-day point prevalence and verified by expired CO level < 10ppm) Reduction of smoking measured by expired CO level and self-report number of cigarettes smoked. Effects on mental state measured by PANSS and BDI. Parkinsonism symptoms measured by Webster Extrapyramidal symptoms scale and AIMS.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports
Blinding? All outcomes	Yes	Both participants and outcome assessors were blinded.

***George 2002** (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	2/16 (bupropion) and 5/16 (control) lost in follow up. Dropouts were considered smokers.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

***George 2008**

Methods	RCT, USA. Subjects recruited from the community.
Participants	59 smokers (at least 10 CPD and expired CO > 10 ppm) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects were clinically stable and on a stable dose of antipsychotic for at least 1 month before randomization. Subjects with alcohol or substance misuse or dependence 3 months before study were excluded. Subjects also did not have any history of seizure disorder. All participants interested in quitting; TQD set at day 15. 35 males; mean age 40.3; 28 Caucasians, 26 African Americans, 4 Hispanics; average CPD 23. 32 had a diagnosis of schizophrenia. 9 subjects were on clozapine and 13 subjects were on typical antipsychotic.
Interventions	1. Bupropion 300 mg/day for 10 weeks (150 mg/day for first 3 days) 2. Placebo for 10 weeks Both groups received ten weekly 50-minute sessions of group behavioural therapy and TNP (21 mg per 24 hours) from day 15 to day 70.
Outcomes	Abstinence was measured by self report as seven-day point prevalence at day 70, continuous abstinence for last 4 weeks of trial (day 43 to day 70) and 6 months post target quit date. Abstinence was verified by expired CO level <10ppm. Reduction of smoking was not reported. Effects on mental state were measured by PANSS, BDI and HAM-D.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Unclear	Reported double-blind but uncertain who were blinded.

***George 2008** (*Continued*)

Incomplete outcome data addressed? All outcomes	No	1 subject did not receive treatment after randomization and was excluded in the analysis. 6 subjects from the bupropion group and 10 from the placebo group were lost to follow-up. Another 6 subjects from bupropion group and 12 subjects from the placebo group discontinued intervention. Subjects who discontinued intervention or were lost to follow-up were included in analysis as smokers.
Free of selective reporting?	Yes	
Free of other bias?	Yes	

***Li 2009**

Methods	RCT, China. Subjects recruited from a psychiatric in-patient unit.
Participants	80 smokers with DSM-IV diagnosis of schizophrenia and nicotine dependence. All subjects smoked at least 10 CPD for minimum of 1 year. Their BPRS scores were ≤ 35 and CGI ≤ 3. Subjects with history of epilepsy, unstable physical problem, alcohol or other substance dependence and prominent psychotic symptoms were excluded. Subjects' interest in quitting smoking and whether a target quit date was set were not mentioned in the report. All subjects were men. Mean age 38.0. Average number of CPD 30 and average years of smoking 17.
Interventions	1. Bupropion 75 mg bd for 1 week then 150 mg bd for remaining 3 weeks 2. Placebo for 4 weeks No other addition intervention for both groups.
Outcomes	Abstinence was defined as self-report continuous abstinence for past weeks at week 1, 2, 4 and 8. There was no biological verification. Reduction of smoking measured by reduction in CPD and reduction of scores on scale measure of nicotine dependence. Effects on mental state measured by BPRS.
Notes	Article in Chinese.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	The report mentioned the use of random number table. However, we have contacted the investigators to clarify the exact method of sequence generation. They told us that

***Li 2009** (*Continued*)

		they used a random number table from a statistics textbook and five investigators were given copies of this random number table. When a subject was included, the investigators selected a random number from the table. From the description, our opinion was that the investigators did not use the random number table properly.
Allocation concealment?	No	From our correspondence with the investigators as above, there was definitely no concealment of allocation sequence.
Blinding? All outcomes	Unclear	Mentioned double-blind in the report but unclear who were blinded.
Incomplete outcome data addressed? All outcomes	No	4/40 bupropion and 7/40 placebo dropped out within first 2 days because of non-compliance. However, no intention-to-treat analysis was used.
Free of selective reporting?	Yes	
Free of other bias?	No	No biochemical verification of smoking status.

***Weiner 2007**

Methods	RCT, USA. Subjects recruited from the community.
Participants	46 smokers (at least 10 CPD) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects had a FTND score $\geq$4 and they did not have any change in their usual medication regime. Subjects with current depressive episode, current substance misuse or seizure disorder were excluded. Interest in quitting smoking was uncertain. TQD set at 2 weeks after start of bupropion. 38 males; mean age 48.7.
Interventions	1. Bupropion 300 mg/day for 12 weeks (week 2 to week 14) 2. Placebo for 12 weeks Both groups received 9 weekly sessions of group therapy according to American Cancer Society Fresh Start Programme.
Outcomes	Abstinence defined as expired CO level <10ppm and measured as point prevalence every week till week 14. Reduction of smoking was measured by expired CO level, FTND score and urine cotinine level. Measurements at baseline and weekly till week 14. Effects on mental state measured by BRPS and SANS.

***Weiner 2007** (*Continued*)

Notes	Conference proceeding only.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Unclear	Reported double-blind but uncertain who were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	2 subjects dropped out from each group prior to medication treatment. 5 subjects in bupropion group and 2 in the placebo group dropped out because of side effects. 1 participant from each group withdrew consent during trial. 1 subject in the placebo group no longer met inclusion criteria during trial. However, the report did not mention how drop-outs and missing data were handled.
Free of selective reporting?	No	Only some of the outcome measures mentioned in the protocol were reported.
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists.

***Williams 2007**

Methods	RCT, USA. Subjects recruited from the community.
Participants	51 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects were stable on antipsychotic medications. Subjects who took bupropion or clonidine were excluded. All participants interested in quitting. No TQD set. Baseline characteristics not reported.
Interventions	1. TNP 42mg daily for 8 weeks 2. TNP 21mg daily for 8 weeks No other additional intervention for all groups.

***Williams 2007** (*Continued*)

Outcomes	Abstinence measured at week 8 by self report of seven-day point prevalence and verified by expired CO < 8ppm. Reduction of smoking was not reported. Effects on mental state were not reported.
Notes	Conference proceeding only.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Unclear	Reported double-blind but uncertain who were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Unclear whether there was any drop-out and how missing data were handled.
Free of selective reporting?	Yes	According to protocol, only outcome measure was continuous abstinence from smoking and it was reported in the conference proceeding.
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists.

+Dalack 1999

Methods	Cross-over study, USA. Subjects recruited from the community but they stayed in hospital during study.
Participants	10 subjects with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Moderate to severe nicotine addiction (≥20 cigarettes per day). No current non-nicotine substance use disorder (confirmed by urine toxicology). Stable on antipsychotic medication for at least 3 months. Participants had not expressed interest in quitting smoking. No TQD set. All males; mean age 42.1; 8 Caucasian; average CPD 35; average number of years smoking 26. 4 subjects on clozapine. 6 subjects with diagnosis of schizophrenia. Average length of illness 23 years.

+Dalack 1999 (*Continued*)

Interventions	Transdermal nicotine patch (TNP) (22mg per 24 hours) versus placebo patch for 32 hours (Day 1 and Day 2). Washout period for the next 5 days. Cross-over to the other intervention for 32 hours. No other addition intervention for both groups.
Outcomes	Abstinence was not defined or measured. Reduction of smoking was measured by number of cigarettes smoked during the hospital stay and expired CO level. Measurements taken at baseline, the end of Day 1 and Day 2 (both weeks). Effects on mental state measured by BPRS, SANS, HAM-D. Parkinsonism symptoms measured by SAS and AIMS.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	A random number generator was used to generate sequence.
Allocation concealment?	Yes	Allocation was performed centrally at pharmacy.
Blinding? All outcomes	Yes	Both participants and the outcome assessors were blinded to the allocation.
Incomplete outcome data addressed? All outcomes	Yes	All subjects were included in data analysis.
Free of selective reporting?	No	Only some of the outcomes were reported in the reports.
Free of other bias?	No	Cross-over study with short washout period.

+Fatemi 2005

Methods	Cross-over study, USA. Subjects recruited from the community.
Participants	10 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Subjects encouraged to reduce their smoking, rather than to quit. No TQD set. Demographics for smokers were not reported.
Interventions	Bupropion (dose uncertain) vs. placebo for 21 days. Washout period for 1 week afterwards. Cross-over to the other intervention for another 21 days. No other addition intervention for both groups.

