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	7	14 (5 to 31)	7 (3 to 20)	5	10	4	7 (0 to 24)	15 (4 to 1350)
TNP vs. placebo	Data not combined because of heterogeneity of studies					No trial found				
Varenicline vs. placebo	2	20	4	16 (1 to 65)	6 (2 to 71)	1	2	0	2	#
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, especially in people aged 35 to 54 years. (Brown 2000; Lichtermann 2001; Kelly 2011). 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 of the positive symptoms of the condition, 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. Individuals 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, disorganised 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. Recent research also showed that they perceived a lower risk to their health associated with smoking when compared to people without schizophrenia (Kelly 2012). Furthermore, smoking is sometimes condoned in mental health settings, and in the past cigarettes were used in token economies to reinforce positive patient behaviour (Gustafson 1992). Smoking has also been recently shown as a possible way for social facilitation and stimulation enhancement among individuals with schizophrenia (Kelly 2012)

Tobacco control specialists and healthcare providers previously have not offered tobacco dependence treatment to patients with schizophrenia, probably secondarily 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 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 been shown to be in the general population. We also need to consider the safety of these interventions, particularly those involving 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). Some case reports have suggested that varenicline (another medication which has been proven to be effective for smoking cessation in the general population) may exacerbate psychiatric symptoms including psychosis and mood symptoms (Freedman 2007; Liu 2009). Moreover, drug treatment for smoking cessation and reduction may interact with and alter the effectiveness of the antipsychotic medications commonly used among patients with schizophrenia. In addition, nicotine withdrawal can cause symptoms like depression, anxiety and irritability. All these factors may contribute to changes in the mental state of these patients, and the extent of these changes remains unclear. The aim of this review is to summarize existing evidence for different interventions in smoking cessation and reduction for individuals 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 randomised controlled trials (RCTs) or quasi-randomised 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 Organization 2003) or Diagnostic and Statistical 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. We did not exclude patients with a diagnosis of schizophrenia or schizoaffective disorder who had other substance misuse disorder or additional psychiatric disorders, 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, we included that trial only when separate data for people with schizophrenia or schizoaffective disorder were available. We included people who may or may not have expressed an interest in stopping or reducing 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. We included interventions intended for another purpose (e.g. antipsychotics for treating schizophrenia) 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' (i.e. 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 six months 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 were 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 carbon monoxide (CO) level; or reduction of scores on scale measures of nicotine dependence (e.g. Fagerström Test for Nicotine Dependence (FTND)).

Other adverse events

We recorded and assessed any other reported adverse events.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Tobacco Addiction Group Specialised Register in November 2012, using the topic-related free-text term 'schiz*'. See the Specialised 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* 2012 issue 6, using the strategy ((SR-SCHIZ) and (smoking):ti,ab,kw) AND NOT (SR-TOBACCO).

In addition, we searched the following electronic databases in October 2012:

1. MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations via OVID (1948 onwards)
2. EMBASE via OVID (1980 onwards)

3. PsycINFO via OVID (1806 onwards)
4. CINAHL Plus with Full Text (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 randomised 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 randomised trials, we used the search strategies suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). 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 Organization 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/);
5. UK Clinical Trials Gateway (www.controlled-trials.com/ukctg/).

Where we suspected duplicate reporting of the same trial, 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

All of the authors (DTT, MP and ACW) independently screened the titles and abstracts identified by the search, and decided on the possible reports to be included. We obtained and examined full text reports of all potentially relevant trials, to decide whether the studies fulfilled the inclusion criteria. Any disagreement between the authors was resolved through discussion. All studies excluded at this stage are reported in the Characteristics of excluded studies table.

Data extraction and management

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

1. Methodology - comprising the inclusion and exclusion criteria, method of randomisation 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 another 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 excluded studies table, 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 and MP) also independently assessed each trial for risk of bias according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We recorded sequence generation during randomisation, concealment of allocation, blinding, completeness of outcome data (including use of intention-to-treat (ITT) analysis) and selective outcome reporting for each trial. We also identified other potential sources of bias. We categorised each trial as being at low, uncertain or high risk of bias for each domain, based on the standards described in the *Cochrane Handbook for Systematic Reviews of Interventions*.

Measures of treatment effect

We calculated summary estimates for the extracted data. Results for dichotomous outcomes were expressed as risk ratios (RR). The RR was calculated as: ((number of participants with the outcome in intervention group / number of participants randomised to intervention group) / (number of participants with the outcome in the control group / number of participants randomised 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. We also addressed the potential impact of the missing data 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, we assessed potential publication bias 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 (CIs) of the risk ratios. We calculated the summary estimates for continuous outcomes using the inverse variance approach, also with 95% CIs. Change-from-baseline measurements and final measurements were combined for continuous outcomes if the mean difference was used to express the summary results, following the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We pooled data 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 analyses when appropriate, to assess whether the estimate of treatment effect was influenced by various factors, such as location of the trials or publication types etc.

Results

RESULTS

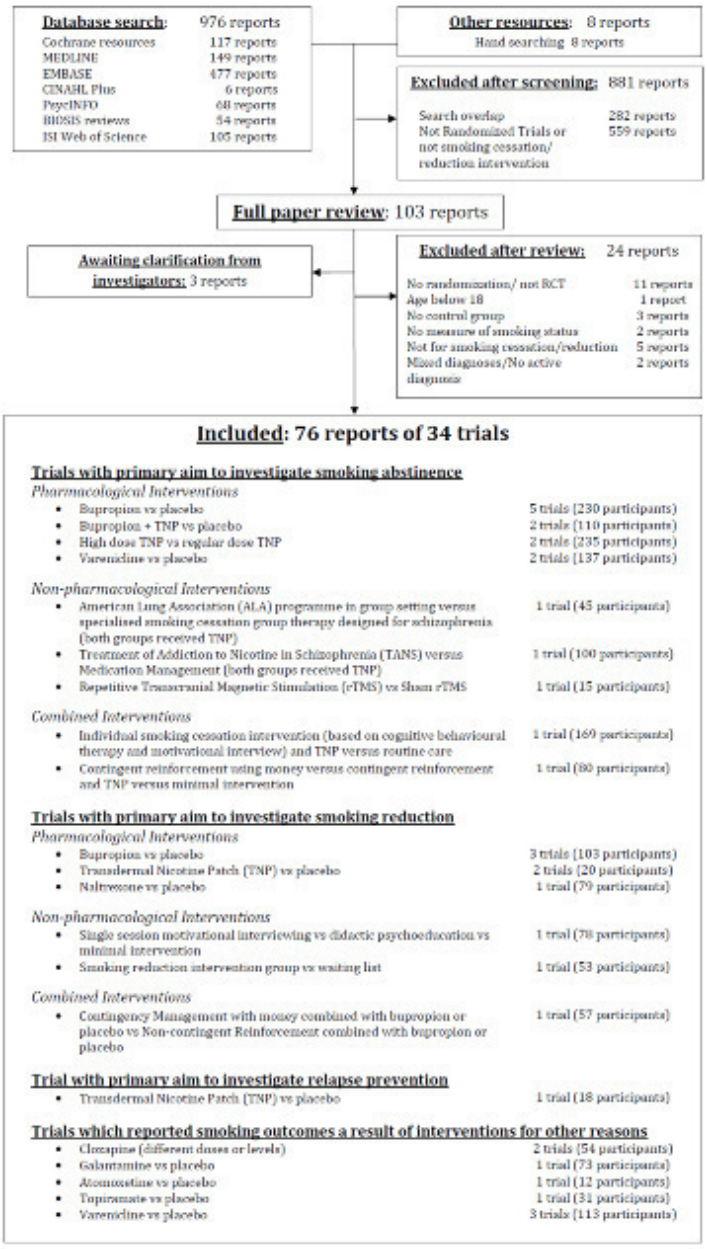
Description of studies

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

Results of the search

We identified 976 reports from the electronic search of the databases (149 reports from MEDLINE, 477 from EMBASE, 68 from PsycINFO, 6 from CINAHL Plus, 54 from BIOSIS reviews, 105 from ISI Web of Science with Conference Proceedings, and 117 reports from CENTRAL and the Cochrane Tobacco Addiction Group Specialised Register) (Figure 1). We identified eight further trial reports from handsearching and nine ongoing studies from the online clinical trials registers and from handsearching (See Characteristics of ongoing studies). After screening, we reviewed the full text of 103 reports which were considered potentially eligible. We excluded 24 reports of 22 trials 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 randomised because of the uneven number of participants among the treatment groups. We have not received any response; see Characteristics of studies awaiting classification.

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



The final review includes 34 trials; see the Characteristics of included studies table. The primary aim of 16 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; *Williams 2007; *George 2008; *Li 2009; *Williams 2010; *Weiner 2011; *Chen 2012; *Weiner 2012; *Williams 2012; *Wing 2012). Nine studies focused on smoking reduction (studies prefixed with a cross; +Hartman 1991; +Dalack 1999; +Steinberg 2003; +Fatemi 2005; +Akbarpour 2010; +Bloch 2010; +Szombathyne 2010; +Tidey 2011; +Gelkopf 2012). One trial investigated the use of nicotine patch for relapse prevention after smoking cessation (^Horst 2005). The remaining eight 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; Hong 2011; Meszaros 2012; Shim 2012)

Included studies

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

Study and participant characteristics

There were 26 trials in this category; most were conducted in the United States and reported in English, apart from *Baker 2006, conducted in Australia; *Wing 2012, conducted in Canada; +Akbarpour 2010, conducted in Iran; +Bloch 2010 and +Gelkopf 2012, conducted in Israel; *Chen 2012 conducted in Taiwan; and *Li 2009, conducted in China and reported in Chinese. Most of the reports were published in journals, except for four trials which were only reported as letters to editors or conference proceedings (+Fatemi 2005; *Williams 2007; +Szombathyne 2010; *Wing 2012). 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 randomised controlled trial; in this review we only considered data from the randomised trial phase.

Most trials recruited participants from the community. Four trials (*Chen 2012; *Li 2009; +Akbarpour 2010; +Gelkopf 2012) recruited only smokers in inpatient units, 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 smokers with mixed psychiatric diagnoses, but data for participants with schizophrenia or schizoaffective disorder were available for separate analysis. A significant number of studies explicitly excluded participants with any active substance misuse other than nicotine (+Dalack 1999; *Evins 2001; *George 2002; *Evins 2005; *Evins 2007; *George 2008; +Akbarpour 2010; +Bloch 2010; +Tidey 2011; *Weiner 2011; +Gelkopf 2012; *Weiner 2012; *Williams 2012; *Wing 2012). +Szombathyne 2010 investigated schizophrenia patients with both nicotine and alcohol dependence.

Sixteen trials explicitly stated that participants had expressed interest in quitting or reducing smoking (*George 2000; *Evins 2001; *George 2002; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *Williams 2007; *George 2008; +Bloch 2010; *Williams 2010; +Tidey 2011; +Gelkopf 2012; *Weiner 2012; *Williams 2012; *Wing 2012). +Steinberg 2003 measured changes in quitting motivation after motivational interviewing, where the participants had different levels of interest in quitting smoking at the baseline. Participants in *Chen 2012 also varied in their motivation and readiness to quit smoking. Target quit dates were set in 13 studies (*George 2000; *Evins 2001; *George 2002; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *George 2008; *Williams 2010; *Weiner 2011; *Weiner 2012; *Williams 2012; *Wing 2012).

Interventions

We evaluated a range of interventions. Of the studies comparing pharmacotherapy with placebo, the commonest interventions were bupropion (*Evins 2001; *George 2002; *Evins 2005; +Fatemi 2005; *Li 2009; +Akbarpour 2010; +Bloch 2010; *Weiner 2012), transdermal nicotine patch (TNP) (+Hartman 1991; +Dalack 1999; ^Horst 2005) and varenicline (*Weiner 2011; *Williams 2012). +Szombathyne 2010 investigated the effect of naltrexone in smoking and alcohol reduction. Two studies compared the combination of bupropion and TNP, with TNP and placebo (*Evins 2007; *George 2008). Two trials compared the efficacy of different dosages of TNP (*Williams 2007; *Chen 2012) for smoking cessation. 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; +Bloch 2010), group therapy for motivational enhancement, psychoeducation and relapse prevention (*George 2002); group behavioural therapy (*George 2008; *Wing 2012); smoking cessation educational classes along with discussions with health educators (^Horst 2005); group psychoeducation (*Chen 2012); group therapy using the American Cancer Society Fresh Start Program (*Weiner 2012) and individual smoking cessation counselling (*Weiner 2011; *Williams 2012). The duration of drug treatment varied

from seven hours (+Hartman 1991) to six months (^Horst 2005). Five 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. *Williams 2010 investigated the effect of the Treatment of Addiction to Nicotine in Schizophrenia (TANS) programme (individual 45-minute weekly sessions for 26 weeks) and compared this with Medication Management (MM) (nine individual 20-minute sessions over 26 weeks). Participants also received TNP in both groups in this trial. +Gelkopf 2012 in Israel examined the effect of a weekly group session for five weeks, focusing on smoking reduction in a hospital setting. Apart from psychosocial interventions, *Wing 2012 used repetitive transcranial magnetic stimulation (rTMS) to investigate whether this was effective for smoking cessation among individuals with schizophrenia or schizoaffective disorder.

Three other trials investigated the combined effect of pharmacological and psychosocial interventions. In *Baker 2006, a combination of individually administered motivational interviewing with CBT and TNP was compared with routine care. In a three-arm study, *Gallagher 2007 compared contingent reinforcement (CR) using money, with and without additional TNP, and a self quit control without TNP. In +Tidey 2011, participants were randomised to four different combinations of interventions: bupropion and contingency management (CM); placebo and CM; bupropion and non-contingent reinforcement (NR); placebo and NR.

Outcomes

Abstinence was defined and measured in 16 trials (*George 2000; *Evins 2001; *George 2002; *Evins 2005; *Baker 2006; *Evins 2007; *Gallagher 2007; *Williams 2007; *George 2008; *Li 2009; *Williams 2010; *Weiner 2011; *Chen 2012; *Weiner 2012; *Williams 2012; *Wing 2012). Three of these studies did not explicitly report whether participants expressed any interest in quitting smoking (*Li 2009; *Weiner 2011; *Chen 2012). Five trials did not report any continuation of follow-up beyond the end of the intervention; *Williams 2007; *Li 2009; and *Chen 2012 reported abstinence at eight weeks; *Weiner 2011 and *Weiner 2012 after 12 weeks. *Wing 2012 reported abstinence at week 10, i.e. six weeks after the end of the intervention which last for four weeks. The other 10 studies provided results for longer follow-up, of at least 24 weeks 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).

Nine trials only reported smoking reduction as the main outcome measure (+Hartman 1991; +Dalack 1999; +Steinberg 2003; +Fatemi 2005; +Akbarpour 2010; +Bloch 2010; +Szombathyne 2010; +Tidey 2011; +Gelkopf 2012). Most of the studies which measured smoking abstinence also reported some measures of smoking reduction. Self report of reduction in cigarettes per day (CPD) was commonly used 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;+Akbarpour 2010; +Bloch 2010; +Szombathyne 2010; *Williams 2010; +Tidey 2011; +Gelkopf 2012; *Williams 2012). These outcomes were reported after a range of follow-up periods which varied from two days (+Hartman 1991) to four years (*Baker 2006). Expired carbon monoxide (CO) level reduction was also frequently reported as a measure of smoking reduction (+Dalack 1999; *George 2000; *George 2002; +Steinberg 2003; *Evins 2005; ^Horst 2005; *Gallagher 2007; +Tidey 2011; *Weiner 2011; *Williams 2010; *Weiner 2012; *Wing 2012). Other measures of smoking reduction included plasma cotinine level (*Evins 2001), scale measure of nicotine dependence (e.g. Fagerström Test for Nicotine Dependence (FTND)) (+Steinberg 2003; +Fatemi 2005; *Gallagher 2007; *Li 2009; +Bloch 2010; *Weiner 2012), urine cotinine level (+Fatemi 2005; *Weiner 2012) and salivary cotinine level (*Gallagher 2007).

Most 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; +Akbarpour 2010; +Bloch 2010; *Williams 2010; +Tidey 2011; *Weiner 2011; *Chen 2012; +Gelkopf 2012; *Weiner 2012; *Williams 2012; *Wing 2012; *Chen 2012).

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

Eight 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; Hong 2011; Meszaros 2012; Shim 2012). Weinberger 2008 only included participants with schizoaffective disorder, bipolar type. Meszaros 2012 included people with both nicotine and alcohol dependence. Five 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; Hong 2011; Shim 2012). Although varenicline has been shown to be an effective treatment for smoking cessation in the general population, three studies investigated its possible uses in schizophrenia other than primarily for smoking cessation. Hong 2011 and Shim 2012 examined the effect of varenicline on cognitive function in schizophrenia. Meszaros 2012 investigated the use of varenicline as a treatment for alcohol dependence among individuals with schizophrenia or schizoaffective disorder. 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 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 11 trials to have used an adequate method for generating the randomisation sequence (+Dalack 1999; *Evins 2001; +Steinberg 2003; *Evins 2005; ^Horst 2005; *Baker 2006; *Evins 2007; *Gallagher 2007; *Williams 2010; +Tidey 2011; +Gelkopf 2012). Most of the other studies were classified as unclear because there was no description of the randomisation process and we could not clarify details with the investigators. We obtained additional information on *Li 2009 and +Bloch 2010 (see details in Characteristics of included studies), and judged these two trials as having a high risk of bias.

We judged five studies to have used an adequate method of allocation concealment (+Dalack 1999; *Evins 2001; *Evins 2005; *Evins 2007; *Williams 2010). 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 judged to be unclear. Correspondence with *Li 2009, showed that there was 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. +Bloch 2010 reported that people were randomly allocated based upon their order of arrival and we judged that it was unlikely that allocation concealment was done properly and hence that it had a high risk of bias. We also obtained information from +Gelkopf 2012 regarding their randomisation (see details in Characteristics of included studies), and we believe that it is likely that allocation concealment would be compromised at the very end of the drawing, as the next person's allocation group would become obvious. As a result, we also judged it as high risk of bias.

Adequate blinding to treatment allocation in assessment of outcomes was observed in 10 trials (+Hartman 1991; +Dalack 1999; *Evins 2001; *George 2002; *Evins 2005; +Fatemi 2005; *Evins 2007; +Tidey 2011; *Williams 2012; *Wing 2012). Some studies reported double-blinding but their reports did not explicitly state who was blinded, and we were not able to clarify this with the investigators (*Williams 2007; *George 2008; *Li 2009; +Akbarpour 2010; +Bloch 2010; +Szombathyne 2010; *Weiner 2011; *Chen 2012: *Weiner 2012). We judged that double-blinding implied that it was likely that participants and investigators were blinded, but we declared all these studies as having an unclear risk of bias even though it was likely that the possible bias introduced into 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 reported reduction of cigarettes used) and subjective assessment (e.g. assessment of psychiatric symptoms) were used for outcome assessments. Three studies did not report any blinding (*George 2000; *Gallagher 2007; +Gelkopf 2012). Only the outcome assessor was blinded in another three studies (+Steinberg 2003; *Baker 2006; *Williams 2010). ^Horst 2005 blinded participants but not the outcome assessor.

There were wide-ranging variations in how missing outcome data were handled. We judged nine studies as having a low risk of bias secondary to incomplete outcome data (+Dalack 1999; *George 2002; *Baker 2006; *Evins 2007; +Akbarpour 2010; *Weiner 2011; *Chen 2012; +Gelkopf 2012; *Weiner 2012). These studies included all participants who were randomised and used true intention-to-treat analysis. Those with missing data were classified either as non-abstinent or as failing to achieve smoking reduction in these studies (*Baker 2006; *Evins 2007; *Weiner 2012). Some trials used the 'last observation carried forward' approach to handling missing data (+Steinberg 2003; *Gallagher 2007). We had a concern whether this approach was appropriate, as those who were lost to follow-up may be more likely to relapse, so that the 'last observation carried forward' assumption would probably have overestimated the intervention effect by assuming these participants to have maintained abstinence. Hence, we categorised these trials as having a high risk of bias for incomplete outcome data. In other trials, participants who were randomised were excluded from the analysis for various other reasons. These reasons included dropping out before the start of the intervention (*Evins 2001; *Evins 2005; *George 2008; *Williams 2010; +Tidey 2011; *Williams 2012); the need for dose change for symptom stabilisation or side effects of medications (*George 2000); stopping the intervention during the trial (^Horst 2005; *Li 2009; +Bloch 2010); 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 were classified as having an unclear risk of bias (+Fatemi 2005; *Williams 2007; +Szombathyne 2010). *Wing 2012 mentioned that an intention-to-treat analysis was employed but we could not confirm this. As a result, we classified this trial as at unclear risk of bias.

Three studies did not report all outcome results as predicted in their 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).

There were large differences in contact time between the intervention and control groups in a number of trials which examined the effect of non-pharmacological interventions. *Baker 2006 com-

pared 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; Contingent Reinforcement (CR) with transdermal nicotine patch (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. In *Williams 2010, the Treatment of Addiction to Nicotine in Schizophrenia (TANS) group received 24 sessions of 45-minute individual psychological intervention, compared to the Medication Management (MM) group only received nine 20-minute sessions. +Gelkopf 2012 compared the smoking reduction intervention group which had a weekly one-hour session for five weeks, with the waiting list which only received one lecture on the dangers of smoking.

There were some other possible biases. Despite randomisation, four studies had statistically significant differences in some characteristics between the intervention and the control groups (*George 2000; *Evins 2005; *Williams 2010; +Tidey 2011). In ^Horst 2005, where the RCT phase 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. Six trials lacked biochemical validation of smoking status (+Hartman 1991; *Li 2009; +Akbarpour 2010; +Bloch 2010; +Szombathyne 2010; +Gelkopf 2012). Two of the three cross-over studies had relatively short washout periods, of 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 (*Williams 2007; *Weiner 2011; *Wing 2012), there was insufficient information to assess whether any other important bias existed, and we judged them as unclear. *Williams 2012 was sponsored by the drug company that manufactured varenicline, and we judged it as unclear whether any other important bias existed.

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

Within this group we only judged two trials to have a low risk of bias in sequence generation (Kelly 2008; Meszaros 2012), and one trial as having a low risk of bias in allocation concealment. Other trials did not explicitly describe the way in which the randomisation sequence was generated, and we could not clarify this with the investigators, so the risks of bias in sequence generation and allocation concealment were rated as unclear. Four 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; Meszaros 2012; Shim 2012). The study by de Leon 2005b excluded four participants from the analysis without stating the reason. Another study used the 'last observation carried forward' method for missing data (Weinberger 2008). In Hong 2011 and Meszaros 2012, there were no intention-to-treat analyses and they did not include all people who were randomised in their denominators. Hence, we judged these four trials as having a high risk of bias for incomplete outcome data.

In Kelly 2008 and Weinberger 2008, the results in the reports were subgroup analyses of larger related trials, and some people who smoked were not included in the analysis. The reason for not including these people was unclear, 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 levels. There were also baseline differences between comparison groups in the study by McEvoy 1995. We therefore judged all these trials as having a high risk for other biases.

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

We have grouped the included studies under the following categories:

1. Trials in which the primary aim was smoking cessation;
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 for both treatment and placebo groups), 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

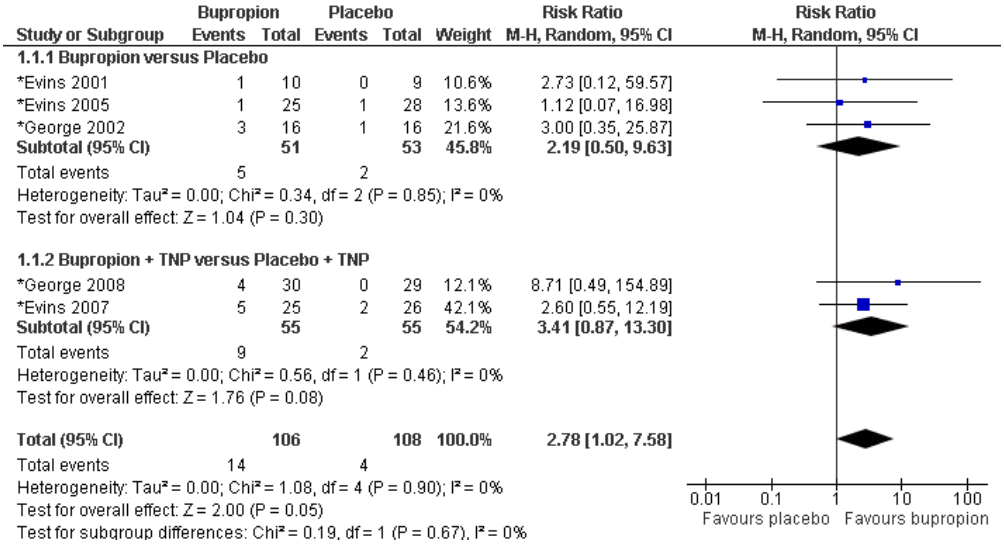
Intervention rationale: Bupropion is an atypical antidepressant with both dopaminergic and adrenergic actions. There is robust

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. *Weiner 2012 and these five trials recruited participants who were interested in quitting smoking, and set a target quit date. The study in China by *Li 2009 did not report whether participants had any interest in quitting. At six-months 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 (five trials, N = 214, risk ratio (RR) 2.78, 95% confidence interval (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 transdermal nicotine patch (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 on smoking cessation from a 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 person who was abstinent at the end of the trial. The investigators reported that three of the four abstinent after two years received bupropion slow release (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 (i.e. statistically non-significant).

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

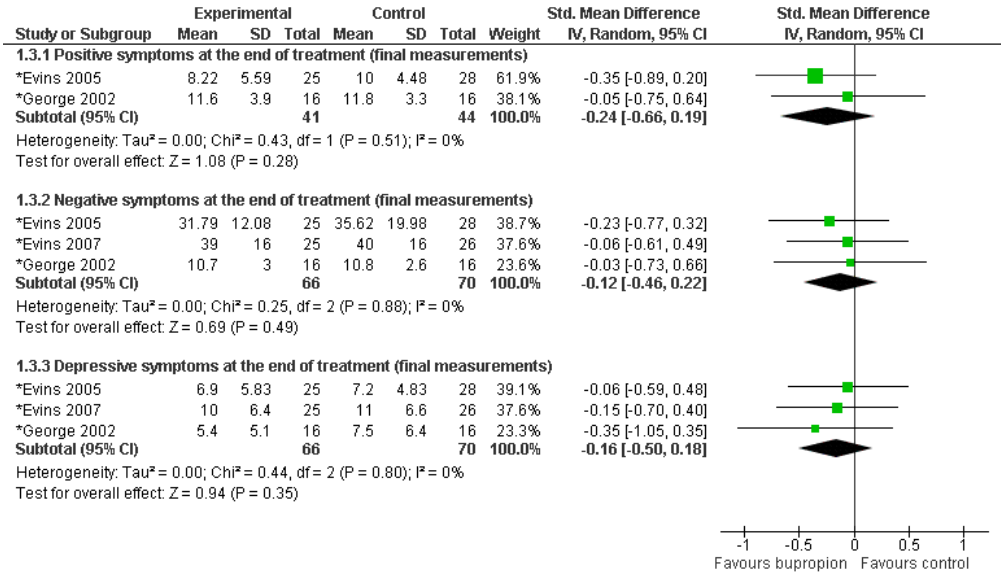


The effect size was similar for the secondary outcome of abstinence at the end of treatment, but the confidence intervals were narrower, reflecting the two additional trials and the larger number of successful short-term quitters (seven trials, N = 340; RR 3.03, 95% CI 1.69 to 5.42, I^2 = 0%; Analysis 1.2). Sensitivity analyses detected no important difference in effect from omitting any of the following: one trial was conducted outside the USA and the participants' interests in quitting were uncertain (*Li 2009); or one trial using the lower dose of 150 mg bupropion daily (*Evins 2001), compared with 300 mg daily in other trials.

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 (two trials, N = 85; standardised mean difference (SMD) -0.24, 95% CI -0.66 to 0.19; I^2 = 0%), in negative symptoms (three trials, N = 136; SMD -0.12, 95% CI -0.46 to 0.22; I^2 = 0%) or depressive symptoms (three 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 (*George 2008; *Li 2009; *Weiner 2012). In *Evins 2001, 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. Three studies also reported the effect of abstinence on the mental state of the participants, and found 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



Adverse effects

Regarding other adverse effects of bupropion, one participant who took bupropion had a seizure at the end of the trial (*Weiner 2012). However, this patient had a history of polydipsia and was found to have hyponatraemia when he had the seizure. It was likely that the seizure related to polydipsia rather than to bupropion. No seizures were reported in any other trial.

The prevalence of dry mouth was significantly higher in the bupro-

pion group compared to the control group in one study (P < 0.05; *George 2002). The same research group, in a second study (*George 2008), reported significant differences in concentration, jitteriness, light-headedness, muscle stiffness and frequent nocturnal awakening in the bupropion group. Three of the 59 participants (two in the placebo group and one in the bupropion group) had a 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 people from this trial had a recurrence of psychotic symptoms, but the author did not report to which group they had been allocated. One participant in *Evins 2005, randomised 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. In *Weiner 2012, they did not find any significant group differences in any of the major adverse events measured by Side Effect Checklists (SEC). The SEC included common bupropion side effects such as restlessness, insomnia, dry mouth and sedation. Five participants from the bupropion group dropped out because of side effects (two people complained of restlessness and increased anxiety in the first week, one complained of worsening of psychosis, one developed a rash at week two, and one developed a seizure, as reported above). 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 for these outcome measures were probably from the entire sample (i.e. including participants who successfully abstained from smoking and those who continued to smoke). Three trials reported data for smoking reduction measured by expired carbon monoxide (CO) level. At the end of treatment, there was a significant reduction of expired CO in the bupropion group compared to the control group (four trials, N = 169; MD -6.80 parts per million (ppm), 95% CI -10.79 to -2.81 ppm, I^2 = 0%; Analysis 1.4). *Evins 2001 reported incomplete data for expired CO level and did not contribute to the meta-analysis, but both favoured bupropion at the end of the treatment. At six months after the start of treatment there was no significant difference in expired CO level (three trials, N = 123; MD -5.55 ppm, 95% CI -17.89 to 6.78 ppm; 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 cigarettes per day (CPD). At the end of bupropion treatment, there was a significant reduction of CPD in the bupropion group compared to controls (three 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 who 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 starting 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 and placebo groups (two 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 TNP (42 mg) with regular dose TNP (21 mg) 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 the two groups. However, the authors reported that tolerability and compliance was good for both groups.

Another trial in Taiwan (*Chen 2012) investigated the effect of different doses of TNP (31.2 mg for the first four weeks, then normal 20.8 mg for the next four weeks, (high dose)), compared 20.8 mg for eight weeks (low dose) among 184 patients with schizophrenia in the chronic wards of two psychiatric hospitals. Their motivation and readiness to stop smoking were variable. Seven-day abstinence rates at week eight were higher in the low dose compared to the high dose TNP group, although the difference was not significant (low dose: 4.3%; high dose: 1.1%). The investigators reported that the low dose TNP group reduced smoking by three more cigarettes on average, compared to the high dose group, although it is likely that this included people who succeeded in quitting entirely. There were no statistically significant differences between expired CO level and FTND scores between the two groups at the end of the intervention. There were also no significant differences between the two groups in positive and negative symptom scores. 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) was significantly higher in participants who used TNP compared to those without TNP; both groups also received money as contingent reinforcement. Results of these two studies are summarised in the 'combined interventions' section below.

1.3 Pharmacological intervention - Varenicline

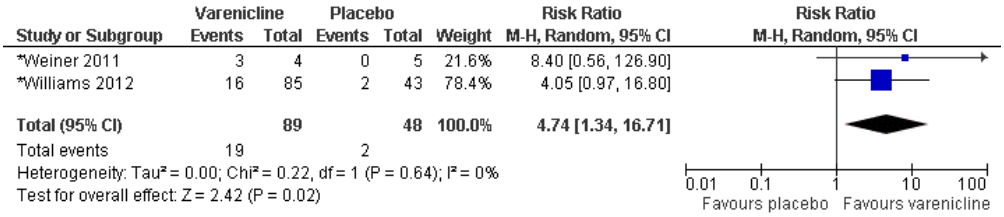
Intervention rationale: Varenicline is a nicotinic acetylcholine $\alpha_4\beta_2$ receptor partial agonist and an α_7 full agonist. Varenicline is effective in treating tobacco dependence and its efficacy is prob-

ably superior to bupropion (Cahill 2012). The main adverse effect of varenicline is nausea, but this tends to subside over time. There has been concern that varenicline may be associated with psychiatric symptoms including hostility, aggression and suicidal behaviour and psychosis among individuals with and without psychiatric disorders. In February 2008, the US Food and Drug Administration issued a public health advisory, reporting an association between varenicline and an increase in neuropsychiatric adverse events (FDA 2008). This warning continues to be in place after a recent review (FDA 2011).

Abstinence outcomes

Two trials with a total of 137 participants reported smoking abstinence rates after 12 weeks of treatment with varenicline (*Weiner 2011; *Williams 2012). Both trials set the target quit date (TQD) at around one week after the start of medication. *Williams 2012 also provided data at six-month follow-up after starting varenicline. According to this trial, at six-month follow-up, participants who took varenicline were around five times as likely to abstain from smoking compared to the placebo group. However, this result did not reach statistical significance and had a wide confidence interval (one trial, N = 128, RR 5.06, 95% CI 0.67 to 38.24, P = 0.12; Analysis 2.1). Both trials contributed data to a meta-analysis for the secondary outcome of abstinence at the end of treatment. Participants who took varenicline were also nearly five times as likely to abstain from smoking at the end of the treatment, compared to the placebo group (two trials, N = 137, RR 4.74, 95% CI 1.34 to 16.71, I^2 = 0%; Analysis 2.2; Figure 4). Although the RR reached statistical significance, the confidence interval was wide. A sensitivity analysis omitting *Weiner 2011 (reported as a 'letter to the editor' rather than a full paper), resulted in the RR being reduced to 4.04, just reaching statistical significance (P = 0.05).

Figure 4. Varenicline versus placebo: Abstinence at the end of treatment (secondary outcome)



Mental state outcomes and other adverse events

Both studies reported that there were no significant differences between the varenicline and placebo groups in positive symptoms during the trial period. *Williams 2012 also did not find any difference between the two groups in negative symptoms throughout the trial, while *Weiner 2011 reported that the two groups did not differ in depressive symptoms.

*Williams 2012 mentioned that there were 13 serious adverse events (SAEs) in 10 participants (nine from the varenicline group and one from the placebo group). In the varenicline group, two patients had three SAEs which were considered to be related to varenicline use. One patient with a history of depression and suicidal ideation, as well as a history of a suicide attempt by overdose, was hospitalised for one day following six days of using varenicline. Another patient with a history of four previous suicide attempts took an overdose and suffered a seizure for which he was hospitalised ('varenicline suicidal patient 1'). No treatment-related adverse events were reported in the placebo group. One death was reported during the post-therapy follow-up period, from accidental drowning 51 days after the last dose of varenicline. The investigators did not consider this to be treatment-related. They did not find any between-group differences for other adverse effects, including neuropsychiatric SAEs or study discontinuations. The most common adverse events in the varenicline group were nausea (23.8%), headache (10.7%) and vomiting (10.7%). In *Weiner 2011, no participant reported any suicidal ideation at baseline or throughout the trial. The varenicline group reported worsening of constipation, insomnia and nausea, which have all been noted previously as side effects of varenicline in the general population.

Smoking reduction

*Williams 2012 reported that for non-abstinent participants, there was a statistically significant reduction of cigarettes per day (CPD) from baseline, in favour of the varenicline group at week 12, who smoked three fewer CPD compared to the placebo group (95% CI 0.4 to 6.1, P = 0.03). The result was no longer significant at week 24. However, non-abstainers in both groups had reduced levels of expired carbon monoxide (CO) level at week 12, but the difference was not statistically significant (P = 0.11). In *Weiner 2011 from week four onwards the varenicline group showed a significantly

greater reduction of expired CO from baseline compared to the placebo group (P = 0.02), although it was unclear whether this result included those who managed to abstain from smoking.

1.4 Non-pharmacological intervention - American Lung Association (ALA) programme in group setting versus specialised smoking cessation group therapy designed for schizophrenia (both groups receiving transdermal nicotine patch (TNP))

*George 2000 investigated the efficacy of specialised smoking cessation group therapy for patients with schizophrenia, 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 four weeks of treatment) between the American Lung Association (ALA) programme group (23.5%), and the specialised group therapy group (32.1%, P = 0.06). However, at six-month follow-up, the 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 performed a secondary analysis based on whether the participant received atypical or typical antipsychotic medications. Smoking abstinence rates at the end of the trial and at six-months 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.