+Fatemi 2005 (*Continued*)

Outcomes	Abstinence was not defined or measured. Reduction of smoking measured by number of cigarettes smoked, expired CO level, FTND, urine cotinine, urine nicotine and metabolites. Measurements taken at baseline and at the end of 21 days (for both interventions). Effects on mental state measured by BPRS, PANSS, SAPS, SANS, HAM-D and BDI. Parkinsonism symptoms measured by SAS and AIMS.
Notes	The report is a letter to the editors.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports
Blinding? All outcomes	Yes	Participants and investigators were blinded to intervention allocation.
Incomplete outcome data addressed? All outcomes	Unclear	One subject withdrew from the study and unclear whether this participant was included in the analysis or not.
Free of selective reporting?	No	Only the results of some of the outcome measures were reported.
Free of other bias?	No	Cross-over design but uncertain about whether paired analyses were used or not. First period data were not available.

+Hartman 1991

Methods	Cross-over study, USA. Subjects were recruited from both inpatients and outpatients.
Participants	14 smokers with mixed psychiatric diagnoses and smoked at least 10 cigarettes daily. Subjects did not have any other current substance use. Participants were not interested in quitting and no TQD was set. All males; mean age 40.9; 4 White, 7 Black, 2 Asian, 1 Hispanic. Average CPD 23. Average years of smoking - 19. 8 had a diagnosis of schizophrenia and 2 a diagnosis of schizoaffective disorder.
Interventions	Transdermal nicotine patch (TNP) (8mg) vs. placebo patch for 7 hours (Day 1). Subjects stayed for the next 2 entire days in the clinic for observation of smoking behaviour (although unlimited amount of subjects' preferred brand of cigarettes were only provided during the 7 hours on patch). Cross-over to the other intervention one week later.

+Hartman 1991 (*Continued*)

	No other additional intervention for both groups.
Outcomes	Abstinence was not defined or measured. Reduction of smoking measured by collection of cigarette butts in subjects' own container (collection of cigarette butts was observed). Effects on mental state were not measured.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Yes	Participants, investigators and outcome assessors were blinded.
Incomplete outcome data addressed? All outcomes	No	1 subject was lost in follow-up but reason uncertain.
Free of selective reporting?	Yes	
Free of other bias?	No	No biological verification of smoking status. Cross-over design with short washout period.

+Steinberg 2003

Methods	RCT, USA. Setting unclear.
Participants	78 smokers (at least 10 cigarettes per day) with diagnosis of schizophrenia or schizoaffective disorder. 53% of participants also had a history of substance use disorder. Interest in quitting smoking varied among individuals. No TQD set. 53 males; mean age 43.8; 60 Caucasians, 11 African Americans, 4 Africans, 3 Hispanic, 1 Asian; average CPD 27. 40 had a diagnosis of schizophrenia. Average length of illness was 20.8 years.
Interventions	1. Motivational Interview for 40 minutes (a single session) 2. Didactic psychoeducation based on ALA brochure for 40 minutes (a single session) 3. Minimal control intervention for 5 minutes (a single session) No other additional intervention for all groups.

+Steinberg 2003 (*Continued*)

Outcomes	Abstinence not defined or measured. Reduction of smoking measured by number of cigarettes smoked, expired CO level and FTND scores. Measurements taken at baseline, one week and one month after intervention. Effects on mental state not measured.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Mentioned randomization in a ratio of 5:5:2 and the allocation sequence was generated by computer.
Allocation concealment?	Unclear	No description of allocation concealment in the reports
Blinding? All outcomes	No	Participants were not blinded. Outcome assessors were blinded to the participant group assignment.
Incomplete outcome data addressed? All outcomes	No	3 subjects lost follow-up (2 from motivational interview group and 1 from psychoeducation group). Data were carried forward to replace missing values. However, we do not think the "last observation carried forward" approach was appropriate for missing data.
Free of selective reporting?	Yes	
Free of other bias?	No	The minimal control intervention group was not comparable to the other two interventions.

^Horst 2005

Methods	Open-label phase study followed by RCT, USA. Subjects recruited from the community.
Participants	50 smokers with diagnosis of schizophrenia or schizoaffective disorder entered the open label phase. They had stable symptoms for the last 2 months and used tobacco daily. All participants interested in quitting; TQD set. 18 subjects entered the RCT phase as they fulfilled the following criteria: (1) agreed to set a quit date within 2 weeks; (2) reduced their tobacco use by 75% after 60 days from the start of the open-label phase; (3) quit smoking 100% after 90 days from the start of the open-label phase. For all subjects in the open-label phase, 26 were men; mean age was 42.5; average pack-years 39.9.
Interventions	1. TNP (Nicoderm CQ) for 6 months (Dose ranged from 14 mg to 63 mg daily, according to subjects' cotinine saliva levels. The dose was fixed throughout 6 months) 2. Placebo patch for 6 months.

^Horst 2005 (*Continued*)

	All participants received biweekly educational smoking cessation classes and motivational discussions with health educator.
Outcomes	Relapse to smoking - defined by expired CO level greater than 10 ppm for 2 consecutive weeks. Abstinence not defined or measured. Reduction of smoking measured by expired CO level. Measurements taken at baseline, every 2 weeks and at the final session. Effects on mental state not measured.
Notes	Only the data from the RCT were included in this review.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Coin flip by blinded third party.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	No	Only participants were blinded. Investigators and outcome assessors were unblinded.
Incomplete outcome data addressed? All outcomes	No	1 subject was excluded in the analysis as he stopped using any patch during RCT phase.
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Uncertain whether there were any baseline differences for the two groups in the RCT phase

de Leon 2005b

Methods	RCT, USA. Subjects were in-patients and study was conducted in hospital setting.
Participants	50 participants with DSM-IIIR diagnosis of schizophrenia. All were treatment resistant (not responded at least 3 antipsychotics - each antipsychotic was prescribed for at least 6 weeks and at CPZ equivalent dose of above 1000 mg daily). CGI at least moderately ill and BPRS-Anchored scores $\geq$ 45. Only 42 participants who were daily smokers were included in the analysis. Of these 42 subjects, 2 withdrew before completing clozapine trial and another 2 did not provide sufficient cotinine measures. Interest in quitting smoking was uncertain. No target quit date set. Demographics for smokers not reported. Average CPD 19.

de Leon 2005b (*Continued*)

Interventions	1. Clozapine 100mg daily 2. Clozapine 300mg daily 3. Clozapine 600mg daily Duration of clozapine: 16 weeks. No other additional intervention for both groups. All subjects were switched to haloperidol for 4 weeks and then had a washout period for 1 week before clozapine.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by plasma cotinine; measurements at baseline and between 13th and 15th weeks. Effects on mental state measured by BPRS-Anchored, SANS and CGI.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	The method of sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Yes	Participants and outcome assessors were blinded.
Incomplete outcome data addressed? All outcomes	No	4 subjects excluded from the analysis although they were smokers.
Free of selective reporting?	Yes	
Free of other bias?	No	Unequal numbers in the three intervention groups and uncertain whether these three groups were comparable in characteristics and also baseline cotinine level.

Kelly 2008

Methods	RCT, USA. Subjects recruited from both inpatients and outpatients.
Participants	86 subjects with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All were treated by antipsychotics except clozapine. Subjects were not on anticholingeric medications and with SAS score $\leq$4. Subjects with DSM-IV diagnosis of alcohol or substance misuse or dependence (except nicotine) were excluded. 73 subjects smoked (defined as baseline expired CO level $\geq$8 ppm). Only 41 subjects had at least 1 follow-up measurement and were included in the analysis. Among these 41 subjects, 39 were men; mean age 47.5; 14 White, 28 Black.

Kelly 2008 (*Continued*)

	Participants not interested in quitting; no TQD.
Interventions	1. Galantamine for 12 weeks (up to 24 mg/day) 2. Placebo for 12 weeks No other additional intervention for both groups.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by expired CO level and FTND scores. Measurements taken at baseline and every 2 weeks till week 12. Effects on mental state measured by BPRS, SANS and CGI. Parkinsonism symptoms measured by SAS and AIMS.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random sequence was generated by computer.
Allocation concealment?	Yes	Allocation was performed centrally at the research pharmacy.
Blinding? All outcomes	Yes	Participants, outcome assessors and investigators were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Uncertain how missing data were handled.
Free of selective reporting?	Yes	
Free of other bias?	No	Subgroup analysis of another trial with significant number of smokers not included in the analysis.

McEvoy 1995

Methods	RCT, USA. Subjects were chronically hospitalised patients.
Participants	12 smokers with DSM-IIIR diagnosis of chronic schizophrenia. All subjects had persistent psychopathology despite extended course of typical antipsychotics. Interest in quitting smoking was uncertain. No TQD set. 8 males; mean age 34; average CPD 7. Average length of illness 16 years.
Interventions	1. Low clozapine (dose varied but plasma clozapine level 50-150ng/ml) for 12 weeks 2. Medium clozapine (plasma level 200-300 ng/ml) for 12 weeks 3. High clozapine (plasma level 350-450 ng/ml) for 12 weeks

McEvoy 1995 (*Continued*)

	No other additional intervention for all groups.
Outcomes	Abstinence was not defined or measured. Reduction of smoking measured by number of cigarettes smoked and expired CO level. Measurements taken at baseline and week 12. Effects on mental state measured by BPRS and CGI.
Notes	Subjects were allowed free access to cigarettes for 120 minutes only.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of allocation sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Unclear	Mentioned double-blind in the report but unclear who were blinded.
Incomplete outcome data addressed? All outcomes	Yes	All participants were included.
Free of selective reporting?	Yes	
Free of other bias?	No	Potential baseline difference between groups: the low clozapine group had lower baseline expired CO level.