1.5 Non-pharmacological intervention - treatment of addiction to nicotine in schizophrenia (TANS) versus medication management (MM) (both groups receiving transdermal nicotine patch (TNP))

Williams 2010 examined two manualised individual behavioural counselling approaches - treatment of addiction to nicotine in schizophrenia (TANS) and medication management (MM), alongside TNP. There were no statistically significant differences in abstinence rates between the two groups at 12 weeks after the target quit date (TANS: 15.6%; MM: 26.2%, P = 0.22), at six months (TANS: 14%; MM: 16%, P = 0.78) and at 12 months (TANS: 12%; MM: 12%, P = 0.90).* There were overall significant reductions of expired CO levels and CPD from baseline in both groups, but there were no differences in CO reduction and reduction of CPD between the two groups. The author also reported that there was a positive association between the percentage of sessions attended and the smoking abstinence rate at 12 weeks, regardless of the treatment conditions.

1.6 Non-pharmacological intervention - active repetitive transcranial magnetic stimulation (rTMS) versus sham rTMS

Intervention rationale: repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that can induce changes in brain cortical function. High frequency (>1 Hz) rTMS to the dorsolateral prefrontal cortex (DLPFC) has shown potential as a smoking cessation therapy by reducing tobacco craving and consumption in smokers without a psychiatric diagnosis (Eichhammer 2003; Amiaz 2009).

In *Wing 2012, active rTMS (four weeks with five treatments per week) was compared with sham rTMS. Active rTMS did not increase smoking abstinence rates. While it significantly reduced tobacco craving in the first week, active rTMS did not alter craving in the following three weeks.

1.7 Combined interventions - individual smoking cessation intervention (based on cognitive behavioural therapy (CBT) and motivational interview) and transdermal nicotine patch (TNP) versus routine care

*Baker 2006 compared the effect of an individual smoking cessation intervention (based on CBT and motivational interview) and TNP versus routine care in a group of patients with psychotic disorders of mixed diagnoses. All the participants expressed interest in quitting smoking. The authors provided a subgroup analysis of people with a 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 rates at three months, six months, twelve months and four years 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 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 with 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 subsequent follow-up sessions at six months,12 months and four years after the initial assessment.

1.8 Combined interventions - Contingent reinforcement (CR) using money versus contingent reinforcement and transdermal nicotine patch (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 a diagnosis of schizophrenia or schizoaffective disorder (N = 80). About 32.5%

of participants expressed interest in quitting smoking. The abstinence rates at weeks 20 and 36 (the end of the trial) were significant higher in the CR with TNP group, compared with 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 Fagerström Test for Nicotine Dependence (FTND) scores in the CR with TNP group both at week 24 and at week 36, compared with the CR group without TNP, and with the minimal intervention group. The CR with TNP group had a significantly lower expired CO level both at week 20 and at 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 groups with and without TNP. Number of 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 either at week 20 or at week 36 between the CR group and the minimal intervention group, nor between the CR groups with and without TNP.

2. Trials with a primary aim of smoking reduction

2.1 Pharmacological intervention - bupropion

Three trials investigated primarily the effect of bupropion for smoking reduction (+Fatemi 2005; +Akbarpour 2010; +Bloch 2010). +Tidey 2011 investigated the effect of bupropion with contingency management, compared with placebo and non-contingent reinforcement. Two trials (+Akbarpour 2010; +Bloch 2010) provided data contributing to a meta-analysis for smoking reduction measured by number of CPD. At the end of about three months of bupropion treatment, there was no significant difference in the number of CPD between the bupropion group and the placebo group (two trials, N = 93; mean difference (MD) -2.61, 95% CI -7.99 to 2.77, I^2 = 0%; Analysis 1.8). +Bloch 2010 reported scores measuring positive and negative symptoms before and after the intervention, and analysis showed that there were no significant differences between bupropion and placebo groups for positive and negative symptoms at the end of the treatment. Neither trial reported any other adverse effects related to bupropion.
In the cross-over study by +Fatemi 2005, 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, compared with the placebo phase. These participants were encouraged to reduce the amount they smoked, rather than to quit entirely. Their results also showed that during the trial, bupropion did not exacerbate positive and negative symptoms in these patients.
In +Tidey 2011, the investigators did not find that the 300 mg dose of bupropion for 22 days reduced smoking, as measured by expired CO level, urinary cotinine level and CPD. The researchers commented that their participants did not actively seek smoking cessation treatment and may have had lower motivation levels compared with other studies. They also reported that bupropion did not increase psychiatric symptoms. In addition, there were no significant differences in adverse events between the bupropion and placebo groups. There were no reports of seizure or of suicidal behaviour in the bupropion group.

2.2 Pharmacological intervention - transdermal nicotine patch

Two cross-over trials investigated the efficacy of the 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 whether the participants were using the TNP or 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 of ten people 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 those 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 either patch, nor did they or the observers notice any changes in their mental status.

2.3 Pharmacological intervention - naltrexone

Intervention rationale: naltrexone is an opioid-receptor antagonist and has been found to be useful as an adjunct in the treatment of alcohol dependence after successful withdrawal. Smoking and alcohol dependence frequently occur together. Quitting drinking

may increase the likelihood of successful smoking cessation among individuals with both alcohol and nicotine dependence.

+Szombathyne 2010 investigated naltrexone's efficacy for smoking reduction in patients with schizophrenia who were also dependent on alcohol and nicotine. They did not detect any significant reduction of CPD between the naltrexone and placebo groups. Five per cent of the participants managed to quit smoking at the end of the 12 weeks (abstinence was not clearly defined), and there was no statistically significant difference between naltrexone and placebo for smoking rates. The authors noted that patients who quit drinking successfully during the trial were more likely to quit smoking as well.

2.4 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 postintervention, although there was no statistically significant difference among the groups in their motivation to quit smoking. The participants showed mixed levels of interest in quitting smoking.

2.5 Non-pharmacological intervention - smoking reduction intervention group versus waiting list

+Gelkopf 2012 compared a smoking reduction intervention group with people on a waiting list, measuring by reduction of CPD at three months without biological verification, in a group of chronic inpatients with schizophrenia. They found a significant reduction of CPD in the intervention group compared with the waiting list control group. They also found a significant reduction in the PANSS scores (Positive And Negative Syndrome Scale - a measure of positive and negative symptoms in schizophrenia) in the intervention group compared with the control group.

2.6 Combined Interventions - contingency management with money combined with bupropion or placebo versus non-contingent reinforcement combined with bupropion or placebo

+Tidey 2011 found a significant reduction in urinary cotinine, expired CO level and CPD in weeks three and four among people who received contingency management with money for 22 days, compared with those who received non-contingent reinforcement. Bupropion, however, did not increase the efficacy of contingency management.

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 randomised either to 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 participants. In addition, the authors did not report any dropouts due to adverse events.

4. Trials of other interventions reporting smoking outcomes

4.1 Clozapine

Intervention rationale: clozapine is an atypical antipsychotic medication with a significant risk of agranulocytosis and seizure. Hence, it is restricted to 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 randomised controlled trials (RCTs) (McEvoy 1995 and de Leon 2005b), which examined the effect of different doses or blood levels of clozapine on the mental state of patients with treatment-resistant schizophrenia. These two trials measured the smoking behaviour of the participants; it was uncertain whether participants had any interest in quitting smoking.

McEvoy 1995 investigated the number of cigarettes smoked and expired CO levels in people with different blood levels of clozapine. Participants with a therapeutic plasma level of clozapine (> 200 ng/ml) showed a significant decline of between 25 and 35% in the number of cigarettes smoked and expired CO level. Participants with subtherapeutic clozapine plasma levels (50 - 150 ng/ml) did not show any change in these measures of smoking. However, the authors also recommended a cautious interpretation of the results, as those assigned to subtherapeutic 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 analyses to support clozapine for reducing smoking. However, the authors stated that they could not rule out a small decrease in smoking in some participants, which did not yield significant changes in total sample mean values.

4.2 Galantamine

Intervention rationale: galantamine is an acetylcholinesterase inhibitor. It has been used as a cognitive enhancing medication for dementia. Recent literature suggests its effect on cognitive enhancement may extend to other mental illnesses like schizophrenia. It also acts as a positive allosteric modulator of nicotine acetylcholine receptors (nAchR), which some research has suggested 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 weeks of galantamine treatment in participants who received galantamine or placebo. On the contrary, there was a significant and moderate increase in the mean score of FTND in those who took galantamine compared with placebo (effect size of 0.4). These participants had not expressed interest in quitting smoking.

4.3 Atomoxetine

Intervention rationale: atomoxetine is a norepinephrine (noradrenaline) reuptake inhibitor, 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, which may help to improve the neurocognitive deficits in patients with schizophrenia. Nicotine may improve selected cognitive deficits in these patients. One theory for the high rates of smoking in schizophrenia is that patients may remediate their neurocognitive deficits by smoking. Hence, there is a suggestion that atomoxetine may moderate nicotine dependence by improving the cognitive function of people with schizophrenia.

Sacco 2009 investigated the effects of atomoxetine on cognitive function and cigarette smoking among people with schizophrenia. They did not detect any statistically significant changes in smoking behaviour, measured by cigarette consumption or expired CO levels in smokers with schizophrenia taking atomoxetine for two weeks, compared with those on placebo. The authors did not report whether or not 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.

4.4 Topiramate

Intervention rationale: topiramate is an 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 reported a secondary analysis of the level of smoking in their trial investigating the efficacy of topiramate as a treatment for schizoaffective disorder (bipolar type). The authors did not detect any significant change in the expired CO level in a subgroup of 24 smokers treated for eight weeks with topiramate or placebo. There were also no significant differences in the reduction of psychiatric symptoms between the topiramate and placebo groups.

4.5 Varenicline (used for reasons apart from smoking cessation or reduction)

Three trials examined the effect of varenicline for purposes other than smoking cessation or reduction. Two studies focused on its effect on cognitive function in people with schizophrenia (Hong 2011; Shim 2012), and the third investigated its use to reduce alcohol dependence in smokers with schizophrenia as a primary outcome (Meszaros 2012).

Hong 2011 used a reduced dose of varenicline (i.e. 0.5 mg twice daily) instead of the usual dose of 1mg twice daily. This trial included both smokers and non-smokers with schizophrenia, with the smokers expressing no desire to quit. The investigators reported a significant reduction in CPD in those who received varenicline compared with the placebo group (P = 0.04). Expired CO levels were also reduced in the varenicline group compared with the placebo group, but the result did not reach statistical significance (P = 0.21). They also reported that two people who received varenicline and one who received placebo quit smoking by the end of the eight-week trial. Regarding the mental state of participants and adverse effects, the investigators reported a trend toward reduced psychosis in the varenicline group compared with the placebo group, but this analysis included both smokers and non-smokers. Nevertheless, they note that there were no differences in treatment effects between smokers and non-smokers. They did not find any statistically significant differences of negative or depressive symptoms between smokers on varenicline or placebo. Both smoking and non-smoking participants in the varenicline group reported no increase in suicidal ideation during the trial, nor was there a higher incidence of common side effects compared with the placebo group.

Shim 2012 included both smokers and non-smokers with schizophrenia in their study investigating the effect of varenicline on cognitive function in individuals with schizophrenia in Korea. They reported that during the eight-week study, levels of smoking (measured by expired CO levels) in the varenicline group were significantly reduced compared with the placebo group. Regarding mental state and adverse effects, there was no significant change in positive and negative symptoms during varenicline treatment compared with the placebo group. The investigators also reported that no-one displayed significant depressive symptoms or suicidal ideation. Nausea (30.5% versus 10.3%) and headache (10.2% versus 0%) were significantly higher in the varenicline group compared with the placebo group. However, all the results for mental state and adverse effects included both smokers and non-smok-

ers, and we were unable to obtain subgroup analyses restricted to smokers from the investigators. Four people (two from each group) were withdrawn from the trial because of worsening of psychotic symptoms, with the investigators commenting that it was not clear if varenicline had caused the deterioration in mental state.

Published as a conference proceeding, Meszaros 2012 reported a study of varenicline for the treatment of alcohol and nicotine dependence in people with schizophrenia. They reported recruitment difficulties; since the beginning of the study in 2008, only 10 patients had been randomised and started on treatment (five each on varenicline and placebo). Four participants (two from each group) had dropped out of the study prior to completion, and two more patients (one from each group) were lost to follow-up. The study was terminated in 2011. In a personal communication, the authors reported that among the four remaining participants the mean reduction in the number of cigarettes per week was 47 (Standard Deviation 77) in the placebo group and 66 (Standard Deviation 65) in the varenicline group. This difference did not reach statistical significance, and the authors commented that this was probably due to the small sample size. Regarding mental state and adverse events, the investigators found no significant change in positive, negative and general symptoms of schizophrenia during the study. For the people in the varenicline group who did not complete the study, one dropped out because of vomiting, irritability and passive suicidal ideation seven days after starting varenicline ("varenicline suicidal patient 2"). Another dropped out at week four, due to nausea and vomiting. The third was lost to follow-up as he was incarcerated for violating a restraining order. The investigators also found that nausea, vomiting and abdominal pain was more frequent in the varenicline group. They concluded that varenicline treatment in schizophrenia patients with both smoking and alcohol dependence may be problematic, due to safety concerns and limited tolerability because of gastrointestinal adverse effects.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Comparison (data were from abstinence study)	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	4	14.8	21.5	6.8 (2.8 to 10.8)	3	18.8	22.7	ns
TNP vs. placebo	Data not combined because of heterogeneity of studies				No trial found			
Varenicline vs. placebo	1	# 11.0	# 7.1	ns	No follow-up data available			
CR + TNP vs. minimal	1	17.7	27.5	9.8	No follow-up data available			

' ns' = difference not statistically significant

- these figures represent the mean reduction of expired CO level (in ppm) compared to the baseline level.

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 summarize the main results of this review for the most important outcomes. Smokers with schizophrenia who used bupropion to aid smoking cessation were nearly three times as likely as those on placebo to be abstinent at the end of the drug therapy. Although there were fewer trials with follow-up of six months or longer, the relative effect on abstinence seemed to be sustained at six months, and the results appeared consistent among trials. However, the evidence for 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 cigarettes per day (CPD), than those who took placebo. A reduction of expired carbon monoxide (CO) level also occurred in the bupropion group, compared with the placebo group, but was not sustained to six months. The findings for smoking reduction should be interpreted with caution, as these data included the entire sample, combining abstainers and continuing smokers. Hence, the mean reduction included smoking abstinence, as well as reduction in those who did not manage to stop smoking. This explanation may be further supported by the lack of evidence of significant reduction in smoking in those trials aimed primarily at smoking reduction. We found no evidence in support of bupropion as an adjunct to contingency management. We found no evidence to suggest that smokers with schizophrenia had significant deterioration in positive, negative or depressive symptoms of schizophrenia linked with bupropion. Although some adverse effects of treatment which may be important to patients were noted, there were no serious adverse clinical events such as seizure or suicide. However, the total number of people on bupropion was small (170 in trials for abstinence and 94 in trials for reduction), so there may not be adequate power to test for differences in risks of low event rates, such as seizure; the risk of seizure with bupropion in the general population is between 0.1% and 0.4%.

It was unclear whether transdermal nicotine patch (TNP) helped smoking cessation in this group of patients, as it was tested in only a few 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 Fagerström Test for Nicotine dependence (FTND) score (*Gallagher 2007), but the available evidence 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.

We found some evidence that smokers with schizophrenia who used varenicline for smoking cessation were nearly five times more likely to abstain from smoking at the end of treatment, compared with those who took placebo. However, this evidence was based on only two trials, one of which reported preliminary results with a small number of participants. In addition, there was insufficient evidence from one trial as to whether an effect was sustained at six-month follow-up. There was no study investigating the efficacy of varenicline used primarily for smoking reduction. After considering studies for abstinence and studies that examined the effect of varenicline for other non-smoking purposes, we did not find consistent evidence suggesting that varenicline reduced smoking among people with schizophrenia. Regarding the mental state of the participants, there was no evidence that varenicline caused worsening of positive, negative or depressive symptoms. However, two people out of a total of 144 smokers receiving varenicline reported suicidal ideation or behaviour.

We found no evidence to support the use of naltrexone for smoking reduction in smokers with schizophrenia and alcohol dependence. There were inconclusive findings that the antipsychotic clozapine helped in smoking reduction in people with schizophrenia. There was also no evidence to support the use of galantamine, atomoxetine or topiramate as aids to smoking cessation or to smoking reduction for individuals with schizophrenia.

Regarding non-pharmacological interventions, there was some evidence to support the use of financial contingency reinforcement (CR) for smoking cessation and reduction in people with schizophrenia. In one study, CR, with and without TNP, increased the abstinence rate for smoking in schizophrenia sufferers at week 20 and week 36. There was also some evidence from two trials that CR, with and without TNP or bupropion, significantly reduced the level of smoking in those with schizophrenia. Nevertheless, there was no evidence that CR produced sustained results for these outcomes once it was withdrawn. In addition, these findings should be treated with caution, as the evidence was based on only two trials.

We found evidence from one small trial that a smoking reduction intervention group, compared to waiting list controls, may reduce the number of CPD in inpatient smokers with schizophrenia who had been in hospital for at least one year. However, there were some concerns with the methodology of this study, and they did not use biological verification. Otherwise, we found no evidence that a single session of motivational interviewing reduced smoking in people with schizophrenia. There was also no evidence that specialised smoking cessation group therapy specifically designed for patients with schizophrenia was more effective for either smoking cessation or reduction, compared with a standard smoking cessation programme. We did not find any evidence to suggest that intensive individual behavioural counselling sessions designed for people with schizophrenia improved smoking cessation or reduction. In addition, repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex (DLPFC)

did not increase the smoking abstinence rate among smokers with schizophrenia.

There were design limitations in most of the included trials. For example, most studies had small numbers of participants and only a few studies reported outcomes beyond 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 inpatient units, the community, or from outpatient psychiatric treatment sites, and represent a range of patients with schizophrenia. Interest in quitting smoking varied across sites and studies. As a result, there was significant clinical heterogeneity between the included trials. We therefore considered it was appropriate to perform a meta-analysis and report the pooled estimates only for studies testing bupropion and varenicline, because they were relatively more homogenous.

Our review includes 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 these drug treatments for smoking cessation and reduction in schizophrenia, including those who investigated varenicline for other purposes rather than primarily for smoking cessation or reduction. There are also a number of ongoing studies which investigate the use of varenicline (Evins (NCT00621777); Fatemi (NCT01111149); Smith (NCT00802919)) and hopefully these trials will be able to provide more evidence of the effectiveness of varenicline in the near future. 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 people with schizophrenia (Williams (NCT01010477)).

Apart from one trial which investigated the use of naltrexone in smokers with schizophrenia and alcohol dependence, we 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 and selegiline. We also examined the effects of antipsychotics (in particular clozapine) in smoking reduction in those with schizophrenia, as there have been a number of reports about the possible link between antipsychotic use and nicotine dependence in schizophrenia patients (Ereshefsky 1985; McEvoy 1995a). In addition, smokers with schizophrenia may use nicotine to improve their cognitive function (Adler 1998; Sacco 2004). We found studies which examined the effects of medications such as galantamine and atomoxetine for 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 on 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 are 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 increase smoking cessation rates in the general public (Lancaster 2005b; Stead 2008). Motivational interviewing, especially by primary care physicians and trained practitioners, may also increase the rate of smoking cessation in the general public (Lai 2010). There was no evidence that single session motivational interviewing reduced smoking in people with schizophrenia, or that specialised smoking cessation therapies (group or individual) designed for patients with schizophrenia were superior to non-specialised therapy. We found no studies comparing group therapy with individual therapy in participants with schizophrenia, nor any studies of telephone counselling, simple advice from a physician, or self help interventions in smoking cessation or reduction in those with schizophrenia. There was no evidence to support the use of active repetitive transcranial magnetic stimulation (rTMS) for smoking cessation in people with schizophrenia.

Interestingly, we found some evidence from two studies with different designs to support the use of money as an incentive to increase abstinence rates and reduce smoking in people with schizophrenia, at the end of the trial. The durations of these two trials was 22 days and 36 weeks respectively, with no follow-up data after withdrawal of the incentive. A previous review has suggested that incentives do not enhance long-term cessation rates, and that early success may not be maintained when the rewards are no longer offered (Cahill 2011).

A recent review suggests that combined pharmacotherapy and behavioural support increase smoking cessation success in the general public when compared with a minimal intervention, or with usual care (Stead 2012). We found three trials of combined pharmacological and non-pharmacological interventions (two with contingent reinforcement and one with an individual counselling intervention). Although both the CR trials showed a higher rate of smoking reduction, with or without smoking cessation, there was no direct conclusive evidence that adding drug treatment (TNP or bupropion) increased the effectiveness of the non-pharmacological intervention. The other study, examining the effect of an intervention based on cognitive behavioural therapy and motivational interviewing among smokers with schizophrenia, did not demonstrate increased abstinence rates.

In this review, we report smoking reduction as one of the secondary outcomes. Smoking cessation is the recommended method

to reduce the harms to smokers (US Department of Health and Human Services 2000). Smoking reduction has been proposed as a non-cessation method to reduce harm from tobacco. There is evidence to suggest that smokers who are not interested in quitting can make significant reductions in their smoking when they receive appropriate treatment, and that 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 that they want or are able to achieve. Nevertheless, recent literature has shown that smoking reduction 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 a step towards cessation. We hypothesize that this step towards accomplishing the 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, which 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), or have been reported to have possible serious neuropsychiatric side effects (e.g. varenicline). It is important to monitor whether these medications have a major impact on mental stability in these patients. Additionally, 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 organization 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 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

For this review, the largest body of evidence was for bupropion, including seven studies and a total of 340 participants in the meta-analysis. The number of studies was relatively small, and there was no significant heterogeneity between them. In addition, we found some evidence for varenicline from two studies with a total of 137 participants, and no significant heterogeneity between them. There was also some evidence for contingency reinforcement with money from two trials, but their clinical heterogeneity meant that we did not combine the data.

The evidence for the other interventions, including NRT, individual counselling and group therapy, was limited, even though there is good evidence of their benefit for other populations of smokers. Hence, gaps in the evidence for treatments other than bupropion in patients with schizophrenia is probably due to a low number of trials rather than to unpublished studies with negative findings.

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 (McEvoy 1995 and de Leon 2005b for clozapine; Kelly 2008 for galantamine; Weinberger 2008 for topiramate; Sacco 2009 for atomoxetine; Hong 2011, Meszaros 2012 and Shim 2012 for varenicline). Apart from Meszaros 2012, all these trials included smokers who were not trying to quit. These studies all reported smoking status as a secondary outcome, with subgroup analyses used in some of them to investigate the effects of the interventions for smokers. In three of the trials, some of the smokers were excluded from the subgroup analyses without justification. The results of these studies should therefore be viewed with caution.

Potential biases in the review process

We have used comprehensive search strategies and wide inclusion criteria, thereby improving the chances of identifying all relevant trials. We obtained reports in any language and unpublished data such as conference abstracts, to reduce potential selection and publication biases. Outcomes had to be at least six months after the intervention and at the end of the intervention, so that the immediate effect and long-term sustained abstinence could be compared. We conducted sensitivity analyses in the meta-analysis, and evaluated the robustness of the findings.

There are two issues to consider in this review. Firstly, the number of studies which were included in the meta-analysis for bupropion and varenicline is relatively small, so we did not produce a funnel plot to explore potential publication bias. We can not exclude the possibility that we may have missed studies with negative results and small sample size. Publication bias can significantly distort the results of a 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 explicitly excluded patients with a diagnosis of both schizophrenia and a co-morbid substance misuse other than nicotine.

There has been more emphasis recently on the importance of evaluating the potential harms associated with interventions in both clinical trials and systematic reviews (Cuervo 2003; Tunis 2003). This review also examines as one of its outcomes, the effect of different interventions on the mental state of smokers with schizophrenia. This allows us to address the question of whether different interventions can safely be used in this population.

Agreements and disagreements with other studies or reviews

In the Cochrane review of antidepressants for smoking cessation, Hughes 2007 estimated that bupropion increased the odds of quitting smoking after at least six months by approximately 70%, when used as the sole pharmacotherapy (odds ratio (OR) 1.69, 95% confidence interval (CI) 1.53 to 1.85, 36 trials, 11440 participants). It did not detect a significant effect from combining bupropion and nicotine replacement therapy (NRT), compared with NRT alone after six months (OR 1.23, 95% CI 0.67 to 2.26, 6 trials, 1106 participants). Although our pooled estimates suggest that bupropion may have a significant beneficial effect on smoking abstinence in people schizophrenia, neither the subgroup analysis for bupropion alone, or for bupropion and TNP, reached statistical significance.

Cahill 2012 reported that varenicline at standard dose at least doubles the chances of successful smoking cessation after six months or more, compared with placebo (risk ratio (RR) 2.27, 95% CI 2.02 to 2.55, 14 trials, 6166 participants). Lower dose regimens also increased the rate of smoking cessation, while reducing the incidence of adverse events (RR 2.09, 95% CI 1.56 to 2.78, 4 trials, 1272 participants). More participants quit successfully with varenicline than with bupropion (RR 1.52, 95% CI 1.22 to 1.88, 3 trials, 1622 participants). In this review, current evidence from the limited number of studies suggests that varenicline may increase the smoking cessation rate among individuals with schizophrenia in the short term, but the effect did not last in the longer term. Regarding safety, Cahill 2012 reported that possible serious adverse events including significant psychiatric side effects cannot be ruled out on the current evidence. There were a number of studies investigating a possible association between varenicline and suicidality using different data sources and methodology, focusing on studies in the general public (Gunnell 2009; Kasliwal 2009; Harrison-Woolrych 2011; Moore 2011). These results need to be viewed with caution in view of the difficulties in disentangling treatment-related events with other potential confounding factors (e.g. psychiatric effects of nicotine withdrawal, increased suicide rates among smokers). In addition, it is essential to remember that these trials routinely excluded participants with psychiatric disorders and/or other alcohol or substance misuse. A recent review of published case reports, case series and prospective studies of the use of varenicline in patients with schizophrenia and schizoaffective disorder suggested that 5% of participants (13 out of 260) experienced the onset or worsening of psychiatric symptoms (Cerimele 2012). Three of the 13 participants experienced a very brief negative effect after one dose of varenicline. They did not find any report of patients with suicidal ideation or suicidal behaviour. However, the authors only included studies published until July 2011, and as a result they missed the two trials which reported two participants with suicidal ideation or behaviours (*Williams 2012; Meszaros 2012) as summarised in this review.

Regarding using contingent reinforcement for smoking cessation, Cahill 2011 concluded that incentives did not enhance long-term smoking cessation rates among general populations. In addition, early success usually disappeared when rewards were no longer offered, although in one trial of 878 smokers, it achieved high and long-lasting success rates by giving large cash rewards (up to USD750). Our review found some evidence that contingent reinforcement using money increased the smoking cessation rate, as well as reducing the amount of smoking among people with schizophrenia when the rewards were offered. We did not find any follow-up data to examine the effect of longer-term efficacy.

We did not find evidence to support the use of nicotine replacement therapy for smoking cessation or reduction in people with schizophrenia, which does not square with the strong evidence supporting the efficacy of all forms of NRT (Stead 2012b). Neither did higher doses of NRTshow any additional benefit for individuals with schizophrenia who smoke more heavily, compared to the general population. However, there are only a handful of small studies of the use of NRT for smoking cessation in people with schizophrenia, suggesting a lack of research in this area.

The results of this review largely concur with national guidelines, which make some recommendations about the treatment of nicotine dependence in people with 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 makes a similar suggestion for individuals with schizophrenia in the non-systematically reviewed Australian guidelines on pharmacotherapy for tobacco addiction.

The Schizophrenia Patient Outcomes Research Team (PORT) has also published treatment guidance (Kreyenbuhl 2009). They recommend that those with schizophrenia who want to quit or to reduce cigarette smoking should be offered 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

AUTHORS' CONCLUSIONS

Implications for practice

Our review supports the effectiveness of bupropion for smoking cessation in patients with schizophrenia. The evidence is relatively weak with wide confidence intervals, especially for longer-term benefit, because of the low number of participants. We found

no evidence of any significant deterioration of mental state secondary to use of bupropion in people with schizophrenia. Bupropion use in individuals with schizophrenia did not increase the risk of seizure. The evidence for bupropion as an aid to smoking reduction in people with schizophrenia is inconclusive.

We also found some evidence in support of varenicline for smoking cessation among individuals with schizophrenia. Compared with the bupropion trials, the number of participants is lower and the evidence weaker with wider confidence intervals. There is no evidence at present to suggest that the varenicline's effectiveness will last in the longer term. In addition, although there is no evidence that varenicline worsens symptoms in schizophrenia, there is some concern about serious adverse events such as suicidal ideation or behaviour among schizophrenia patients on varenicline. Based on the current data, we do not think this possibility can be fully ruled out.

There is some evidence that rewards using money may increase smoking cessation and reduction rates among people with schizophrenia. However, we do not find any evidence for a sustained effect, after the rewards are withdrawn. For other drug treatments (including NRT) and psychosocial interventions, we did not find sufficient convincing evidence in to support their use in clinical practice.

Implications for research

Evidence for the effectiveness of interventions for smoking cessation and reduction in people with schizophrenia is limited to a few small studies without adequate power to detect reasonable treatment effects. Further trials with adequate sample size would be informative. Moreover, reporting of future studies should include more detailed and specific information. Some current reports do not specify whether participants were motivated to quit, which can significantly affect the abstinence rate. It will also be useful to be explicit about reduction rates in reports of trials primarily aimed at abstinence, specifying whether or not they include the entire sample, or only participants who did not quit. It is important that future trials report outcomes beyond the end of treatment, so that longer-term effects of the intervention can be better evaluated.

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

1. The safety of varenicline for smoking cessation in people schizophrenia;

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

3. The interaction of antipsychotic medication treatment with smoking behaviour and cessation in people schizophrenia;

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

5. Any sustained effect on smoking cessation and reduction in contingency reinforcement and other treatments;

6. The level of treatment compliance for smoking cessation among people with schizophrenia;

7. The effect of interventions at systematic and policies level (e.g. smoking ban in psychiatric wards) on smoking behaviours in patients with schizophrenia;

8. How to integrate treatment for smoking cessation into routine psychiatric care;

9. 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. Pts recruited in the community.
Participants	298 smokers (at least 15 CPD) with ICD-10 diagnosis of psychotic disorder. Pts who were acutely psychotic, had an 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 wk 3. 156 male, mean age of all 298 pts: 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 wkly sessions and 2 boosters at wks 8 and 10, 1 hour each): based on motivational interviewing and CBT + TNP (21 mg from wk 3 to 8; 14 mg from week 9 to 10; 7 mg from wk 11 to 12) 2. Routine care Both groups received booklets on smoking cessation.
Outcomes	Abstinence measured at 3, 6, 12 ms and 4 yrs by continuous abstinence from TQD to point of assessment, and 7-day PPA. Both were self reported and confirmed with expired CO level < 10 ppm. Reduction of smoking measured at 3, 6, 12 ms and 4 yrs by at least 50% reduced CPD. Effects on mental state were measured by BPRS, BDI and STAI.
Source of funding	National Health and Medical Research Council; Rotary; Community Health and Tuberculosis Australia. TNP provided free of charge by GlaxoSmithKline and self help booklets provided at a discounted price by SANE Australia
Primary aim of the study	Smoking cessation
Notes	Results here only included pts with diagnosis of schizophrenia or schizoaffective disorder; data supplied by authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pts drew a sealed envelope from a set in which there was initially an equal distribution of the treatment or control allocations at each site
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.

*Baker 2006 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessors were blinded. However, the experimental design did not allow participants to be blinded and self report was used in both primary and secondary outcome measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were classified either as non-abstinent or as a failure to achieve smoking reduction
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	The control group were not comparable to the intervention group 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 10 ppm, the pt was still classified as abstinent

*Chen 2012

Methods	RCT, Taiwan. Pts were long stay inpatients and study was conducted in hospital setting
Participants	184 "regular daily smokers" with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts were long-stay patients in two psychiatric hospitals (average term of current hospitalisation 8.8 yrs). Exclusion criteria included acute exacerbation of psychosis that was required transfer to acute ward, as well as severe respiratory and heart disease Interests in quitting smoking varied among pts. No TQD set. 171 male; mean age 45.2; average CPD 13. 141 participants with a diagnosis of schizophrenia; 68% on typical antipsychotic medications
Interventions	1. Low dose TNP (20.8 mg) for 8 wks 2. High dose TNP (31.2 mg for 4 wks, then 20.8 mg for next 4 wks) Both groups received 6 sessions of smoking cessation group psychoeducation (20 minutes each; 2 sessions per wk) after starting TNP
Outcomes	Abstinence measured as self report 7-day PPA at wk 8 (verified by expired CO level < 10ppm) Reduction of smoking measured by reduction of CPD, expired CO level and FTND scores at baseline, wk 5 (CPD only) and wk 8 Effects on mental state measured by PANSS. Parkinsonism symptoms measured by SAS
Source of funding	National Health Bureau, Department of Health, Taiwan
Primary aim of the study	Smoking cessation (although investigators state that smoking reduction is their primary outcome, because of very low % of pts achieved smoking cessation in their pilot study)

*Chen 2012 (*Continued*)

Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported double-blind, but unclear who were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Included every pt who had been randomised in the analyses.
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Nothing stated

*Evins 2001

Methods	RCT, USA. Pts recruited from the community.
Participants	19 smokers (at least half a pack of CPD) with DSM-IV diagnosis of schizophrenia. All pts were on stable dose of antipsychotic medications for at least 4 wks. Patients excluded if co-morbid substance abuse, bulimia, a history of seizure disorder or current major depressive episode. All pts were interested in quitting; TQD set between wks 3 and 4. 11 male; mean age 44.1; 16 white; average CPD 34. 8 pts were on clozapine and 7 on typical antipsychotic. Average length of illness 12 yrs
Interventions	1. Bupropion 150 mg/day for 12 wks 2. Placebo for 12 wks Both groups received 9 wkly 1-hour sessions of group CBT.
Outcomes	PPA measured at wks 12 and 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 yrs. Reduction of smoking measured by serum cotinine, and ≥ 50% reduction in CPD verified with a 30% reduction of expired CO level. Measurements at baseline, wks 12 and 24. Effects on mental state measured by BPRS, SANS and HAM-D. Parkinsonism symptoms measured by SAS and AIMS
Source of funding	NIDA & NARSAD. GlaxoSmithKline provided medications including placebo

*Evins 2001 (*Continued*)

Primary aim of the study	Smoking cessation	
Notes	Two-yr follow-up data were also available.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Allocation sequence was generated by a computer programme.
Allocation concealment (selection bias)	Low risk	Randomisation was performed at the research pharmacy which was separated from the main research personnel
Blinding (performance bias and detection bias) All outcomes	Low risk	Pts, outcome assessors and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	1/19 dropped out prior to start of medication and was not included in the analysis
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Nothing stated

*Evins 2005

Methods	RCT, USA. Pts recruited from the community.
Participants	57 smokers (at least 10 CPD) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type. All pts were on antipsychotic medication for more than 30 days and had stable psychiatric symptoms. Pts excluded with substance use disorder (other than nicotine or caffeine) within 6 ms, or with a history of seizure disorder, bulimia, mania or current major depressive episode. All pts were interested in quitting; TQD set at wk 3. 39 male; mean age 45.7; average CPD 30. 12 pts were on clozapine, 5 on typical antipsychotic.
Interventions	1. Bupropion 300 mg/day for 12 wks (150 mg/day for first wk) 2. Placebo for 12 wks Both groups received 12 wkly 1-hour sessions of group CBT.
Outcomes	7-day PPA and 4-wk CA at wks 12 and 24 (self report verified by expired CO level < 9 ppm). Reduction measured by expired CO level and number of cigarettes smoked. Measurements at baseline, wks 12, 14, 18 and 24.