Sacco 2009

Methods	RCT, conducted in the USA. Settings unclear.
Participants	12 smokers with DSM-IV diagnosis of schizophrenia. Demographics of participants unclear. Uncertain whether subjects have interest in quitting smoking.
Interventions	1. Atomoxetine 40mg daily for 2 weeks 2. Atomoxetine 80mg daily for 2 weeks 3. Placebo for 2 weeks No other additional intervention for all groups.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by number of cigarettes smoked and expired CO level. Measurements were taken at baseline, day 8 and day 15. Effects of mental state were measured by PANSS.

Sacco 2009 (*Continued*)

Notes	The report is a letter to the editors.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	The method of sequence generation was not described.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Unclear	Reported double-blind but uncertain who were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Unclear whether there was any drop-out and how they handled drop-outs.
Free of selective reporting?	No	Only report part of the results.
Free of other bias?	Unclear	Insufficient information to assess whether an important risk of bias exists

Weinberger 2008

Methods	RCT, USA. Subjects recruited from both inpatients and outpatients.
Participants	48 subjects with DSM-IV TR diagnosis of schizoaffective disorder, bipolar type. All subjects had a PANSS score at least 60 and a CGI score at least 4. Participants were on a stable dose of lithium and/or valproate for at least 2 weeks before the study. Subjects with alcohol or marijuana dependence or other substance misuse were excluded. Subjects did not have an interest in quitting smoking; no TQD set. 31 daily smokers but only 24 participants (daily smoker and baseline expired CO level $\geq$ 10 ppm) were included in the data analysis. Among these 24 participants; 12 males; 13 Whites, 10 African Americans; mean age uncertain; average CPD 20.
Interventions	1. Topiramate (dose variable from 100mg to 400mg daily) for 8 weeks (after titration of dose) 2. Placebo for 8 weeks No other additional intervention for all groups.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by expired CO level. Measurements at baseline, week 4 and week 8. Effects of mental state measured by PANSS, MADRS, YMRS and CGI.
Notes	The report is a letter to the editors.

Weinberger 2008 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Mentioned randomization in a ratio of 2: 1 (favouring topiramate) but unclear how the allocation sequence was generated.
Allocation concealment?	Unclear	No description of allocation concealment in the reports.
Blinding? All outcomes	Yes	Participants and outcome assessors were blinded.
Incomplete outcome data addressed? All outcomes	No	Missing data were imputed with the last observation carried forward. We do not think the "last observation carried forward" approach was appropriate for missing data. The number of dropouts was also not reported for the smoking analysis.
Free of selective reporting?	Yes	
Free of other bias?	No	Only 24 participants were analysed although there were 31 smokers.

AIMS: Abnormal Involuntary Movement Scale
BDI: Beck Depression Inventory
BPRS: Brief Psychiatric Rating Scale
CBT: cognitive behavioural therapy
CGI: Clinical Global Impression
CPD: cigarettes per day
HAM-D: Hamilton Depression Rating Scale
m: month
PANSS: Positive and Negative Syndrome Scale
SANS: Scale for the Assessment of Negative Symptoms
SAPS: Scale for the Assessment of Positive Symptoms
SAS: Simpson Agnus Scale
STAI: State and Trait Anxiety Inventory
TNP: transdermal nicotine patch
TQD: target quit date
YMRS: Young Mania Rating Scale

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

Brown 2003	Subjects aged below 18
Kisely 2006	Before and after study without randomization
McEvoy 1999	Before and after study without randomization
McKee 2009	The primary purpose of the study was to utilize mecamylamine as a mechanistic probe because of its ability to increase smoking behaviour.
Roll 1998	Before and after study without randomization
Tidey 2002	Before and after study without randomization
Weiner 2001	No comparison group
Wells 2003	No measures of cigarettes consumption or smoking status. Only reported measure for motivation to quit smoking.

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

Chen 2002

Methods	Controlled trial, conducted in Taiwan. Subjects were recruited from a day-care ward in a psychiatric hospital.
Participants	65 subjects with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects smoked more than 20 cigarettes daily and are willing to stay for 60 minutes for participating in the smoking cessation group. Subjects with acute confusion, violent behaviours or did not attend more than half of the sessions were excluded from the study. Interest in quitting smoking was uncertain. No target quit date set. 60 subjects were men. Mean age 40.1.
Interventions	1. Smoking cessation group programme (total 8 hourly sessions in 4 weeks), modified from the American Lung Association 7-steps. The programme included providing information of smoking cessation, enhancing motivation, discussions of strategy in smoking cessation and relapse prevention. 2. Control group with no intervention. No other addition intervention for all groups.
Outcomes	Self-report seven-day point abstinence measured at one week after participating in the smoking cessation programme (i.e. week 5) and week 8. No biochemical verification. Reduction of smoking was not reported. Effects of mental state were not reported.
Notes	Attempts through different means have been made to contact the authors to clarify method of randomization (it mentions in the report that subjects were randomly assigned to the two groups. However, the allocation was uneven: 23 in the experimental group and 42 in the control group). So far, there is no response from the authors.

Chou 2004

Methods	Controlled trial, conducted in Taiwan. Subjects were recruited from a day-care ward in a psychiatric hospital.
Participants	68 subjects with diagnosis of schizophrenia. All subjects smoked at least 15 cigarettes per day for minimum of 1 year. Subjects with history of using NRT within 6 months before study enrolment and any current use of other smoking cessation treatments were excluded. Interest in quitting smoking was uncertain. No target quit date set. 61 participants were men. Mean age 38.6. Average number of CPD 23.
Interventions	1. TNP for 8 weeks (14mg daily for week 1 to 6; 7mg daily during week 7 and 8) 2. No intervention for control group No other addition intervention for all groups.
Outcomes	Abstinence was defined as expired CO level <10ppm and measured as self-reported continuous prevalence at the end of TNP treatment (i.e. week 8) and 3-month follow-up. Reduction of smoking was measured by expired CO level and FTND score. Measurements were taken at baseline, weekly for first 4 weeks, week 8 and 3-month follow-up. Effects on mental state were measured by BRPS and HAS.
Notes	Attempts through different means have been made to contact the authors to clarify method of randomization (it mentions in the report that subjects were randomly assigned to the two groups, matched by the CO level. However, the allocation was uneven: 26 in the experimental group and 42 in the control group). So far, there is no response from the authors.

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

Baker(ACTRN1260900103927)

Trial name or title	Healthy lifestyle intervention for cardiovascular disease risk reduction among smokers with psychotic disorders
Methods	RCT. Study is conducted in Australia.
Participants	Adult smokers (at least 15 cigarettes per day) with a diagnosis of a psychotic disorder or bipolar disorder. All subjects take antipsychotic medication as prescribed for at least 2 months. Exclusion criteria: (1) non-English speaking; (2) organic brain damage; (3) medical condition that would preclude NRT; (4) actively suicidal or acutely unwell.
Interventions	1. One initial 2-hour session of feedback + individual sessions of Motivational Interviewing and Cognitive-behavioural therapy (MICBT), as well as Contingency Management (CM) with nicotine replacement therapy (NRT) [7 weekly sessions then 3 fortnightly sessions then 6 monthly sessions] + one final session 2. One initial 2-hour session of feedback + brief telephone and face contact + NRT
Outcomes	Continuous and point prevalence of abstinence (confirmed by expired CO level} and self reported number of cigarettes per day at week 15 and 12 months after initial assessment
Starting date	July 2009

Baker(ACTRN1260900103927) (*Continued*)

Contact information	Amanda Baker (amanda.bake@newcastle.edu.au)
Notes	Includes subjects with mental illness other than schizophrenia

Evins (NCT00621777)

Trial name or title	A study of Varenicline for Prevention of Relapse to Smoking in Patients with Schizophrenia (SCRP)
Methods	RCT. Study is conducted at multi-sites in Massachusetts, Michigan and New Hampshire, USA.
Participants	Adult smokers (at least 10 cigarettes per day and expired CO level > 9ppm) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All subjects are willing to quit smoking and set a quit date within 2 to 3 weeks. Exclusion criteria: (1) diagnosis of dementia, neurodegenerative disease or organic mental disorder; (2) substance use disorder other than nicotine or caffeine in the last 6 months; (3) major depressive disorder within the last 6 months; (4) serious unstable medical illness; (5) elevated liver function tests over twice normal; (6) estimated creatinine clearance <40ml/min; (7) use other tobacco products apart from cigarettes (e.g. cigar, pipe); (8) current suicidal or homicidal ideation.
Interventions	1. Varenicline (1mg twice daily) for 12 weeks 2. Placebo for 12 weeks Both groups also receive 13-session weekly CBT programme for smoking cessation. Those subjects who have been abstinent for more than 2 weeks at the last 4 weeks of 12-week treatment will enter a 40-week relapse prevention programme. They will again be randomized to receive Varenicline or placebo in addition to CBT for relapse prevention.
Outcomes	Abstinence is measured by the seven-day point prevalence abstinence rate at the end of the relapse prevention phase at week 53. Safety and tolerability of extended duration pharmacotherapy when added to antipsychotic medications in schizophrenia patients who have recently quit smoking is also examined.
Starting date	February 2008
Contact information	Annie R. Shawn (ashawn@partners.org)
Notes	Principal Investigator: A. Eden Evins, Massachusetts General Hospital

George (NCT00736710)

Trial name or title	Effects of rTMS on Smoking Cessation and Cognitive Outcomes in Outpatients with Schizophrenia Treated With Transdermal Nicotine Patch
Methods	RCT. Study is conducted at Centre for Addiction and Mental Health, Toronto, Ontoraio, Canada.
Participants	Adult smokers (at least 10 cigarettes per day and a FTND score of at least 4) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All participants are willing to quit smoking in the next 30 days.

George (NCT00736710) (*Continued*)

	Exclusion criteria: (1) active alcohol or illicit drug abuse or dependence in the past 3 months; (2) history of seizures, head trauma or space occupying lesions; (3) history of alcohol or illicit drug abuse in the past 6 months; (4) intolerance of the nicotine patch; (5) evidence for psychiatric instability as judged by acute psychotic exacerbations, suicidal or homicidal ideation; (6) females who are pregnant.
Interventions	1. Repetitive Trancranial Magnetic Stimulation (rTMS) - five times per week for 4 weeks 2. Sham rTMS All participants also receive TNP (21mg/24 hour) and weekly group behavioural therapy (psychoeducation, social skills training and relapse-prevention skills training) for smoking cession for 10 weeks.
Outcomes	Smoking abstinence (7-day point prevalence) at week 10, as assessed by self-reported smoking abstinence plus expired CO level <10ppm. Reduction of smoking is measured by expired CO level.
Starting date	December 2008
Contact information	Tony George (tony˙george@camh.net)
Notes	

Josiassen (NCT00231101)

Trial name or title	Quetiapine Decreases Smoking in Patients With Chronic Schizophrenia
Methods	RCT. Study is conducted in Pennsylvania, USA. Both in-patients and out-patients are recruited.
Participants	Adults smoker (at least one pack of cigarettes per day) with DSM-IV diagnosis of schizophrenia (all subtype including schizoaffective disorder). The participants also show a less-than-optimal clinical response to an adequate course of risperidone. Exclusion criteria: (1) treatment refractory schizophrenia (as defined by treatment failure with 3 different antipsychotics of adequate duration in a sufficient dose); (2) significant extra-pyramidal side effects or akathisia; (3) significant cardiac disease or unstable blood pressure; (4) history of seizures or significant neurological disease; (5) active drug or alcohol addiction in the past 3 months; (6) pregnancy or breastfeeding; (7) serious suicidal risk.
Interventions	1. Quetiapine (400mg to 800mg daily) for 12 weeks. Subjects start with Risperidone for 1 week and switch to Queatiapine over 2 weeks before the 12-week trial. 2. Risperidone (4mg to 10mg daily) for 12 weeks No other additional interventions for both groups.
Outcomes	Abstinence is not measured. Smoking reduction is measured by changes of FTND scores, expired CO level and blood levels of cotinine. Mental state is monitored by PANSS, SANS and CGI.
Starting date	January 2004
Contact information	Richard C Josiassen (richardjosiassen@noyesfoundation.net)

Josiassen (NCT00231101) (*Continued*)

Notes	

Kosten (NCT00435370)

Trial name or title	Effectiveness of Tropisetron Plus Risperidone for Improving Cognitive and Perceptual Disturbances in Schizophrenia
Methods	RCT. Study conducted in Beijing, China.
Participants	Adults with diagnosis of schizophrenia or schizophreniform disorder and no previous history of antipsychotic treatment. All participants resides in Beijing and their psychotic symptoms are less than 60 months in duration and at least moderately severe. Exclusion criteria: (1) other DSM-IV diagnosis apart from schizophrenia or schizophreniform disorder; (2) significant neurological disease; (3) significant and unstable medical conditions; (4) Pregnancy or breastfeeding; (5) alcohol or illegal substance dependence; (6) use of other antipsychotics, psychostimulants or antidepressants.
Interventions	1. Tropisetron (10mg daily) for 12 weeks 2. Placebo for 12 weeks Both groups also receive Risperidone 6mg daily.
Outcomes	Abstinence is not measured or defined. Smoking reduction is measured by number of CPD. Uncertain whether there is any biochemical verification. Cognitive function and negative symptoms of schizophrenia is monitored.
Starting date	November 2006
Contact information	Thomas Kosten (kosten@bcm.edu)
Notes	

Meszaros (NCT00727103)

Trial name or title	Varenicline Treatment in Alcohol and Nicotine Dependent Patients With Schizophrenia - a Double Blind, Placebo Controlled Trial
Methods	RCT. Study is conducted in the USA. Subjects are recruited from the community.
Participants	Adult smokers (at least 20 cigarettes per day over the 7 days prior to intake) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Subjects take antipsychotic medication for at least 4 weeks and with a current DSM-IV diagnosis of nicotine dependence and alcohol dependence. Subjects also express desire to cut down or quit smoking and drinking. Exclusion criteria: (1) unable to give informed consent; (2) currently receiving any pharmacological smoking cessation treatment including bupropion; (3) currently taking naltrexone, Campral or Anatabuse; (4) history of suicide attempt in the past year; (5) suicidal ideation at baseline; (6) female of childbearing potential without contraception; (7) pregnancy; (8) unstable medical or psychiatric disorder; (9) positive urine drug screen for cocaine, opioids or amphetamine at baseline, or current DSM-IV diagnosis of cocaine, opioid or

Meszaros (NCT00727103) (*Continued*)

	cannabis dependence (1 month prior to enrolment).
Interventions	1. Varenicline 1mg bd for 8 weeks 2. Placebo (matched in appearance) for 8 weeks
Outcomes	Smoking reduction is measured by expired CO level at the end of the treatment phase. Safety of Varenicline including any adverse effects is recorded. Negative symptoms will be assessed with PANSS.
Starting date	June 2008
Contact information	Ynesse Abdul-Malak (abdulmay@upstate.edu)
Notes	Prinicipal Investigator: Zsusa Szombathyne Meszaros, SUNY Upstate Medical University, Department of Psychiatry

Pfizer (NCT00644969)

Trial name or title	Smoking Cessation Study for Patients With Schizophrenia or Schizoaffective Disorder
Methods	RCT. Study is conducted at different sites in USA and Canada.
Participants	Adult smokers (at least 15 cigarettes per day during the past year with no period of abstinence greater than 3 months in the past year) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder and judged to be stable. Participants are on psychiatric treatment for at least the past 6 months. They are motivated to stop smoking. Exclusion criteria: (1) PANSS score at baseline > 70; (2) serious suicidal ideation or behaviour in the past six months; (3) active suicidal ideation or behaviour; (4) taking bupropion.
Interventions	1. Varenicline 1mg twice daily for 12 weeks 2. Placebo for 12 weeks
Outcomes	Abstience is defined as 7-day point prevalence of non-smoking at week 12 and week 24. Smoking reduction is measured by proportion of subjects with at least 50% reduction from baseline in CPD averaged over the past 7 days at week 12 and week 24. The change of CPD from baseline at week 12 and week 24 is also monitored. Mental state is measured with PANSS and CGI.
Starting date	May 2008
Contact information	Pfizer CT.gov call centre (1-800-718-1021)
Notes	

Saxon (NCT00508560)