*Evins 2005 (*Continued*)

	Effects on mental state measured by PANSS, SANS, HAM-D and HAM-A. Parkinsonism symptoms measured by SAS and AIMS
Source of funding	NIDA & NARSAD. GlaxoSmithKline provided medications.
Primary aim of the study	Smoking cessation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated by a computer program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed at the research pharmacy which was separated from the main research personnel
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Nothing stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nothing stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	More clozapine-treated pts were randomised to the placebo group (1/25 versus 11/28)

*Evins 2007

Methods	RCT, USA. Pts recruited from the community.
Participants	51 smokers (at least 10 CPD for past yr) with DSM-IV diagnosis of schizophrenia. All pts were on antipsychotic medication for > 30 days and had stable psychiatric symptoms. Patients excluded with substance use disorder (other than nicotine or caffeine) within 6 ms, or with a history of seizure disorder, bulimia, mania or current major depressive episode. All pts were interested in quitting; TQD set at wk 4. Gender distribution uncertain; mean age 44.2; average CPD 26. 16 pts were on clozapine.

*Evins 2007 (*Continued*)

Interventions	1. Bupropion SR 300 mg/day for 12 wks. (150 mg/day for first 7 days) 2. Placebo for 12 wks Both groups received: (1) 12 wkly 1-hour sessions of group CBT; (2) TNP (from wk 4) 21 mg/day for 4 wks, then 14 mg/day for 2 wks, 7 mg/day for 2 wks + up to 18 mg per day nicotine gum as required
Outcomes	CA at wks 8, 12, 24 and 52 (defined by meeting 7-day PPA by self report every assessment after TQD at the time point , verified by expired CO level ≤ 8 ppm). Reduction measured by number of cigarettes smoked. Measurement at baseline, wk 12 and 24. Effects on mental state measured by PANSS, SANS, HAM-D and STAI. Parkinsonism symptoms measured by SAS and AIMS
Source of funding	Massachusetts Department of Mental Health Federal Block Grant. GlaxoSmithKline provided medications including placebo
Primary aim of the study	Smoking cessation
Notes	6-m abstinence used in meta-analysis for comparability with other trials. 2 pts in the intervention group relapsed by 1 yr

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated by a computer program.
Allocation concealment (selection bias)	Low risk	Randomisation was performed at the research pharmacy which was separated from the main research personnel
Blinding (performance bias and detection bias) All outcomes	Low risk	Pts, investigators and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5/25 (bupropion) and 8/26 (control) lost in follow-up. Dropouts were considered smokers
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Nothing stated

*Gallagher 2007

Methods	RCT, USA. Pts recruited from the community and study conducted in a clinic
Participants	181 participants (60 pts in each arm, 1 died shortly after enrolment because of lung cancer) with DSM-IV Axis 1 diagnosis of psychotic spectrum or affective disorders. At least 10 CPD and smoked regularly for > 3 yrs. CO level ≥ 10 ppm after at least 15 minutes smoke-free at baseline visit. Pts with co-morbid substance misuse disorder were not excluded. No TQD set. 80 had a diagnosis of schizophrenia or schizoaffective disorder. 50/80 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. CR with money for 36 wks (up to USD480) if pts abstained from smoking. Pts did not receive CR at the visit if they relapsed but they would be able to resume receiving CR if they abstained again. 2. CR with money for 36 wks (as above) + TNP (dose varies between pts) for first 16 wks 3. Controls (no active intervention - just attended assessment) 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 wks 20 and 36 (defined as expired CO level ≤ 10 ppm or salivary cotinine level ≤ 15 ng/ml). Reduction measured by expired CO level, FTND score, salivary cotinine level and number of CPD. Measurements were taken at baseline and various points including wks 20 and 36. Effects on mental state measured by BSI.
Source of funding	Arizona Disease Control Research Commission
Primary aim of the study	Smoking cessation
Notes	Results in this review only include pts with diagnosis of schizophrenia or schizoaffective disorder; data supplied by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generated by a computer random number generator.
Allocation concealment (selection bias)	High risk	A list of random numbers was used to allocate the participants by the research staff
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Nothing stated

*Gallagher 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Nothing stated
Selective reporting (reporting bias)	High risk	Only a few outcome measures were reported.
Other bias	High risk	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 pts were interested in quitting; TQD set at wk 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 pts were on atypical antipsychotics
Interventions	1. American Lung Association (ALA) programme wkly for 10 wks (60 minutes each session): first 7 wks behavioural group therapy + final 3 wks supportive group counselling 2. Specialised group therapy designed for pts with schizophrenia, wkly for 10 wks (60 minutes each session): first 3 wks motivational enhancement therapy + last 7 wks psychoeducation, social skills training and relapse prevention strategy. Both groups also received TNP (21 mg/day for first 6 wks then 14 mg/day for another 2 wks and 7 mg/day for final 2 wks)
Outcomes	Abstinence at wk 10 (end of therapy) and at 6 ms follow-up (defined as continuous abstinence for last 4 wks - by self report of cigarette use and verified by expired CO level <10 ppm). Reduction measured by expired CO level; measurements at baseline and wkly for 12 wks. Effects on mental state measured by PANSS and BDI. Parkinsonism symptoms measured by Webster Extrapyramidal symptoms scale and AIMS
Source of funding	NIMDA, NARSAD & VISN 1 Mental Illness Research Education and Clinical Centre grant from Department of Veteran Affairs, USA
Primary aim of the study	Smoking cessation
Notes	
Risk of bias	

*George 2000 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned block randomisation but unclear how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Baseline difference between two groups: specialised group therapy had significantly more pts with schizoaffective disorder and pts in that group also had a significantly lower negative syndrome score; the ALA group had significantly more pts prescribed atypical antipsychotics

*George 2002

Methods	RCT, USA. Pts recruited from the community.
Participants	32 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts were clinically stable on psychotic or affective symptoms. They also fulfilled the following criteria: (1) FTND score ≥ 5; (2) expired CO level ≥ 10ppm; (3) plasma cotinine level ≥ 150 ng/ml. Pts were excluded if they had (1) history of epilepsy or seizure; (2) history of alcohol or drug abuse 6 ms before the study; (3) a change of dose of antipsychotic for symptom control or side effect in the past 6 ms. All pts were interested in quitting; TQD set at wk 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 wks (150 mg/day for first 3 days) 2. Placebo for 10 wks Both groups received 10 wkly 1-hour sessions of group therapy for motivational enhancement, psychoeducation and relapse prevention
Outcomes	Abstinence at wk 10 and 6 m follow-up (defined as 7-day PPA verified by expired CO level < 10 ppm) Reduction of smoking measured by expired CO level and self report number of CPD. Effects on mental state measured by PANSS and BDI. Parkinsonism symptoms measured by Webster Extrapyramidal symptoms scale and AIMS

*George 2002 (*Continued*)

Source of funding	NIMDA, NARSAD & VISN 1 Mental Illness Research Education and Clinical Centre grant from Department of Veteran Affairs, USA	
Primary aim of the study	Smoking cessation	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Not stated

*George 2008

Methods	RCT, USA. Pts 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 pts were clinically stable and on a stable dose of antipsychotic for at least 1 m before randomisation. Pts with alcohol or substance misuse or dependence 3 m before study were excluded. Pts also did not have any history of seizure disorder. All pts were interested in quitting; TQD set at day 15. 35 males; mean age 40.3; 28 white, 26 black, 4 Hispanics; average CPD 23. 32 had a diagnosis of schizophrenia. 9 pts were on clozapine and 13 pts were on typical antipsychotic
Interventions	1. Bupropion 300 mg/day for 10 wks (150 mg/day for first 3 days) 2. Placebo for 10 wks Both groups received 10 wkly 50-minute sessions of group behavioural therapy and TNP (21 mg per 24 hours) from day 15 to day 70

*George 2008 (*Continued*)

Outcomes	Abstinence was measured by self report as 7-day PPA at day 70, CA for last 4 wks of trial (day 43 to day 70) and 6 ms post TQD. Abstinence was verified by expired CO level < 10ppm. Reduction was not reported. Effects on mental state were measured by PANSS, BDI and HAM-D
Source of funding	NIDA & NARSAD
Primary aim of the study	Smoking cessation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Not stated

*Li 2009

Methods	RCT, China. Pts recruited from a psychiatric inpatient unit.
Participants	80 smokers with DSM-IV diagnosis of schizophrenia and nicotine dependence. All pts smoked at least 10 CPD for minimum of 1 yr. Their BPRS scores were ≤ 35 and CGI ≤ 3. Pts excluded with history of epilepsy, unstable physical problem, alcohol or other substance dependence and prominent psychotic symptoms Pts' interest in quitting smoking and TQD information were not mentioned in the report All pts were men. Mean age 38.0. Average number of CPD 30 and average yrs of smoking 17
Interventions	1. Bupropion 75 mg twice a day for 1 wk then 150 mg twice a day for remaining 3 wks 2. Placebo for 4 wks No other intervention for both groups.

*Li 2009 (*Continued*)

Outcomes	Abstinence defined as self reported CA for past wks at wk 1, 2, 4 and 8. There was no biological verification. Reduction measured by reduction in CPD and reduction of scores on scale measure of nicotine dependence. Effects on mental state measured by BPRS.
Source of funding	Not reported
Primary aim of the study	Smoking cessation
Notes	Article in Chinese.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	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 they used a random number table from a statistics textbook and five investigators were given copies of this random number table. When a participant 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 (selection bias)	High risk	From our correspondence with the investigators as above, there was no concealment of allocation sequence
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	No biochemical verification of smoking status.

*Weiner 2011

Methods	RCT, USA. Pts recruited from the community.
Participants	9 smokers (at least 10 CPD for a yr and FTND score ≥ 4) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts were clinically stable and on a stable dose of antipsychotic for at least 1 m before randomisation. Pts excluded with substance misuse (apart from tobacco) in the last 3 ms or dependence in the last 6 ms before study. Pts also excluded if they (1) had any lifetime history of suicide attempt; (2) had psychiatric hospitalisation within the past 6 ms; (3) had suicidal ideation or were currently depressed; (4) were taking bupropion. Pts' interest in quitting was not mentioned in the report; TQD set at the end of the third counselling session (after wk 1 visit) Demographics of participants were not reported. All pts were on second generation antipsychotic medications
Interventions	1. Varenicline 1mg twice daily for 12 wks 2. Placebo for 12 wks Both groups received individual smoking cessation counselling based on the American Lung Association Freedom from Smoking Program. All pts had 2 sessions of counselling before starting study medication
Outcomes	Abstinence was defined as expired CO < 10ppm at each of the last 4 visits at wk 12 Reduction measured by reduction of the expired CO level. Effects of mental state measured by BPRS (positive symptoms and anxiety/depressive symptoms) and CDSS
Source of funding	NIDA
Primary aim of the study	Smoking cessation
Notes	The report is a letter to the editors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Insufficient information

Other bias	Unclear risk	Insufficient information

*Weiner 2012

Methods	RCT, USA. Pts recruited from the community.
Participants	46 smokers (at least 10 CPD) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts had FTND score ≥ 4 and no change in their usual medication regimen. Pts were excluded with current depressive episode, substance misuse other than nicotine in the past 3 ms, substance dependence other than nicotine in the past 6 ms, or neurological diagnosis or unstable medical condition. All pts were interested in decreasing smoking. TQD set at 2 wks after start of bupropion. 37 males; mean age 48.7. 69.6% white. Baseline mean expired CO level 26.5ppm 28 pts were on second generation antipsychotic medications, another 13 on clozapine; others were on first generation antipsychotic
Interventions	1. Bupropion 300 mg/day for 12 wks (wks 2 to14) 2. Placebo for 12 wks Both groups received 9 wkly sessions of group therapy according to American Cancer Society Fresh Start Program (modified for people with schizophrenia)
Outcomes	Abstinence defined as expired CO level < 10ppm for at least 4 study visits during treatment phase (sustained abstinence) Reduction measured by expired CO level, FTND score and urine cotinine level. Effects on mental state measured by BRPS and SANS. Motor side effects were monitored by SAS. Pts also underwent neuropsychological measures
Source of funding	VA Capitol Network (VISN 5) Mental Illness Research, Education and Clinical Centre
Primary aim of the study	Smoking cessation
Notes	

Risk of bias

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

*Weiner 2012 (*Continued*)

Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	Not stated

*Williams 2007

Methods	RCT, USA. Pts recruited from the community.
Participants	51 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts were stable on antipsychotic medications. pts who took bupropion or clonidine were excluded. All pts interested in quitting. No TQD set. Baseline characteristics not reported.
Interventions	1. TNP 42 mg daily for 8 wks 2. TNP 21 mg daily for 8 wks No other additional intervention for all groups.
Outcomes	Abstinence measured at wk 8 by self report of 7-day PPA and verified by expired CO < 8ppm. Reduction was not reported. Effects on mental state were not reported.
Source of funding	NIDA, New Jersey Department of Health and Senior Services
Primary aim of the study	Smoking cessation
Notes	Conference proceeding only.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	According to protocol, only outcome measure was CA from smoking, reported in the

*Williams 2007 (*Continued*)

		conference proceeding
Other bias	Unclear risk	Insufficient information.

*Williams 2010

Methods	RCT. USA. Pts recruited in the community.
Participants	100 smokers (at least 10 CPD) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts took atypical antipsychotic medications for at least 1 m before the trial. Pts excluded whose MMSE < 22, or concurrent use of clonidine, bupropion, NRT, nortriptyline or other tobacco products (e.g. cigar, smokeless tobacco). All pts were willing to quit smoking. TQD set at wk 5 from the start of trial 55 males; mean age 45.2. 65.5% white. There was a statistically significant difference in baseline CO level between 2 groups
Interventions	1. TANS: 24 individual sessions of 45 minutes psychological intervention over 26 wks (motivational interviewing, social skills training, use of NRT, relapse prevention technique) 2. MM: 9 individual sessions of 20 minutes psychological intervention over 26 wks (medication compliance, education about NRT) Both groups also received TNP for 16 wks after quit date (21 mg for 12 wks then 14 mg for remaining 4 wks)
Outcomes	Abstinencemeasured as PPA by self report and verified by expired CO < 10ppm (TQD, 12, 26 wks and 1 yr after TQD). Reduction measured by reduction in expired CO level and CPD. Effects on mental state measured by PANSS and BDI. Therapeutic relationship was also monitored by Working Alliance Inventory (WAI)
Source of funding	NIDA
Primary aim of the study	Smoking cessation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adaptive urn randomisation procedure used.
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated

*Williams 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Baseline difference between two groups in CO level. The interventions were not comparable as they differed by therapy time

*Williams 2012

Methods	RCT, USA & Canada. Pts recruited from the community.
Participants	128 smokers (aged 18 to 75) with DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder. All pts smoked at least 15 CPD and scored at least 7 on the baseline motivation to quit score of the contemplation ladder. Pts did not have any acute exacerbation of psychiatric symptoms, nor psychiatric hospitalisation for the last 6 ms. Their PANSS score was below 70. Female pts consented for birth control if at child bearing age. Pts with the following conditions were excluded: (1) serious suicidal ideation or behaviour; (2) history of drug or alcohol abuse or dependence; (3) clinically significant cardiovascular or cerebrovascular disease in the last 6 ms; (4) any other unstable medical conditions; (5) previous use of varenicline; (6) uncontrolled hypertension; (7) body mass index <15 or >38; (8) use of other smoking cessation aids; (9) use of another investigational drug within 30 days of baseline visit; (10) use of marijuana or other non-cigarette tobacco products All pts were interested in quitting smoking. TQD set as 8 days after baseline visit 98 males; mean age 41.1; 75 white; 38 African American; 6 Asians and 8 other racial group. Average CPD 23. 91 had a diagnosis of schizophrenia. 109 pts were on atypical antipsychotic
Interventions	1. Varenicline (0.5mg daily for 3 days then twice daily for 4 days then 1mg twice daily) for 12 wks 2. Placebo for 12 wks Both groups received wkly counselling (less than 30 minutes)
Outcomes	Abstinence measured at wk 4, wk 12 and wk 24 (defined as 7-day point prevalence of abstinence, verified by CO ≤ 10 ppm) Reduction of smoking measured by incidence of achieving 50% or greater reduction from baseline in mean CPD over the past 7 days at wk 12 and 24, as well as change of mean CPD over the previous 7 days at wks 12 and 24 Effects on mental state measured by PANSS, SAS, Columbia Suicide Severity Rating Scale (C-SSRS) and Cinical Global Impression (CGI)
Source of funding	Sponsored by Pfizer (manufacturer of varenicline)
Primary aim of the study	Smoking cessation
Notes	Varenicline: Placebo in 2:1 ratio.

***Williams 2012** (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Unclear risk	Sponsored by drug company

***Wing 2012**

Methods	RCT, Canada. Pts recruited from community
Participants	15 smokers (at least 10 CPD, baseline CO level ≥ 10ppm and a FTND score of at least 4) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Exclusion criteria included: (1) substance abuse or dependence in the past 3 ms; (2) current use of tobacco pharmacotherapies; (3) intolerance to TNP; (4) on high dose benzodiazepines; (5) seizure disorder; (6) metallic implant; (7) psychiatric or medical instability (e.g. PANSS score >70 or change in antipsychotic medications in the previous m); (8) pregnancy All participants are willing to quit smoking in the next 30 days. TQD set at wk 3 Demographics of pts were not reported.
Interventions	1. Active Repetitive Trancranial Magnetic Stimulation (rTMS) - bilateral to dorsolateral prefrontal cortex (five times per wk for 4 wks) 2. Sham rTMS All pts also receive TNP (21mg/24 hour) and wkly group behavioural therapy (psychoeducation, social skills training and relapse-prevention skills training) for smoking cession from wk 3 to wk 9
Outcomes	Abstinence measured at wk 10 (7-day point prevalence), as assessed by self reported smoking abstinence and expired CO level <10ppm Reduction measured by expired CO level. Effects on mental state measured by PANSS.
Source of funding	Canadian Institue for Health Research, Canandian Tobacco Control Research Initiative, Centre for Addiction and Mental Health

*Wing 2012 (*Continued*)

Primary aim of the study	Smoking cessation	
Notes	Letters to editors and conference proceedings.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

+Akbarpour 2010

Methods	RCT, Iran. Pts recruited from a psychiatric in-patient unit.
Participants	32 smokers with DSM-IV TR diagnosis of schizophrenia and all smoked cigarettes within 12 ms prior to initial interview Pts were excluded if (1) contraindicated to bupropion including seizure disorder, current or prior diagnosis of bulimia or anorexia nervosa; (2) serious comorbid psychiatric illness including major depression; (3) recent history of alcohol use within the last 3 ms; (4) history of allergy to bupropion Pts' interest in quitting smoking and whether a TQD was set were not mentioned in the report All pts were men. Mean age 47.4. Average number of CPD 14. No information regarding psychiatric medications.
Interventions	1. Bupropion 150mg daily for 3 days then 300mg daily for total 8 wks 2. Placebo for 8 wks No other addition intervention for both groups.
Outcomes	Abstinence was not defined or measured. Reduction of smoking was measured by number of cigarettes smoked (mean number

+Akbarpour 2010 (*Continued*)

	of smoked CPD was recorded immediately before and at the end of treatment). No biological verification. Effects on mental state measured by MMSE.
Source of funding	Not reported
Primary aim of the study	Smoking reduction (although it was reported as smoking abstinence)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	No biochemical verification of smoking status

+Bloch 2010

Methods	RCT. Israel. Pts were recruited from the community.
Participants	61 smokers with DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder. All pts were between 18 and 70 yrs old, clinically stable as judged by their psychiatrists, and were on a stable dose of antipsychotic medication for at least 1 m. They scored at least 5 on a motivation for smoking cessation analogue scale (i.e. strong desire to quit smoking or at least reduce significantly the number of CPD). Any pts with co-morbid Axis 1 psychiatric diagnosis were excluded No TQD set. 46 males; mean age 41.6; 37 Jews and 24 Arabs; average CPD 41. 41 pts with diagnosis of schizophrenia; 19 with diagnosis of schizoaffective disorder. Unclear about psychiatric medications

+Bloch 2010 (*Continued*)

Interventions	1. Bupropion 150mg daily for 3 days then 300mg daily for total 14 wks 2. Placebo for 14 wks Both groups received 15 sessions of group CBT.
Outcomes	Abstinence was not defined or measured. Reduction of smoking was measured by reduction of CPD and FTND scores at wk 7 and 14. No biological verification. Effects on mental state measured by PANSS, BPRS.
Source of funding	NARSAD, Phillip Morris USA and Phillip Morris International
Primary aim of the study	Smoking Reduction and identify the role serotonin transporter polymorphism on smoking behaviour in schizophrenia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Pts were randomly allocated based upon order of arrival to either the treatment or placebo group at a rate of 2:1 ratio
Allocation concealment (selection bias)	High risk	Unlikely that allocation concealment was done properly if pts were allocated based upon order of arrival
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	No biochemical verification of smoking status.

+Dalack 1999

Methods	Cross-over study, USA. Pts recruited from the community but stayed in hospital during study
Participants	10 pts with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Moderate to severe nicotine addiction (≥ 20 CPD). No current non-nicotine substance use disorder (confirmed by urine toxicology). Stable on antipsychotic medication for at least 3 ms.

+Dalack 1999 (*Continued*)

	Pts had not expressed interest in quitting smoking. No TQD set. All males; mean age 42.1; 8 Caucasian; average CPD 35; average number of yrs smoking 26. 4 pts on clozapine. 6 pts with diagnosis of schizophrenia. Average length of illness 23 yrs
Interventions	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 wks). Effects on mental state measured by BPRS, SANS, HAM-D. Parkinsonism symptoms measured by SAS and AIMS
Source of funding	Research Advisory Group, Department of Veterans Affairs
Primary aim of the study	Smoking reduction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random number generator was used to generate sequence.
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally at pharmacy.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Only some of the outcomes were reported in the reports.
Other bias	High risk	Cross-over study with short washout period.

+Fatemi 2005

Methods	Cross-over study, USA. Pts recruited from the community.
Participants	10 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Pts 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 wk afterwards. Cross-over to the other intervention for another 21 days. No other addition intervention for both groups.
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
Source of funding	NIH
Primary aim of the study	Smoking reduction
Notes	The report is a letter to the editors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Only the results of some of the outcome measures were reported
Other bias	High risk	Cross-over design but uncertain about whether paired analyses were used or not. First period data were not available

+Gelkopf 2012

Methods	RCT, Israel. Pts recruited from a psychiatric in-patient unit
Participants	53 smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder (at least for 5 yrs). All pts were between 18 and 65 of age and was admitted to hospital for at least a yr. They expressed interest in participating a smoking reduction programme. They smoked at least 7 cigarettes daily for > 6 ms (self report). They also met the criteria of nicotine dependence based on FTND. All pts were treated with antipsychotic medications. Exclusion criteria included significant physical illness, organic brain damage, mental retardation and diagnosis of alcohol or drug abuse or dependence TQD not set. 28.6% of pts were women. Mean age 46.3. Average number of CPD 21 No information regarding psychiatric medications.
Interventions	1. Smoking reduction intervention group (wkly 1-hour session for 5 wks, delivered by 2 hospital staff) 2. Waiting list (one lecture on danger of smoking) Both groups did not receive any other smoking reduction intervention
Outcomes	Abstinence was not defined or measured. Reduction of smoking was measured by reduction of CPD at 3 ms. No biological verification. Effects on mental state measured by PANSS, HAM-D.
Source of funding	Not reported
Primary aim of the study	Smoking reduction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Information provided from author regarding randomisation: investigators decided beforehand to have 18 individuals in the control group and 35 in the intervention group. They cut out 53 slips of paper each named 0 (control) or 1 (study). The investigators then took the list of participant and starting alphabetically took the slips of paper out of a box for each client
Allocation concealment (selection bias)	High risk	See above. With the method described above, it is likely that towards the very end of the drawing, it would become obvious what the next person was likely to get

+Gelkopf 2012 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Possible contamination between the intervention group and the waiting list group, as they are inpatient in the same hospital. No biochemical verification of smoking status. The interventions were not comparable as they differed significantly in therapy time

+Hartman 1991

Methods	Cross-over study, USA. Pts were recruited from both inpatients and outpatients	
Participants	14 smokers with mixed psychiatric diagnoses and smoked at least 10 cigarettes daily. Pts did not have any other current substance use. Pts 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 yrs of smoking 19. 8 had a diagnosis of schizophrenia and 2 a diagnosis of schizoaffective disorder	
Interventions	TNP (8mg) vs. placebo patch for 7 hours (Day 1). Pts stayed for the next 2 entire days in the clinic for observation of smoking behaviour (although unlimited amount of pts' preferred brand of cigarettes were only provided during the 7 hours on patch). Cross-over to the other intervention one wk later. No other additional intervention for both groups.	
Outcomes	Abstinence was not defined or measured. Reduction of smoking measured by collection of cigarette butts in pts' own container (collection of cigarette butts was observed). Effects on mental state were not measured.	
Source of funding	Not reported	
Primary aim of the study	Smoking reduction	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

+Hartman 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	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 CPD) with diagnosis of schizophrenia or schizoaffective disorder. 53% of pts 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 yrs
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.
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 wk and 1 m after intervention. Effects on mental state not measured.
Source of funding	National Cancer Institute Grant, NIDA and Centre for Substance Abuse Treatment Grant
Primary aim of the study	Smoking reduction
Notes	
Risk of bias	

+Steinberg 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Mentioned randomisation in a ratio of 5:5:2 and the allocation sequence was generated by computer
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	The minimal control intervention group was not comparable to the other two interventions

+Szombathyne 2010

Methods	RCT, USA. Pts recruited from the community.
Participants	79 smokers with a diagnosis of schizophrenia or schizoaffective disorder. All pts also had combined nicotine and alcohol dependence. Demographics of participants unclear. Uncertain whether pts have interest in quitting smoking or TQD set
Interventions	1. Naltrexone (oral - 100mg on Mondays and Wednesdays, 150mg on Fridays) for 12 wks 2. Placebo for 12 wks Both groups also received wkly motivational enhancement therapy addressing alcohol use
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by number of cigarettes smoked. No biological verification. Measurements were taken at baseline, wk 12. Effects on mental state not measured.
Source of funding	NIAAA, NARSAD, the World's Leading Charity Dedicated to Mental Health Research
Primary aim of the study	Smoking reduction in patients with alcohol dependence and schizophrenia
Notes	Conference proceeding only

Risk of bias

Bias	Authors' judgement	Support for judgement

+Szombathyne 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	Insufficient information to assess whether an important risk of bias exists
Other bias	High risk	No biochemical verification of smoking status.

+Tidey 2011

Methods	RCT, USA. Pts recruited from the community.
Participants	57 smokers (at least 20 CPD, FTND ≥ 6) with DSM-IV TR diagnosis of schizophrenia or schizoaffective disorder. All pts were clinically stable on psychoactive medications for at least 2 ms. They also scored at least 4 for the Contemplation Ladder. Exclusion criteria included pregnancy, positive breath alcohol level or positive urine toxicology, medication or medical condition contraindicated the use of bupropion and high psychiatric symptom severity (i.e. ≥ 6 in items at BPRS). No TQD set. 37 males; mean age 45.1; 39 white, 8 African Americans, 5 other races; average CPD 27 Pts were on a variety of antipsychotic medications.
Interventions	4 groups: 1. Bupropion (150mg daily for 3 days then twice daily between day 4 and 22) + Contingency management (CM) - $25 gift card payment for attendance; participants earn cash bonus ($5 each) for reducing their urinary cotinine level by 25% compared to previous sample or to maintain cotinine levels below an abstinence threshold of 80ng/ml. Non-reduced cotinine results or missed visits resulted in no payment for that visit and rest the value of the contingent payment for the next reduced or abstinent sample to $25. However, two consecutive reduced or abstinent sample restored the value to the pre-set level. 2. Placebo for 22 days + CM 3. Bupropion (dosing as above) + Non-contingent reinforcement (NR) - $25 store gift card for attending study sessions and providing urine samples at each visit 4. Placebo for 22 days + NR

+Tidey 2011 (*Continued*)

Outcomes	Abstinence not defined or measured. Reduction of smoking measured by reduction of number of cigarettes smoked, expired CO level and urinary cotinine level. Measurements taken at baseline, wk 2, 3 and 4. Effects on mental state measured by PANSS. Extrapyramidal side effects measured by UPDRS, AIM. Nicotine withdrawal measured by Minnesota Nicotine Withdrawal Scale (MNWS). Cigarette craving measured by Questionnaire on Smoking Urges-brief form (QSU-brief)
Source of funding	NIH
Primary aim of the study	Smoking reduction
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tossing of coin.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Significant differences among group on PANSS positive and negative symptoms score

^Horst 2005

Methods	Open-label phase study followed by RCT, USA. Pts 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 ms and used tobacco daily. All pts interested in quitting; TQD set. 18 pts entered the RCT phase as they fulfilled the following criteria: (1) agreed to set a quit date within 2 wks; (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 pts in the open-label phase, 26 were men; mean age was 42.5; average pack-yrs 39.9
Interventions	1. TNP (Nicoderm CQ) for 6 ms (Dose ranged from 14 mg to 63 mg daily, according to pts' cotinine saliva levels. The dose was fixed throughout 6 ms) 2. Placebo patch for 6 ms. All pts 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 wks. Abstinence not defined or measured. Reduction of smoking measured by expired CO level. Measurements taken at baseline, every 2 wks and at the final session. Effects on mental state not measured.
Source of funding	American Legacy Foundation & Via Christi Foundation. SmithKlineBeecham provided placebo patches
Primary aim of the study	Relapse prevention after smoking cessation.
Notes	Only the data from the RCT were included in this review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Coin flip by blinded third party.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Unclear risk	Uncertain whether there were any baseline differences for the two groups in the RCT phase

de Leon 2005b

Methods	RCT, USA. Pts were in-patients and study was conducted in hospital setting
Participants	50 pts with DSM-IIIR diagnosis of schizophrenia. All were treatment resistant (not responded at least 3 antipsychotics - each antipsychotic was prescribed for at least 6 wks and at CPZ equivalent dose of above 1000 mg daily). CGI at least moderately ill and BPRS-Anchored scores ≥ 45. Only 42 participants who were daily smokers were included in the analysis. Of these 42 pts, 2 withdrew before completing clozapine trial and another 2 did not provide sufficient cotinine measures. Interest in quitting smoking was uncertain. No TQD set. Demographics for smokers not reported. Average CPD 19.
Interventions	1. Clozapine 100mg daily 2. Clozapine 300mg daily 3. Clozapine 600mg daily Duration of clozapine: 16 wks. No other additional intervention for both groups. All pts were switched to haloperidol for 4 wks and then had a washout period for 1 wk before clozapine
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by plasma cotinine; measurements at baseline and between 13th and 15th wks. Effects on mental state measured by BPRS-Anchored, SANS and CGI
Source of funding	NIMH, NARSAD, Universidad Nacional (Medellin, Colombia). Novartis Research Institute provided free medication
Primary aim of the study	Efftect of different doses of clozapine on mental state.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes

Other bias	High risk	Unequal numbers in the three intervention groups and uncertain whether these three groups were comparable in characteristics and also baseline cotinine level

Hong 2011

Methods	RCT, USA. Pts recruited from the community.
Participants	69 pts (43 smokers) with a diagnosis of schizophrenia or schizoaffective disorder. All received antipsychotic medications and they were clinically stable for at least 4 wks. Aged between 18 and 60. Exclusion criteria included: (1) pts were undergoing smoking cessation therapy; (2) major medical conditions; (3) atrioventricular block as identified by ECG; (4) renal insufficiency Interest in quitting smoking is not required. No TQD set. Among 43 smokers, 27 were males. Mean age 42.2. Average CPD 18
Interventions	1. Varenicline 0.5mg daily for 1 wk then 0.5mg twice daily for 7 wks (total 8 wks) 2. Placebo for 8 wks Both groups did not receive any additional intervention.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by reduction of CPD and reduction of the expired CO level. Measurement taken at wk 1, 2, 4, 6, 8 and 10. Effects on mental state measured by BPRS, SANS, HAM-D and CGI
Source of funding	Stanley Medical Research Institute, NIH, Neurophysiology Core of the University of Maryland General Clincial Research Centre
Primary aim of the study	Effect of varenicline on neurobiological and cognitive biomarkers in schizophrenia
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	

Kelly 2008

Methods	RCT, USA. Pts recruited from both inpatients and outpatients
Participants	86 pts with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All were treated by antipsychotics except clozapine. Pts were not on anticholingeric medications and with SAS score ≤ 4. Pts with DSM-IV diagnosis of alcohol or substance misuse or dependence (except nicotine) were excluded 73 Pts smoked (defined as baseline expired CO level ≥ 8 ppm). Only 41 pts had at least 1 follow up measurement and were included in the analysis. Among these 41 pts, 39 were men; mean age 47.5; 14 white, 28 black Pts not interested in quitting; no TQD.
Interventions	1. Galantamine for 12 wks (up to 24 mg/day) 2. Placebo for 12 wks 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 wks till wk 12. Effects on mental state measured by BPRS, SANS and CGI. Parkinsonism symptoms measured by SAS and AIMS
Source of funding	VA Capital Network (VISN 5) Mental Illness, Research, Education and Clinical Centre, Stanley Medical Research Institute and NIMH. Ortho McNeil Neurologics supplied medications
Primary aim of the study	Effect of galantamine on cognitive function.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence was generated by computer.
Allocation concealment (selection bias)	Low risk	Allocation was performed centrally at the research pharmacy.

Kelly 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Subgroup analysis of another trial with significant number of smokers not included in the analysis

McEvoy 1995

Methods	RCT, USA. Pts were chronically hospitalised patients.
Participants	12 smokers with DSM-IIIR diagnosis of chronic schizophrenia. All pts 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 yrs
Interventions	1. Low clozapine (dose varied but plasma clozapine level 50-150ng/ml) for 12 wks 2. Medium clozapine (plasma level 200-300 ng/ml) for 12 wks 3. High clozapine (plasma level 350-450 ng/ml) for 12 wks 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 wk 12. Effects on mental state measured by BPRS and CGI.
Source of funding	Not reported
Primary aim of the study	Efftect of different doses of clozapine on mental state
Notes	Pts were allowed free access to cigarettes for 120 minutes only

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.