Trial name or title	Contingency Management for Smoking Cessation Among Veterans With Schizophrenia or Other Psychoses
Methods	RCT. Study is conducted in the USA.
Participants	Adults smokers (at least 5 or more cigarettes per day for at least 16 of the past 30 days prior to study screening) with a diagnosis of schizophrenia or any other psychotic disorder (including bipolar disorder with psychotic features, major depression with psychotic features). All subjects indicate willingness to attend smoking cessation group therapy. Exclusion criteria: (1) any current substance dependence disorder except nicotine dependence; (2) imminent risk for suicide or violence; (3) severe psychiatric symptoms or psychosocial instability; (4) gross cognitive impairment.
Interventions	1. Contingency Management (participants draw from a fishbowl to obtain tokens when they attend a smoking cessation treatment session. The number of draws is based upon attendance at consecutive sessions. Tokens include messages of encouragement or canteen vouchers of varying monetary value) 2. Reward as control (participants receive set reward [canteen voucher] for each week of smoking cessation treatment they attend. The value of the reward will not change regardless of attendance at consecutive sessions).
Outcomes	Abstinence is measure by 7 and 30-day point prevalence and continuous abstinence from quit date. Smoking reduction is measured by change in CPD.
Starting date	July 2007
Contact information	Kevin Wruck (kevin.wruck@va.gov)
Notes	Principal Investigator: Andrew J. Saxon (VA Puget Sound Health Care System)

Smith (NCT00802919)

Trial name or title	Varenicline for Cigarette Smoking in Schizophrenia - Efficacy and Predictors
Methods	RCT. Study is conducted in New York, USA.
Participants	Audlt smokers with diagnosis of schizophrenia or schizoaffective disorder. Participants are taking antipsychotic medication. Exclusion criteria: (1) significant cardiac disease or past history of stroke; (2) history of using varenicline with serious side effects; (3) suicide attempt or serious suicidal ideation in the past year; (4) pregnant or breastfeeding; (5) significant renal impairment; (6) baseline HDRS score > 20.
Interventions	1. Varenicline 1-2mg daily for 12 weeks 2. Placebo for 12 weeks
Outcomes	Abstinence is not measured. Smoking reduction is measured by cotinine level. Mental state is monitored with PANSS and HDRS.
Starting date	September 2008

Smith (NCT00802919) (*Continued*)

Contact information	James Cornwell (marcjfc@omh.state.ny.us)
Notes	Principal Investigator: Robert C Smith

Tidey (NCT00136760)

Trial name or title	Contingent Incentives Plus Bupropion for Smoking in People With Schizophrenia
Methods	RCT. Study is conducted in Rhode Island, USA.
Participants	Adult smokers (20 to 50 cigarettes per day) with diagnosis of schizophrenia or schizoaffective disorder. Participants are clinically stable and they are on antipsychotic and antidepressant medications. Exclusion criteria: (1) pregnancy or breastfeeding: (2) history of seizure; (3) use drugs that may interact with bupropion; (4) positive urine drug screen or positive breath alcohol test.
Interventions	1. Bupropion (300mg daily for 3 weeks) with CR (gift cards to local grocery stores when their cotinine levels indicate that they have reduced their smoking) 2. Placebo with CR 3. Bupropion (300mg daily for 3 weeks) with non-contingent reinforcement (receive gift cards regardless of cotinine level) 4. Placebo with non-contingent reinforcement
Outcomes	Abstinence is not measured. Smoking reduction is measured by urinary cotinine level and CPD at week 3, as well as follow-up 2 and 4 weeks after the end of trial.
Starting date	September 2003
Contact information	Jennifer W. Tidey (jennifer˙tidey@brown.edu)
Notes	

Weiner (NCT00554840)

Trial name or title	Comparison of Varenicline and Placebo for Smoking Cessation in Schizophrenia
Methods	RCT. Study is conducted in USA.
Participants	Adults smokers (at least 10 cigarettes daily for one year and nicotine dependency score $\geq$4) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Participants have their psychiatric medication regimen unchanged for at least 90 days and dosage unchanged for at least 30 days. Exclusion criteria: (1) psychiatric hospitalisation in past 6 months; (2) meet criteria for current major depressive disorder or score greater than 10 on the Calgary Depression Scale; (3) suicide or homicide plan in the last 6 months; (4) life time history of suicide attempt; (5) diagnosis of schizophrenia or schizoaffective disorder for less than 3 years; (6) current treatment with bupropion; (7) DSM-IV diagnosis of alcohol or substance dependence (apart from nicotine) within last 6 months; (8) DSM-IV diagnosis of alcohol or substance abuse (apart from nicotine) within 3 months; (9) Pregnancy or breastfeeding; (10) use of tobacco product other

Weiner (NCT00554840) (*Continued*)

	than cigarettes; (11) use of nicotine replacement; (12) unstable or serious medical condition in the last 6 months; (13) regular use of cimetidine.
Interventions	1. Varenicline (1 mg twice daily) for 12 weeks 2. Placebo for 12 weeks
Outcomes	Abstinence is measured at point prevalence at week 12 and 4-week continuous abstinence at the last four weeks of the treatment by self report and biochemical verification (expired CO level < 10ppm and urine cotinine measure < 30ng/ml). Mental state is also monitored.
Starting date	November 2007
Contact information	Elaine Weiner (eweiner@mprc.umaryland.edu)
Notes	

Williams (NCT01010477)

Trial name or title	Trial of Nicotine Nasal Spray as an Aid for Smoking Cessation in Schizophrenia
Methods	RCT. Study is conducted in the USA.
Participants	Adult smokers with DSM-IV diagnosis of schizophrenia. Participants smoke at least 10 cigarettes per day and have an expired CO level >9ppm. They are also motivated to quit smoking and on atypical antipsychotic medication for at least one month. Exclusion criteria: (1) current suicidal risk; (2) psychiatric hospitalization in the last 30 days; (3) unable to read or understand questionnaires in English; (4) pregnant or lactating; (5) regular use of non-cigarette forms of tobacco; (6) Mini-mental state examination score <22
Interventions	1. Nicotine Nasal Spray (minimum 8 doses of nasal spray per day; maximum 5 doses per hour, no more than 40 doses per day) for 20 weeks 2. Placebo for 20 weeks Both group will also receive behavioural intervention
Outcomes	Abstinence is defined as self report of no tobacco use for 4 weeks, confirmed by exhaled CO level <10ppm during these period. Abstience will be assessed at week 5, week 12, week 20, week 26 and week 52.
Starting date	August 2009
Contact information	Jill M Williams, University of Medicine and Dentistry, New Jersey
Notes	

Ziedonis

Trial name or title	Treating Addiction to Nicotine in Schizophrenia (TANS) NIDA Stage I Behavioral Therapy Development Study
Methods	RCT in second phase. Study is conducted in the USA.
Participants	Smokers with schizophrenia. Details unclear but participants are motivated to quit smoking. Quit date is set at week 5.
Interventions	1. High Intensity Treament named TANS (24 sessions in 26 weeks). TANS is comprised of first 4 sessions of engagement, another 10 sessions of achieving abstinence and final 10 sessions of relapse prevention. The treatment integrates and modifies Motivational Enhancement Therapy, Relapse Prevention, specific tobacco dependence treatments and Social Skills Training into a single therapy. 2. Moderate Intentsity Treatment called Medication Management (9 sessions in 26 weeks) Both groups also receive 20 weeks of nicotine patch.
Outcomes	Abstinence is measured but details not certain. Reduction is measured with expired CO level, number of CPD and FTND score.
Starting date	2006
Contact information	Douglas Ziedonis, Department of Psychiatry, University of Massachusetts Medical School
Notes	

DATA AND ANALYSES

Comparison 1. Bupropion versus placebo

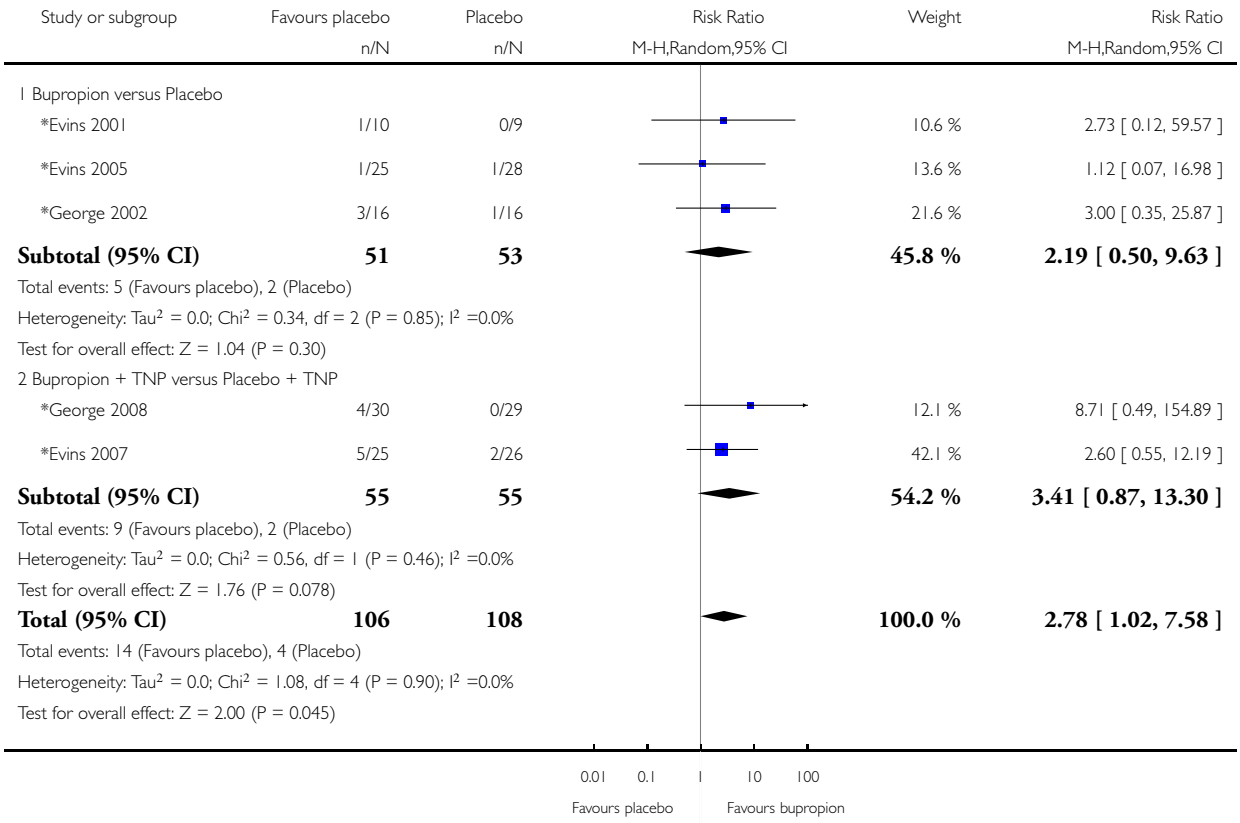
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abstinence at 6-month follow-up (primary outcome)	5	214	Risk Ratio (M-H, Random, 95% CI)	2.78 [1.02, 7.58]
1.1 Bupropion versus Placebo	3	104	Risk Ratio (M-H, Random, 95% CI)	2.19 [0.50, 9.63]
1.2 Bupropion + TNP versus Placebo + TNP	2	110	Risk Ratio (M-H, Random, 95% CI)	3.41 [0.87, 13.30]
2 Abstinence at end of treatment (secondary outcome)	7	340	Risk Ratio (M-H, Random, 95% CI)	2.84 [1.61, 4.99]
2.1 Bupropion + TNP vs. Placebo + TNP	2	110	Risk Ratio (M-H, Random, 95% CI)	2.92 [0.75, 11.33]
2.2 Bupropion vs. Placebo	5	230	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.51, 6.81]
3 Mental state outcomes	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Positive symptoms at the end of treatment (final measurements)	2	85	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.66, 0.19]
3.2 Negative symptoms at the end of treatment (final measurements)	3	136	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.46, 0.22]
3.3 Depressive symptoms at the end of treatment (final measurements)	3	136	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.50, 0.18]
4 Reduction - Expired CO level at the end of treatment (secondary outcome)	3	123	Mean Difference (IV, Random, 95% CI)	-7.03 [-11.38, -2.67]
4.1 Studies using final measurements	2	104	Mean Difference (IV, Random, 95% CI)	-6.10 [-10.71, -1.49]
4.2 Studies using change from baseline	1	19	Mean Difference (IV, Random, 95% CI)	-14.8 [-28.15, -1.45]
5 Reduction - Expired CO level at 6-month follow-up (secondary outcome)	3	123	Mean Difference (IV, Random, 95% CI)	-5.55 [-17.89, 6.78]
5.1 Studies using final measurements	2	104	Mean Difference (IV, Random, 95% CI)	-2.08 [-17.76, 13.59]
5.2 Studies using change from baseline	1	19	Mean Difference (IV, Random, 95% CI)	-14.30 [-27.20, -1.40]
6 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome)	3	184	Mean Difference (IV, Random, 95% CI)	-10.77 [-16.52, -5.01]
7 Reduction - Change in number of CPD from baseline at 6-month follow-up (secondary outcome)	2	104	Mean Difference (IV, Random, 95% CI)	0.40 [-5.72, 6.53]

Analysis 1.1. Comparison 1 Bupropion versus placebo, Outcome 1 Abstinence at 6-month follow-up (primary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

Comparison: 1 Bupropion versus placebo

Outcome: 1 Abstinence at 6-month follow-up (primary outcome)



Analysis 1.2. Comparison 1 Bupropion versus placebo, Outcome 2 Abstinence at end of treatment (secondary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

Comparison: 1 Bupropion versus placebo

Outcome: 2 Abstinence at end of treatment (secondary outcome)

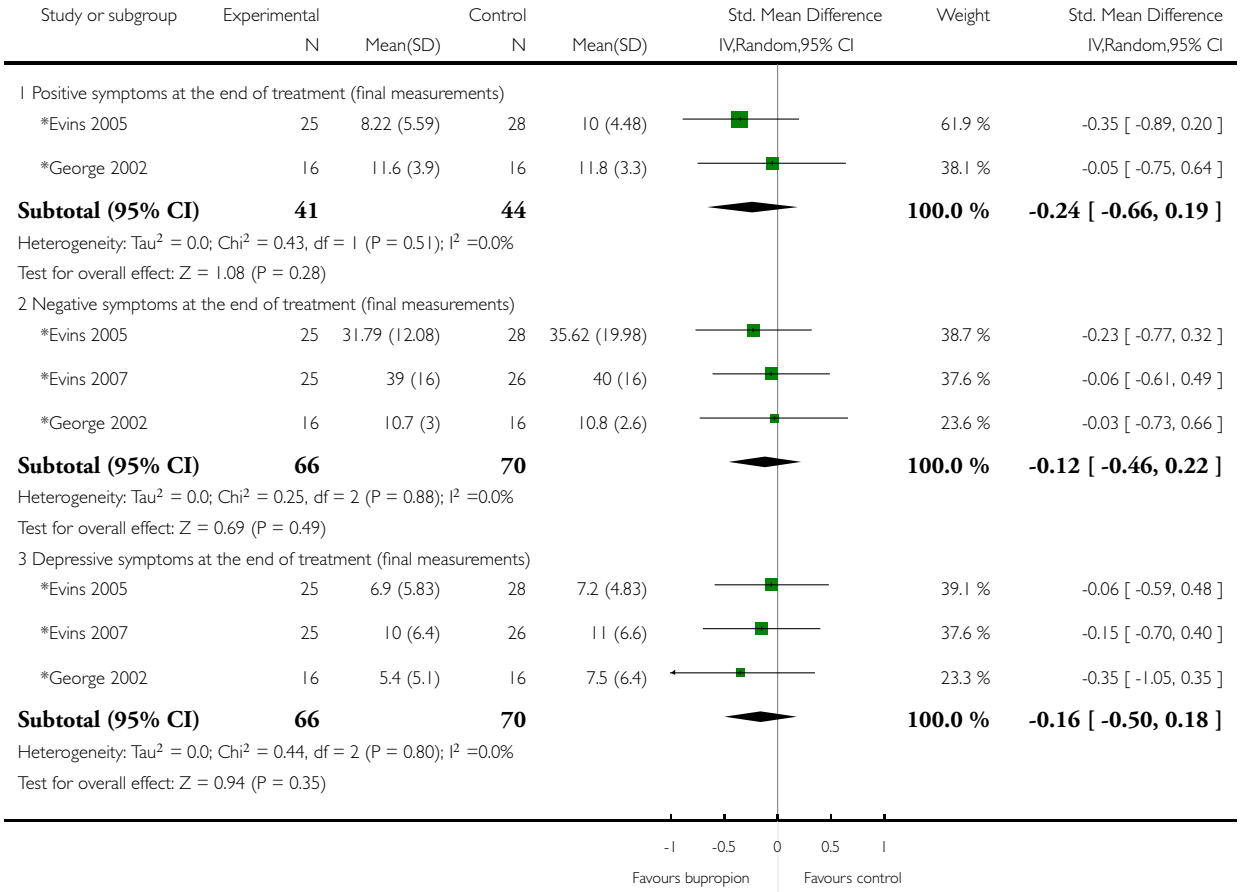
Study or subgroup	Bupropion n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Bupropion + TNP vs. Placebo + TNP					
*George 2008	8/30	1/29		7.9 %	7.73 [1.03, 58.02]
*Evins 2007	9/25	5/26		35.7 %	1.87 [0.73, 4.82]
Subtotal (95% CI)	**55**	**55**		**43.6 %**	**2.92 [0.75, 11.33]**
Total events: 17 (Bupropion), 6 (Placebo)					
Heterogeneity: Tau^2 = 0.46; Chi^2 = 1.72, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 1.55 (P = 0.12)					
2 Bupropion vs. Placebo					
*Evins 2001	1/10	0/9		3.4 %	2.73 [0.12, 59.57]
*Evins 2005	4/25	0/28		3.9 %	10.04 [0.57, 177.65]
*George 2002	6/16	1/16		8.0 %	6.00 [0.81, 44.35]
*Weiner 2007	5/24	3/22		18.6 %	1.53 [0.41, 5.66]
*Li 2009	12/40	3/40		22.6 %	4.00 [1.22, 13.11]
Subtotal (95% CI)	**115**	**115**		**56.4 %**	**3.21 [1.51, 6.81]**
Total events: 28 (Bupropion), 7 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.43, df = 4 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 3.04 (P = 0.0024)					
Total (95% CI)	**170**	**170**		**100.0 %**	**2.84 [1.61, 4.99]**
Total events: 45 (Bupropion), 13 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 4.40, df = 6 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 3.62 (P = 0.00030)					

Analysis 1.3. Comparison 1 Bupropion versus placebo, Outcome 3 Mental state outcomes.