McEvoy 1995 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Potential baseline difference between groups: the low clozapine group had lower baseline expired CO level

Meszaros 2012

Methods	RCT, USA. Pts recruited from the community.
Participants	10 smokers (aged 18 to 69, at least 20 CPD over the 7 days prior to intake) with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Pts took antipsychotic medication for at least 4 wks, and with a current DSM-IV diagnosis of nicotine dependence and alcohol dependence. Exclusion criteria included: (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 yr; (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 cannabis dependence (1 m prior to enrolment) Pts expressed desire to cut down or quit smoking and drinking. No TQD set Demographics of participants were not reported.
Interventions	1. Varenicline 0.5mg daily for first 3 days, then 0.5mg twice daily for 4 days, then 1mg bd for 7 wks (i.e. total 8 wks) 2. Placebo (matched in appearance) for 8 wks Both groups received (1) voucher-based incentives contingent on attendance; (2) manual based individual wkly motivational interviewing sessions every wk for up to 30 minutes each, focusing on increasing motivation to reduce or quit smoking and drinking
Outcomes	Abstinence was not defined or measured. Reduction measured by reduction of CPD and expired CO level at the end of the treatment phase (wk 8) Efffect on mental state measured by PANSS.
Source of funding	NARSAD
Primary aim of the study	Effect of varenicline on alcohol dependence (as primary outcome according to protocol)
Notes	Conference proceedings only but we obtained further information from the investigators. The study terminated because of slow recruitment and high drop out rate

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation schedule provided by biostatistician.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Only reported CPD but not expired CO level
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

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 pts have interest in quitting smoking. No TQD set
Interventions	1. Atomoxetine 40mg daily for 2 wks 2. Atomoxetine 80mg daily for 2 wks 3. Placebo for 2 wks 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.
Source of funding	NARSAD & NIDA.
Primary aim of the study	Effect of atomoxetine on mental state.
Notes	The report is a letter to the editors.
Risk of bias	

Sacco 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	High risk	Only report part of the results.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Shim 2012

Methods	RCT, Korea. Setting unclear.
Participants	120 pts (60 smokers and 60 non-smokers) with DSM-IV diagnosis of schizophrenia, aged between 18 and 60. All pts scored less than 75 in PANSS total score for at least 3 ms before the study. For smokers, they smoked at least 10 CPD for more than 1 yr. Exclusion criteria included: (1) serious or unstable medical disorder within previous 6 ms; (2) other DSM-IV Axis 1 diagnosis; (3) substance abuse or dependence (except nicotine) in the last 12 ms before study; (4) pregnant or breast feeding; (5) high risk of suicide clinically; (6) use of any form of NRT or other tobacco products; (7) history of taking clozapine Interest in quitting or reducing smoking uncertain. No TQD set Among smokers, 55 male. Mean age 41.3. All Koreans. Average CPD 14. Average length of illness 15.1 yrs Pts were on various antipsychotic medications. Fixed dose of psychotropic medications throughout the study in both groups
Interventions	1. Varenicline 0.5mg daily for day 1 to 3, then 0.5mg twice daily for day 4 to 7 then 1mg twice daily for wk 2 to 8 2. Placebo for 8 wks No other additional interventions for both 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, wk 1, 2, 4 and 8. Effects of mental state were measured by PANSS, SANS, HAM-D, CGI. Extrapyramidal side effects measured by SAS and Barnes Akathsia Rating Scale

Shim 2012 (*Continued*)

Source of funding	Stanley Medical Research Institue
Primary aim of the study	Effects of varenicline on cognitive function in schizophrenia
Notes	Subgroup demographic data (smokers vs non-smokers) from supplementary data via journal website

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation was not described.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	Low risk	

Weinberger 2008

Methods	RCT, USA. Pts recruited from both inpatients and outpatients
Participants	48 pts with DSM-IV TR diagnosis of schizoaffective disorder, bipolar type. All pts had a PANSS score at least 60 and a CGI score at least 4. Pts were on a stable dose of lithium and/or valproate for at least 2 wks before the study. Pts with alcohol or marijuana dependence or other substance misuse were excluded. Pts 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 ≥ 10 ppm) were included in the data analysis. Among these 24 pts; 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 wks (after titration of dose) 2. Placebo for 8 wks No other additional intervention for all groups.
Outcomes	Abstinence not defined or measured. Reduction of smoking measured by expired CO level. Measurements at baseline, wk 4

Weinberger 2008 (*Continued*)

	and wk 8. Effects of mental state measured by PANSS, MADRS, YMRS and CGI	
Source of funding	NIDA & Ortho McNeil Neurologics (funded the medications and study)	
Primary aim of the study	Effect of topiramate on mental state.	
Notes	The report is a letter to the editors.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Mentioned randomisation in a ratio of 2: 1 (favouring topiramate) but unclear how the allocation sequence was generated
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the reports.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected outcomes
Other bias	High risk	Only 24 participants were analysed although there were 31 smokers

AIMS: Abnormal Involuntary Movement Scale
BDI: Beck Depression Inventory
BPRS: Brief Psychiatric Rating Scale
BSI: Brief Symptoms Inventory
CA: continuous abstinence
CBT: cognitive behavioural therapy
CGI: Clinical Global Impression
CO: carbon monoxide
CPD: cigarettes per day
DSMIV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition
FTND: Fagerström Test for Nicotine Dependence
HAM-D: Hamilton Depression Rating Scale
ICD: International Classification of Diseases
m(s): month(s)
MM: medical management
MMSE: Mini-Mental State Examination

NRT: nicotine replacement therapy
PANSS: Positive and Negative Syndrome Scale
PPA: point prevalence abstinence
Pt(s): participant(s)
RCT: randomised controlled trial
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
TANS: Treatment of Addiction to Nicotine in Schizophrenia
TNP: transdermal nicotine patch
TQD: target quit date
wk(s): week(s)
YMRS: Young Mania Rating Scale
yr(s): year(s)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Allen 2011	The main purpose of this study is to investigate the effect of nicotine replacement therapy on agitation in smokers with schizophrenia. There was no report on smoking status
Arbour-Nicitopoulos 2011a	No measures of cigarette consumption or smoking status. Only reported measure for cigarette craving and mood changes
Arbour-Nicitopoulos 2011b	Qualitative study - not RCT
Aubin 2012	General review - not RCT
Baker 2010	General review - not RCT
Banham 2010	Systematic review - not RCT
Brown 2003	Pts aged below 18
Brunette 2011	No randomisation but allocated intervention according to location of hospital
Bryant 2011	Systematic review - not RCT
Dutra 2012	No comparison group
Kisely 2006	Before and after study without randomisation
McClure 2010	Participants did not have an active diagnosis of schizophrenia during the trial
McEvoy 1999	Before and after study without randomisation

(*Continued*)

McKee 2009	The primary purpose of the study was to utilize mecamylamine as a mechanistic probe because of its ability to increase smoking behaviour
Morris 2011	Mixed psychiatric diagnoses and subgroup data was not available
Pachas 2012	Before and after study without randomisation
Roll 1998	Before and after study without randomisation
Shiina 2010	Main aim of the study is to investigate the effect of tropisetron on cognitive function of patients with schizophrenia. No comparison between tropisetron and placebo group regarding effect of tropisetron on smoking status
Tidey 2002	Before and after study without randomisation
Tidey 2012	Main aim of study is to investigate the separate and combined effect of acute nicotine replacement and sensorimotor smoking replacement (in the form of Very Low Nicotine Content cigarettes) on cigarette craving, withdrawal symptoms and usual brand smoking in schizophrenia and non-schizophrenia smokers. Intervention only lasted for 25 hours
Weiner 2001	No comparison group
Wells 2003	No measures of cigarette 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. Pts were recruited from a day-care ward in a psychiatric hospital
Participants	65 pts with DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts smoked more than 20 cigarettes daily and are willing to stay for 60 minutes for participating in the smoking cessation group. Pts 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 pts were men. Mean age 40.1.
Interventions	1. Smoking cessation group programme (total 8 hourly sessions in 4 wks), 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 1 wk after participating in the smoking cessation programme (i.e. wk 5) and wk 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 randomisation (it mentions in the report that pts 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. Pts were recruited from a day-care ward in a psychiatric hospital
Participants	68 pts with diagnosis of schizophrenia. All pts smoked at least 15 CPD for minimum of 1 yr. Pts with history of using NRT within 6 ms 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 wks (14mg daily for wk 1 to 6; 7mg daily during wk 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. wk 8) and 3-m follow-up Reduction of smoking was measured by expired CO level and FTND score. Measurements were taken at baseline, wkly for first 4 wks, wk 8 and 3-m 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 randomisation (it mentions in the report that pts 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 CPD) with a diagnosis of a psychotic disorder or bipolar disorder. All pts take antipsychotic medication as prescribed for at least 2 ms 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 wkly sessions then 3 fortnightly sessions then 6 monthly sessions] + one final

Baker(ACTRN1260900103927) (*Continued*)

	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 CPD at wk 15, as well as 12, 18, 24, 30 and 36 ms after initial assessment
Starting date	July 2009
Contact information	Amanda Baker (amanda.bake@newcastle.edu.au)
Notes	Includes pts with mental illness other than schizophrenia

Dixon (NCT00960375)

Trial name or title	Smoking Cessation for Veterans with Severe and Persistent Mental Illness
Methods	RCT. Study is conducted at multi-sites in Washington DC and Maryland, USA
Participants	Adult smokers (at least 10 CPD or FTND score 5 or more) with DSM-IV diagnosis of severe and persistent mental illness including a diagnosis of a psychotic disorder (schizophrenia, affective psychoses, other psychotic diagnoses and major depression with psychotic features) Exclusion criteria: (1) current alcohol or substance dependence (other than nicotine); (2) documented history of severe neurological disorder or severe head trauma with loss of consciousness; (3) severe or profound mental retardation by chart review
Interventions	1. Behavioural Treatment of Smoking Cessation in Severe and Persistent Mental Illness (BTSCS) for 24 sessions - two 60-minute manualised group sessions per wk including the following components: individual motivational enhancement, contingency management and goal-setting, skills for reducing smoking, social skills training, education about severe and persistent mental illness and smoking, relapse prevention training, education and assistance with NRT. 2. Standard ALA-based manualised smoking cessation programme for 24 sessions
Outcomes	Smoking reduction measured by expired CO level and self reported abstinence from tobacco (abstinence was not defined)
Starting date	April 2010
Contact information	Wendy Potts (wendy.potts@va.gov)
Notes	Principal Investigator: Lisa Dixon (ldixon@psych.umaryland.edu). Includes pts 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 or Bipolar disorder (SCRP)
Methods	RCT. Study is conducted at multi-sites in Massachusetts, Michigan, Minnesota and New Hampshire, USA
Participants	Adult smokers (at least 10 CPD and expired CO level > 9ppm) with DSM-IV diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder. All pts are willing to quit smoking and set a quit date within 2 to 3 wks 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 ms; (3) major depressive disorder within the last 6 ms; (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 wks 2. Placebo for 12 wks Both groups also receive 13-session wkly CBT programme for smoking cessation Those pts who have been abstinent for more than 2 wks at the last 4 wks of 12-wk treatment will enter a 40-wk relapse prevention programme. They will again be randomised 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 wk 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	Gladys N Pachas (gpachas1@partners.org)
Notes	Principal Investigator: A. Eden Evins, Massachusetts General Hospital. Includes pts with mental illness other than schizophrenia

Fatemi (NCT01111149)

Trial name or title	Varenicline and Smoking Cessation in Schizophrenia (VSCS)
Methods	RCT. Study is conducted in Minnesota, USA.
Participants	Adult smokers (at least 10 CPD) with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. All pts are motivated to quit smoking and with stabilized psychotic symptoms Exclusion criteria: (1) serious cardiac, renal, hypertensive, pulmonary, endocrine, or neurological disorder; (2) seizure disorder, recent withdrawal from alcohol or anxiolytics; (3) history of bulimia nervosa, anorexia nervosa, or dementia; (4) history of depression, panic, or bipolar disorders; (5) pregnancy or lactation; (6) prior use of varenicline or bupropion within 3 ms prior to initiation of study; (7) current use of other smoking cessation treatments; (8) regular use of non-cigarette tobacco products (more than once a wk); (9) history of substance abuse (alcohol or non-nicotine containing drugs) in the preceding 6 ms; (10) patients with suicidal ideations or plans; (11) florid psychosis or increasing psychosis following varenicline or bupropion treatment;

Fatemi (NCT01111149) (*Continued*)

	(12) history or current alcohol dependence; (13) current use of monoamine oxidase inhibitor
Interventions	1. Varenicline 1mg twice daily for 12 wks 2. Bupropion 300mg daily for 12 wks 3. Placebo for 12 wks
Outcomes	Abstinence is measured by self report and verified by exhaled CO level and blood/urine tests for nicotine and its metabolites Smoking reduction is measured by 50% or greater reduction in self reported CPD and a 30% or greater reduction in CO and cotinine levels Mental state and side effects (including suicidality and abnormal movements) are also measured regularly
Starting date	December 2009
Contact information	S Hossein Fatemi, University of Minnesota
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	Adult smokers (at least one pack of CPD) 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 ms; (6) pregnancy or breastfeeding; (7) serious suicidal risk
Interventions	1. Quetiapine (400mg to 800mg daily) for 12 wks. Pts start with Risperidone for 1 wk and switch to Queatiapine over 2 wks before the 12-wk trial. 2. Risperidone (4mg to 10mg daily) for 12 wks 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)
Notes	

Saxon (NCT00508560)

Trial name or title	Contingency Management for Smoking Cessation Among Veterans With Psychotic Disorders
Methods	RCT. Study is conducted in the USA.
Participants	Adult smokers (at least 5 or more CPD 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 pts 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 wk 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	Michelle Esterberg (michelle.esterberg@va.gov)
Notes	Principal Investigator: Andrew J. Saxon (VA Puget Sound Health Care System). Includes pts with mental illness other than schizophrenia

Smith (NCT00802919)

Trial name or title	Varenicline for Cognitive Deficits and Cigarette Smoking in Schizophrenia - Efficacy and Predictors
Methods	RCT. Study is conducted in New York, USA and in Israel.
Participants	Adult 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 yr; (4) pregnant or breastfeeding; (5) significant renal impairment; (6) baseline HDRS score > 20
Interventions	1. Varenicline 1-2mg daily for 12 wks 2. Placebo for 12 wks
Outcomes	Abstinence is not measured. Smoking reduction is measured by cotinine level. Mental state is monitored with PANSS and CDSS.

Smith (NCT00802919) (*Continued*)

Starting date	September 2008
Contact information	Robert C Smith(rsmith@nki.rfmh.org)
Notes	

Stockings 2011

Trial name or title	A randomised controlled trial linking mental health inpatients to community smoking cessation supports: A study protocol
Methods	RCT. Study is conducted in a large regional inpatient mental health facility located in New South Wales, Australia
Participants	Adult smokers (self report of being a current or occasional smoker). All participants are inpatients in a mental health unit Exclusion criteria: (1) not having a current contact telephone number or address; (2) non-English speaking; (3) current physical or mental wellbeing is judged by clinical staff to be too unstable to participate
Interventions	1. In addition to hospital smoking care, pts are provided with a "base" intervention component, comprising a brief motivational interview and smoking cessation self help material in the inpatient setting. They are also offered "additional" components after discharge from hospital: up to 12 wks of ongoing nicotine replacement therapy, proactive Quitline referral, and a referral to community smoking cessation support groups. Upon discharge, pts receive an initial 2 wk supply of NRT, supportive phone contact at 3 days and 1 wk after hospitalisation. Pts who choose any of the "additional" components will receive up to 16 wks of further fortnightly telephone support. 2. Standard hospital nicotine dependence treatment (NRT during hospitalisation and upon discharge, up to 3 days provision of NRT, as well as a referral to Quitline)
Outcomes	Primary outcome is smoking reduction as measured by CPD at 1 wk, 2 ms, 4 ms and 6 ms post discharge Secondary outcome is self reported abstinence from smoking (5% of pts who abstain are verified with expired CO level)
Starting date	June 2009
Contact information	Jenny Bowman (jenny.bowman@newcastle.edu.au)
Notes	ACTRN12609000465257. Includes pts with mental illness other than schizophrenia

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.

Williams (NCT01010477) (*Continued*)

Participants	Adult smokers with DSM-IV diagnosis of schizophrenia. Participants smoke at least 10 CPD and have an expired CO level >9ppm. They are also motivated to quit smoking and on atypical antipsychotic medication for at least 1 m Exclusion criteria: (1) current suicidal risk; (2) psychiatric hospitalisation 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 wks 2. Placebo for 20 wks Both group will also receive behavioural intervention
Outcomes	Abstinence is defined as self report of no tobacco use for 4 wks, confirmed by exhaled CO level <10ppm during these period. Abstience will be assessed at wk 5, wk 12, wk 20, wk 26 and wk 52
Starting date	August 2009
Contact information	Mia H Zimmermann (hanosma@umdnj.edu)
Notes	Principlal Investigator: Jill M Williams, University of Medicine and Dentistry, New Jersey

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)	3.03 [1.69, 5.42]
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)	3.67 [1.66, 8.14]
3 Mental state outcomes - abstinence studies	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) - abstinence studies	4	169	Mean Difference (IV, Random, 95% CI)	-6.80 [-10.79, -2.81]
4.1 Studies using final measurements	3	150	Mean Difference (IV, Random, 95% CI)	-6.01 [-10.20, -1.83]
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) - abstinence studies	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) - abstinence studies	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) - abstinence studies	2	104	Mean Difference (IV, Random, 95% CI)	0.40 [-5.72, 6.53]
8 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome) - reduction studies	2	93	Mean Difference (IV, Fixed, 95% CI)	-2.61 [-7.99, 2.77]

Comparison 2. Varenicline 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)	1	128	Risk Ratio (M-H, Random, 95% CI)	5.06 [0.67, 38.24]
2 Abstinence at end of treatment (secondary outcome)	2	137	Risk Ratio (M-H, Random, 95% CI)	4.74 [1.34, 16.71]

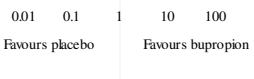
Analysis 1.1. Comparison 1 Bupropion versus placebo, Outcome 1 Abstinence at 6-month follow-up (primary outcome).

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)

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 versus Placebo					
*Evins 2001	1/10	0/9		10.6 %	2.73 [0.12, 59.57]
*Evins 2005	1/25	1/28		13.6 %	1.12 [0.07, 16.98]
*George 2002	3/16	1/16		21.6 %	3.00 [0.35, 25.87]
Subtotal (95% CI)	**51**	**53**		**45.8 %**	**2.19 [0.50, 9.63]**
Total events: 5 (Bupropion), 2 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.34$, df = 2 (P = 0.85); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 Bupropion + TNP versus Placebo + TNP					
*George 2008	4/30	0/29		12.1 %	8.71 [0.49, 154.89]