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

Comparison: 1 Bupropion versus placebo

Outcome: 3 Mental state outcomes



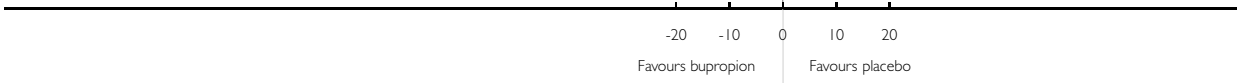
Analysis 1.4. Comparison 1 Bupropion versus placebo, Outcome 4 Reduction - Expired CO level at the end of treatment (secondary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

Comparison: 1 Bupropion versus placebo

Outcome: 4 Reduction - Expired CO level at the end of treatment (secondary outcome)

Study or subgroup	Bupropion N	Mean(SD)[ppm]	Placebo N	Mean(SD)[ppm]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies using final measurements							
*Evins 2007	25	10 (9.83)	26	15 (14.79)		40.2 %	-5.00 [-11.87, 1.87]
*Evins 2005	25	16 (10)	28	23 (13)		49.2 %	-7.00 [-13.21, -0.79]
Subtotal (95% CI)	**50**		**54**			**89.4 %**	**-6.10 [-10.71, -1.49]**
Heterogeneity: Tau² = 0.0; Chi² = 0.18, df = 1 (P = 0.67); I² =0.0%							
Test for overall effect: Z = 2.60 (P = 0.0094)							
2 Studies using change from baseline							
*Evins 2001	10	12.2 (14.82)	9	27 (14.82)		10.6 %	-14.80 [-28.15, -1.45]
Subtotal (95% CI)	**10**		**9**			**10.6 %**	**-14.80 [-28.15, -1.45]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.17 (P = 0.030)							
Total (95% CI)	**60**		**63**			**100.0 %**	**-7.03 [-11.38, -2.67]**
Heterogeneity: Tau² = 0.0; Chi² = 1.64, df = 2 (P = 0.44); I² =0.0%							
Test for overall effect: Z = 3.16 (P = 0.0016)							



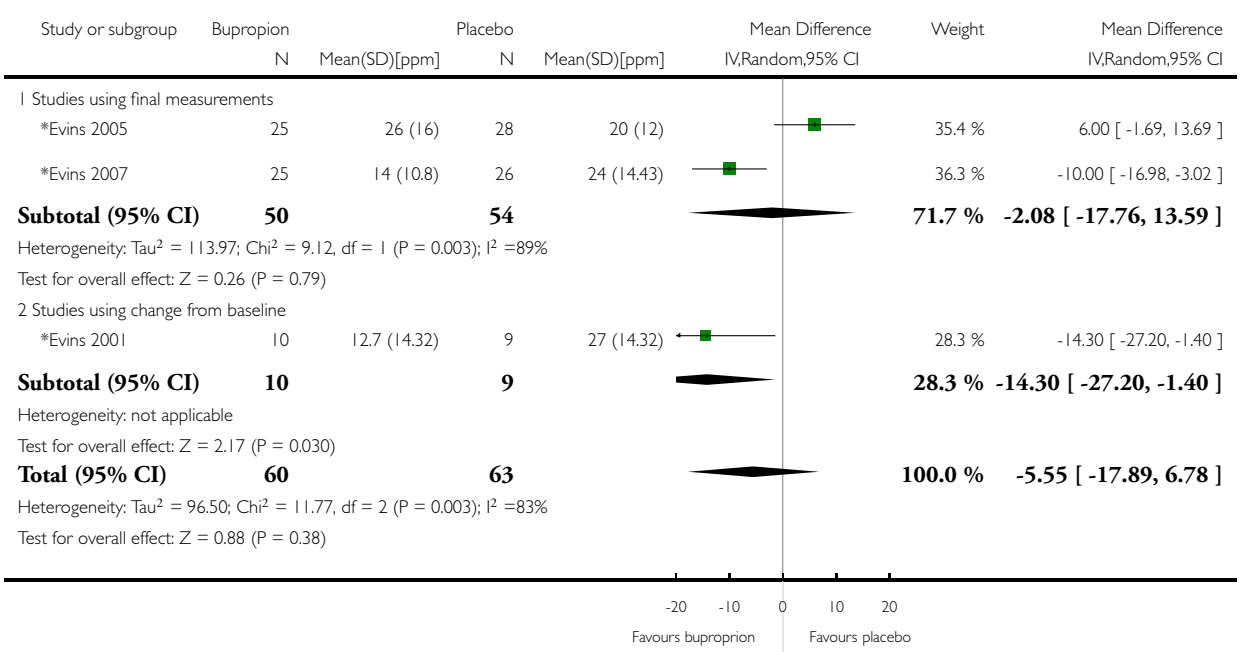
Analysis 1.5. Comparison 1 Bupropion versus placebo, Outcome 5 Reduction - Expired CO level at 6-month follow-up (secondary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

Comparison: 1 Bupropion versus placebo

Outcome: 5 Reduction - Expired CO level at 6-month follow-up (secondary outcome)

Study or subgroup	Bupropion N	Mean(SD)[ppm]	Placebo N	Mean(SD)[ppm]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Studies using final measurements							
*Evins 2005	25	26 (16)	28	20 (12)		35.4 %	6.00 [-1.69, 13.69]
*Evins 2007	25	14 (10.8)	26	24 (14.43)		36.3 %	-10.00 [-16.98, -3.02]
Subtotal (95% CI)	**50**		**54**			**71.7 %**	**-2.08 [-17.76, 13.59]**
Heterogeneity: $Tau^2 = 113.97$; $Chi^2 = 9.12$, df = 1 (P = 0.003); $I^2 = 89\%$							
Test for overall effect: Z = 0.26 (P = 0.79)							
2 Studies using change from baseline							
*Evins 2001	10	12.7 (14.32)	9	27 (14.32)		28.3 %	-14.30 [-27.20, -1.40]
Subtotal (95% CI)	**10**		**9**			**28.3 %**	**-14.30 [-27.20, -1.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.17 (P = 0.030)							
Total (95% CI)	**60**		**63**			**100.0 %**	**-5.55 [-17.89, 6.78]**
Heterogeneity: $Tau^2 = 96.50$; $Chi^2 = 11.77$, df = 2 (P = 0.003); $I^2 = 83\%$							
Test for overall effect: Z = 0.88 (P = 0.38)							



Analysis 1.6. Comparison 1 Bupropion versus placebo, Outcome 6 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

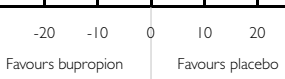
Comparison: 1 Bupropion versus placebo

Outcome: 6 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
*Evins 2007	25	-21 (16.95)	26	-11 (38.13)		11.0 %	-10.00 [-26.09, 6.09]
*Evins 2005	25	-26.5 (16.5)	28	-10.2 (13)		30.7 %	-16.30 [-24.36, -8.24]
*Li 2009	40	-18 (8)	40	-10 (9)		58.3 %	-8.00 [-11.73, -4.27]
Total (95% CI)	**90**		**94**			**100.0 %**	**-10.77 [-16.52, -5.01]**

Heterogeneity: Tau^2 = 11.15; Chi^2 = 3.36, df = 2 (P = 0.19); I^2 =40%

Test for overall effect: Z = 3.67 (P = 0.00025)



Analysis 1.7. Comparison 1 Bupropion versus placebo, Outcome 7 Reduction - Change in number of CPD from baseline at 6-month follow-up (secondary outcome).

Review: Interventions for smoking cessation and reduction in individuals with schizophrenia

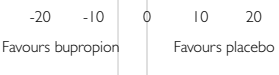
Comparison: 1 Bupropion versus placebo

Outcome: 7 Reduction - Change in number of CPD from baseline at 6-month follow-up (secondary outcome)

Study or subgroup	Bupropion N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
*Evins 2007	25	-9.5 (22.53)	26	-2.9 (51.99)		7.9 %	-6.60 [-28.45, 15.25]
*Evins 2005	25	-5 (13.7)	28	-6 (9.3)		92.1 %	1.00 [-5.38, 7.38]
Total (95% CI)	**50**		**54**			**100.0 %**	**0.40 [-5.72, 6.53]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 0.13 (P = 0.90)



APPENDICES

Appendix 1. MEDLINE search strategy

1. exp schizophrenia/
2. exp paranoid-disorders/
3. schizo*.mp.
4. hebephreni*.mp.
5. oligophreni*.mp.
6. Psychotic*.mp.
7. psychosis.mp.
8. psychoses.mp.
9. chronic*.mp.
10. sever*.mp.
11. mental*.mp.
12. ill*.mp.
13. disorder*.mp.
14. ((chronic* or sever*) adj mental* adj (ill* or disorder*)).mp.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 14
16. tardiv*.mp.
17. dyskine*.mp.
18. (tardiv* adj dyskine*).mp.
19. akathisi*.mp.
20. acathisi*.mp.
21. neuroleptic*.mp.
22. malignant.mp.
23. syndrome.mp.
24. 21 and (malignant adj syndrome).mp.
25. movement.mp.
26. disorder*.mp.
27. 21 and 25 and 26
28. parkinsoni*.mp.
29. neuroleptic-induc*.mp.
30. parkinson's.m˙titl.
31. disease.m˙titl.
32. (parkinson's adj disease).m˙titl.
33. 18 or 19 or 20 or 24 or 27 or 28 or 29
34. 33 not 32
35. exp dyskinesia-drug-induced/
36. exp akathisia-drug-induced/
37. exp neuroleptic-malignant-syndrome/
38. 34 or 35 or 36 or 37
39. 38 or 15
40. smoking cessation.mp.
41. smoking-cessation/ or tobacco-use-disorder/
42. tobacco/
43. nicotine/
44. tobacco, -smokeless/
45. exp Smoking/th, pc [Therapy, Prevention & Control]
46. ((quit$ or stop$ or ceas$ or giv$) adj smok$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
47. tobacco-smoke-pollution/
48. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. smoking/

50. 49 or 48
51. randomized controlled trial.pt.
52. controlled clinical trial.pt.
53. randomized.ab.
54. placebo.ab.
55. clinical trials as topic.sh.
56. randomly.ab.
57. trial.ti.
58. 52 or 53 or 57 or 56 or 51 or 55 or 54
59. (animals not (human and animals)).sh.
60. 58 not 59
61. 60 and 50 and 39

Appendix 2. EMBASE search strategy

1. random$.af.
2. factorial$.af.
3. crossover$.af.
4. cross over$.af.
5. cross-over$.af.
6. placebo$.af.
7. (doubl$ adj blind$).af.
8. (singl$ adj blind$).af.
9. assign$.af.
10. allocat$.af.
11. volunteer$.af.
12. crossover procedure/
13. double blind procedure/
14. Randomized Controlled Trial/
15. Single Blind Procedure/
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. smoking cessation.mp.
18. exp smoking cessation/
19. exp smoking-/
20. ((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
21. exp passive-smoking/ or exp smoking-habit/ or exp cigarette-smoking/ or exp "smoking-cessation"/
22. 17 or 18 or 19 or 20 or 21
23. schizo*.mp.
24. Psychotic*.mp.
25. psychosis.mp. or Psychosis/
26. psychoses.mp.
27. 26 or 23 or 25 or 24
28. exp Schizophrenia/
29. exp Psychosis/
30. chronic*.mp.
31. severe*.mp.
32. persistent*.mp.
33. mental*.mp.
34. psychological*.mp.
35. disorder*.mp.
36. ill*.mp.

37. ((chronic* or severe* or persistent*) adj (mental* or psychological*) adj (disorder* or ill*)).mp.
38. "mental-patient".mp. or exp Mental Patient/
39. tardiv*.mp.
40. dyskine*.mp.
41. (tardiv* adj dyskine*).mp.
42. akathisi*.mp.
43. neuroleptic*.mp.
44. malignant.mp.
45. syndrome.mp.
46. 43 and (malignant adj syndrome).mp.
47. exp Tardive Dyskinesia/
48. exp Akathisia/
49. acathisia.mp.
50. exp Neuroleptic Malignant Syndrome/
51. movement.mp.
52. disorder.mp.
53. 43 and 51 and 52
54. 27 or 28 or 29 or 37 or 38
55. parkinsoni*.mp.
56. neuroleptic-induced.mp.
57. 41 or 42 or 46 or 47 or 48 or 49 or 50 or 53 or 55 or 56
58. parkinson's.m˙titl.
59. 57 not 58
60. 59 or 54
61. 22 and 60 and 16

Appendix 3. PsycINFO search strategy

1. schizo*.mp.
2. hebephreni*.mp.
3. oligophreni*.mp.
4. Psychotic*.mp.
5. psychosis.mp.
6. psychoses.mp.
7. chronic*.mp.
8. sever*.mp.
9. mental*.mp.
10. ill*.mp.
11. disorder*.mp.
12. ((chronic* or sever*) adj mental* adj (ill* or disorder*)).mp.
13. exp schizophrenia/
14. exp psychosis/
15. exp schizoaffective disorder/
16. 1 or 2 or 3 or 4 or 5 or 6 or 12 or 13 or 14 or 15
17. tardiv*.mp.
18. dyskine*.mp.
19. (tardiv* adj dyskine*).mp.
20. akathisi*.mp.
21. acathisi*.mp.
22. neuroleptic*.mp.
23. malignant.mp.
24. syndrome.mp.

25. 22 and (malignant adj syndrome).mp.
26. movement.mp.
27. disorder*.mp.
28. 22 and 26 and 27
29. parkinsoni*.mp.
30. neuroleptic-induc*.mp.
31. parkinson's.m˙titl.
32. disease.m˙titl.
33. (parkinson's adj disease).m˙titl.
34. 19 or 20 or 21 or 25 or 28 or 29 or 30
35. 34 not 33
36. exp Neuroleptic Malignant Syndrome/
37. exp dyskinesia/
38. exp akathisia/
39. exp parkinsonism-/
40. 35 or 36 or 37 or 38 or 39
41. 40 or 16
42. smoking cessation.mp. or exp smoking cessation/
43. (antismoking or anti-smoking).mp.
44. (quit$ or cessat$).mp.
45. (abstin$ or abstain$).mp.
46. (control$ adj smok$).mp. [mp=title, abstract, heading word, table of contents, key concepts]
47. exp behavior modification/
48. 43 or 44 or 45 or 46 or 47
49. tobacco-smoking/
50. (smok$ or cigar$ or tobacco$).mp.
51. prevention/
52. 49 or 50
53. 48 and 52
54. 51 and 52
55. 42 or 53 or 54
56. randomi*.mp.
57. singl*.mp.
58. doubl*.mp.
59. trebl*.mp.
60. tripl*.mp.
61. blind*.mp.
62. mask*.mp.
63. ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).mp.
64. CLIN*.mp.
65. trial*.mp.
66. (CLIN* adj trial*).mp.
67. placebo*.mp.
68. exp Placebo/
69. crossover.mp.
70. exp Treatment Effectiveness Evaluation/
71. exp mental health program evaluation/
72. random*.mp.
73. assign*.mp.
74. allocat*.mp.
75. (random* adj (assign* or allocat*)).mp.
76. 75 or 71 or 70 or 69 or 68 or 67 or 66 or 63 or 56
77. 76 and 55 and 41

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 6, 2010

CONTRIBUTIONS OF AUTHORS

DTT and ACW conceived and designed the review. DTT conducted the search. Both DTT and ACW screened retrieved papers. DTT and MP extracted data from the paper, with contribution from ACW to resolve disagreement. DTT entered the data into RevMan and performed data analysis. DTT wrote the review with the input from MP and ACW.

DECLARATIONS OF INTEREST

None known

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Internal sources

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- School of Public Health, University of Sydney, Australia.

External sources

- NHS National Institute for Health Research, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We widened the inclusion criteria in two ways:

a) To include patients with schizoaffective disorder, since individuals with this diagnosis share certain core symptoms with patients with schizophrenia.

b) To include trials of interventions for other purposes that reported smoking-related outcomes, if the trials met the type of study and type of participant inclusion criteria. Trials which tested an intervention for another primary purpose were reported separately and did not contribute to any meta-analysis.

2. We changed the primary outcome measure to abstinence from smoking assessed at least six months from the start of the intervention, to be consistent with other reviews by the Cochrane Tobacco Addiction Group, and the "Russell standard". We reported smoking abstinence at the end of the trial and smoking reduction as secondary outcomes.

NOTES

The earlier part of this work (bupropion) was presented as a poster at the 17th European Congress of Psychiatry (Lisbon, 2009), and published as a review article in the British Journal of Psychiatry (Tsoi 2010).