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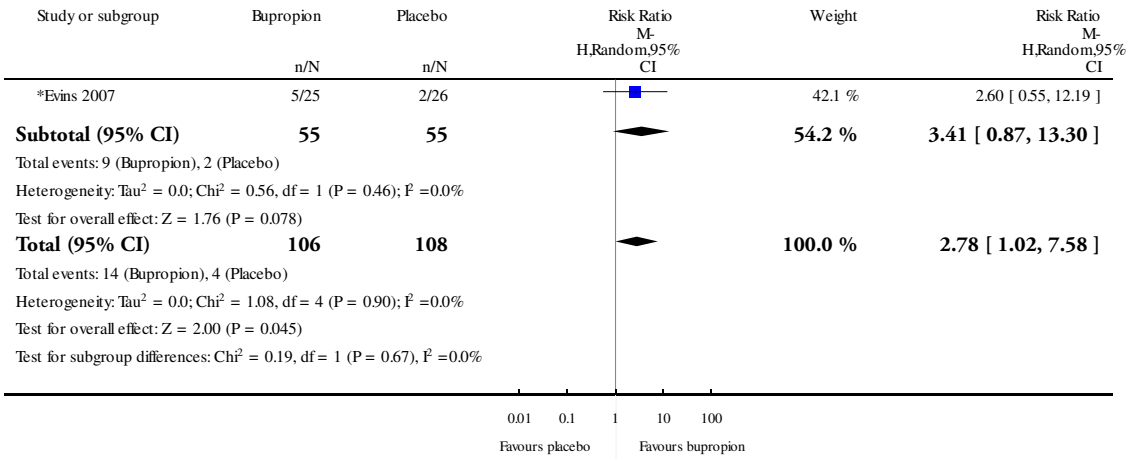
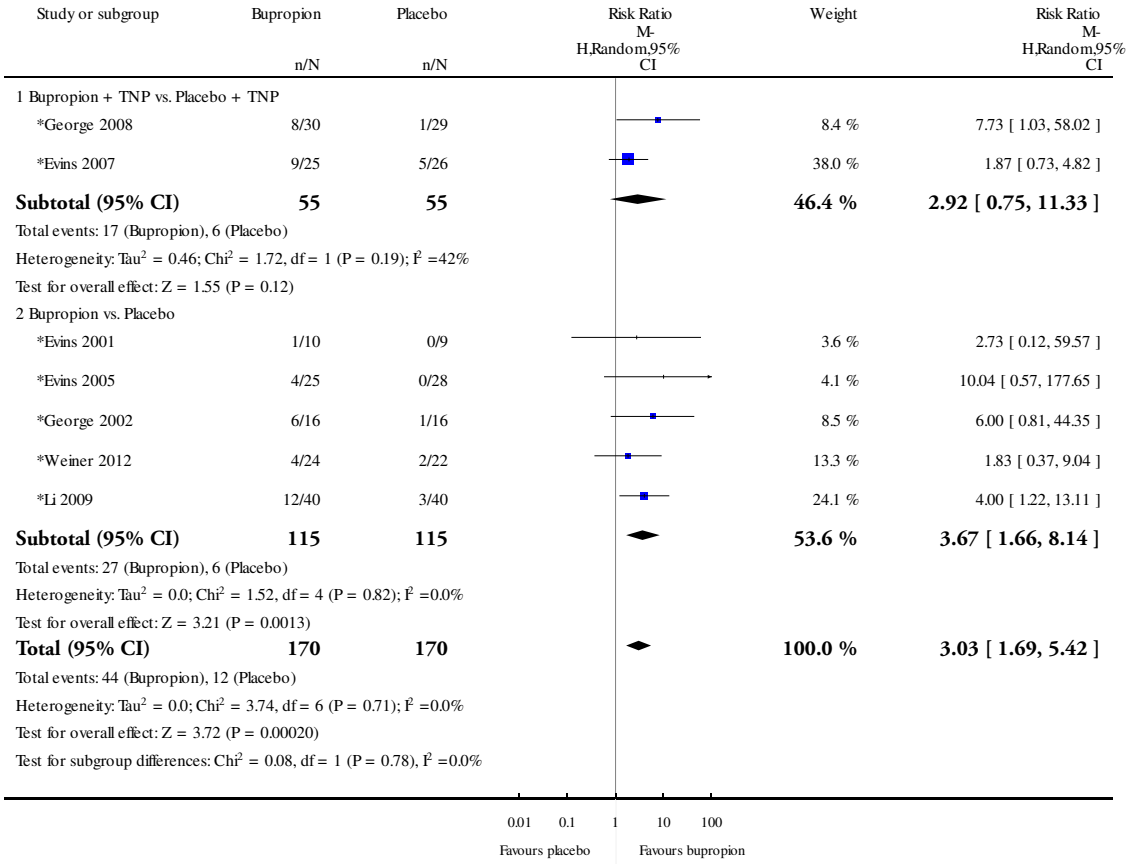


Analysis 1.2. Comparison 1 Bupropion versus placebo, Outcome 2 Abstinence at end of treatment (secondary outcome).

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)

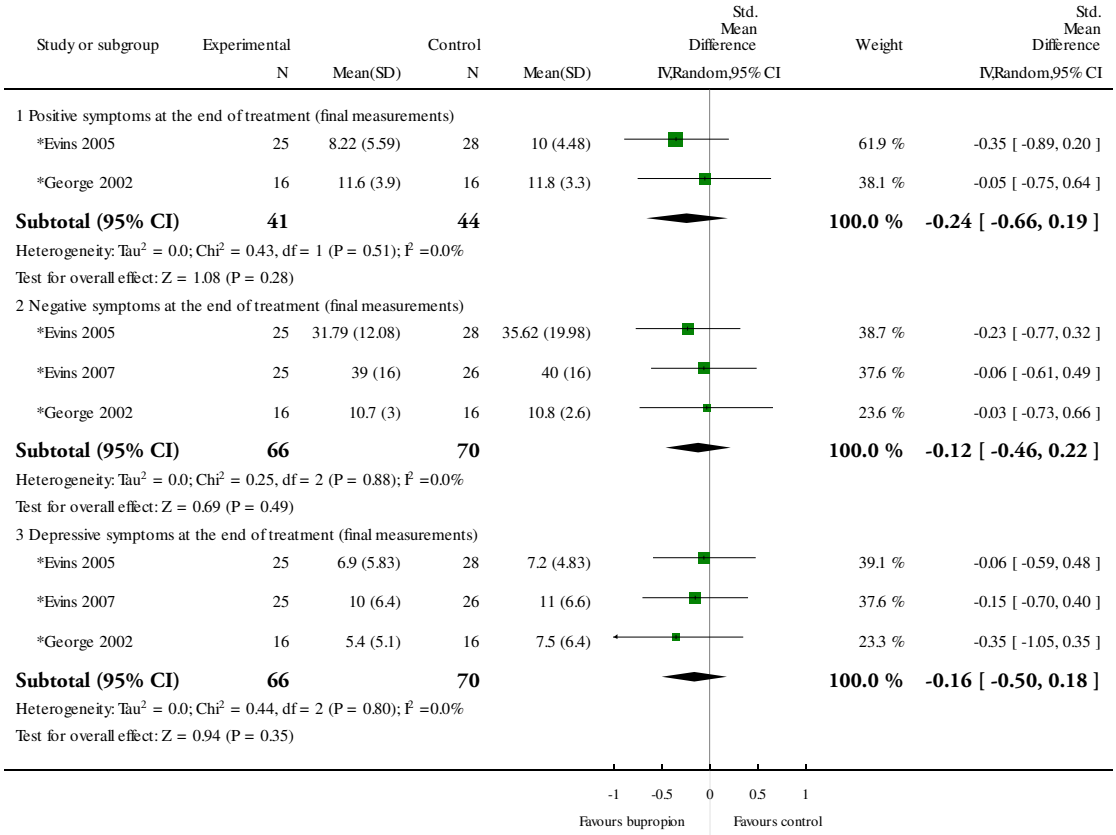


Analysis 1.3. Comparison 1 Bupropion versus placebo, Outcome 3 Mental state outcomes - abstinence studies.

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

Comparison: 1 Bupropion versus placebo

Outcome: 3 Mental state outcomes - abstinence studies

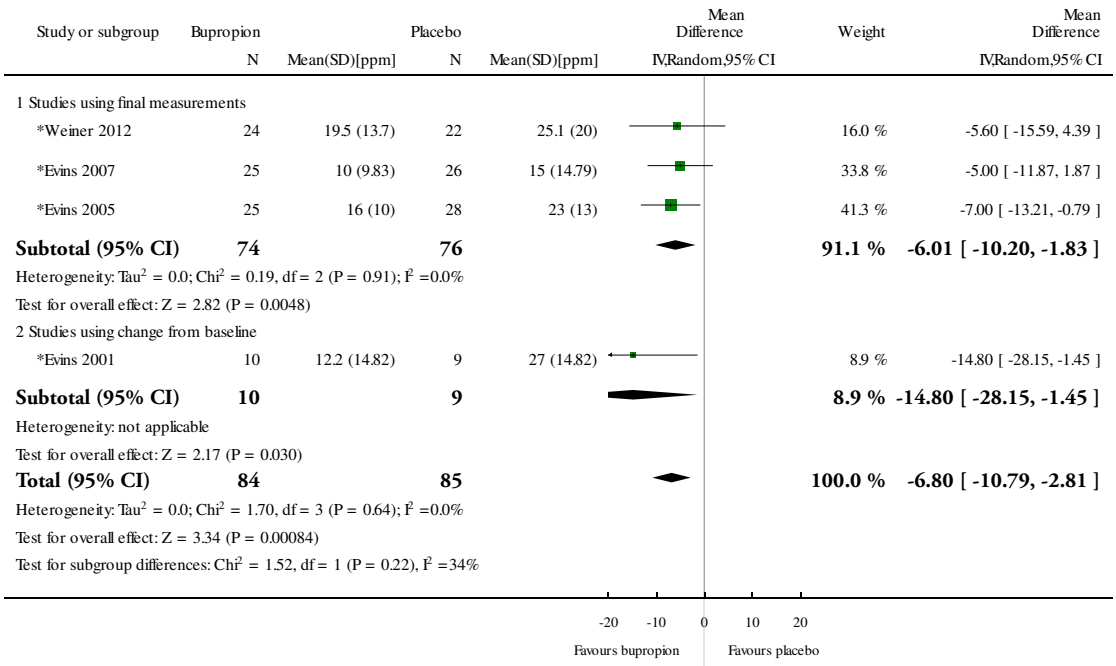


Analysis 1.4. Comparison 1 Bupropion versus placebo, Outcome 4 Reduction - Expired CO level at the end of treatment (secondary outcome) - abstinence studies.

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) - abstinence studies

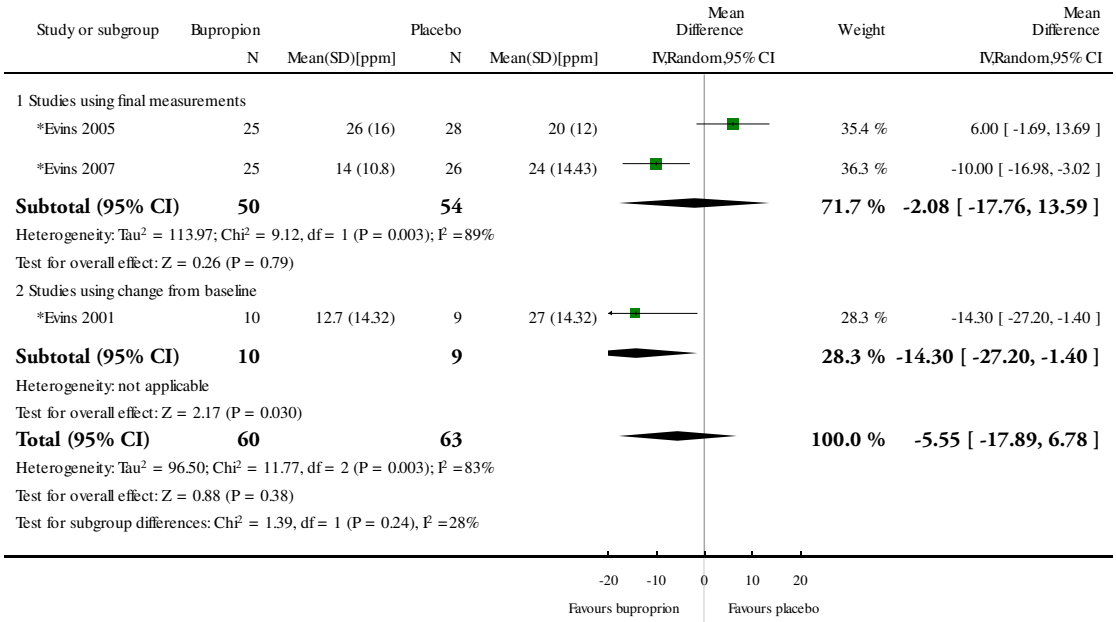


Analysis 1.5. Comparison 1 Bupropion versus placebo, Outcome 5 Reduction - Expired CO level at 6-month follow-up (secondary outcome) - abstinence studies.

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) - abstinence studies



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) - abstinence studies.

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) - abstinence studies

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)

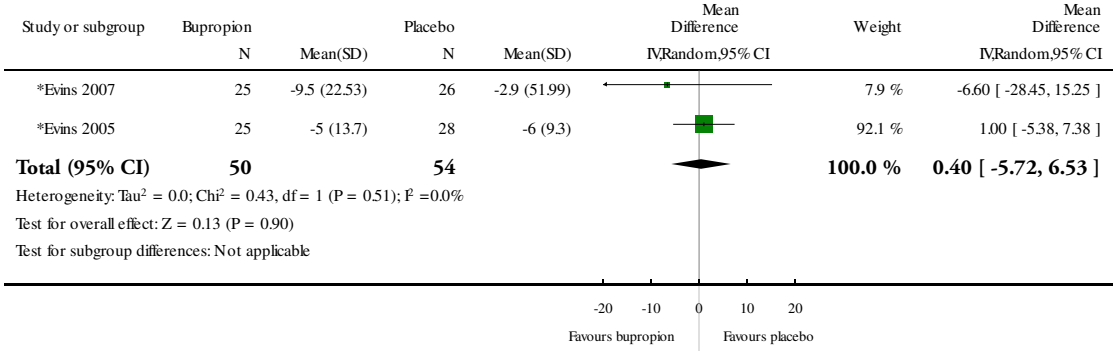
Test for subgroup differences: Not applicable

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) - abstinence studies.

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) - abstinence studies

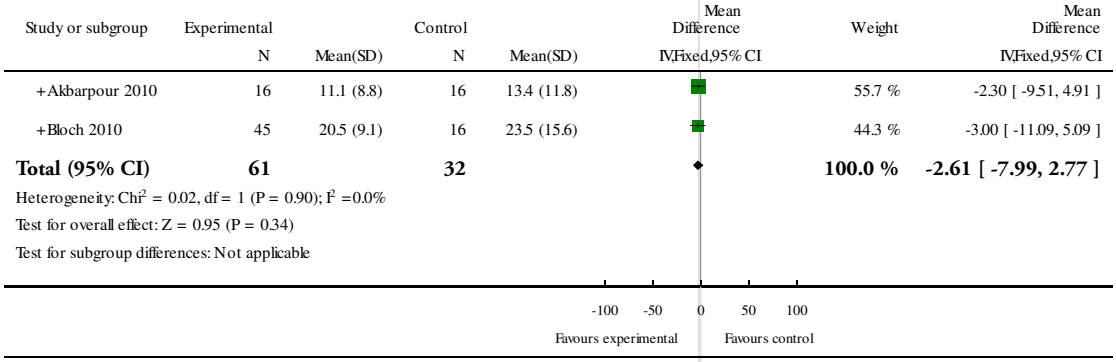


Analysis 1.8. Comparison 1 Bupropion versus placebo, Outcome 8 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome) - reduction studies.

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

Comparison: 1 Bupropion versus placebo

Outcome: 8 Reduction - Change in number of CPD from baseline at the end of treatment (secondary outcome) - reduction studies

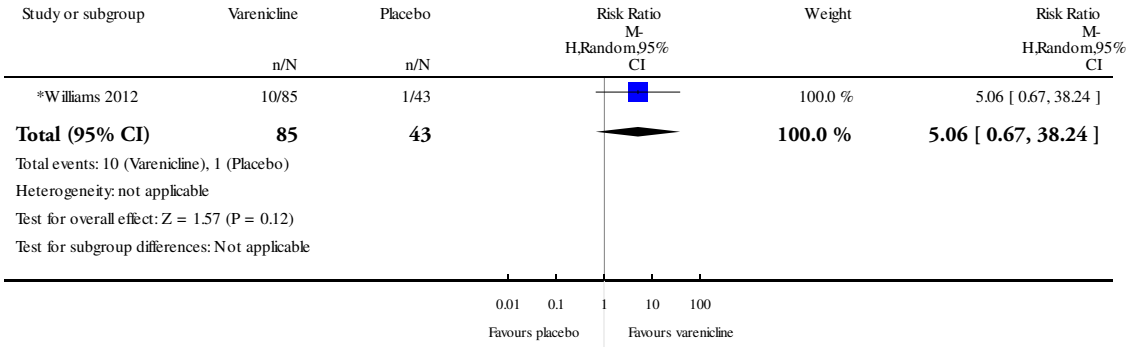


Analysis 2.1. Comparison 2 Varenicline versus placebo, Outcome 1 Abstinence at 6-month follow-up (primary outcome).

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

Comparison: 2 Varenicline versus placebo

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

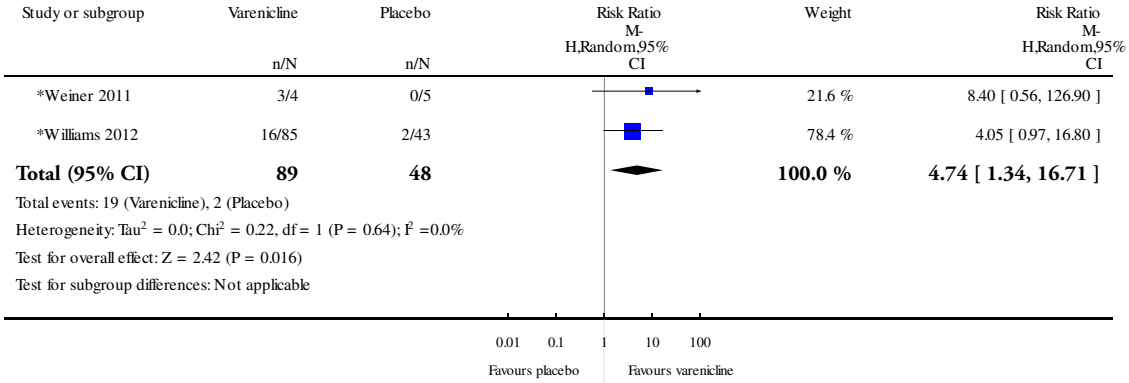


Analysis 2.2. Comparison 2 Varenicline versus placebo, Outcome 2 Abstinence at end of treatment (secondary outcome).

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

Comparison: 2 Varenicline versus placebo

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



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. randomised 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

WHAT'S NEW

Last assessed as up-to-date: 10 January 2013.

Date	Event	Description
10 January 2013	New search has been performed	Updated with new search;

(*Continued*)

10 January 2013	New citation required but conclusions have not changed	New citation version; updated with 14 new included studies; no major changes to conclusion, but with more information on varenicline studies and adverse effects

HISTORY

Protocol first published: Issue 3, 2008

Review first published: Issue 6, 2010

Date	Event	Description
16 February 2011	Amended	Date for assessed as up-to-date corrected
7 July 2010	Amended	Graph label corrected

CONTRIBUTIONS OF AUTHORS

DTT and ACW conceived and designed the review. DTT conducted the search. DTT, ACW and MP screened retrieved papers. DTT and MP extracted data from the papers, with contribution from ACW to resolve disagreement. DTT entered the data into RevMan 5 and performed data analysis. DTT wrote the review with input from MP and ACW.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Nottinghamshire Healthcare NHS Trust, UK.
- Division of Psychiatry, University of Nottingham, UK.
- Academic Clinical Psychiatry, University of Sheffield, UK.
- 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 study and 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).

INDEX TERMS

Medical Subject Headings (MeSH)

*Schizophrenia; Antidepressive Agents, Second-Generation [*therapeutic use]; Benzazepines [therapeutic use]; Bupropion [*therapeutic use]; Nicotine [administration & dosage]; Nicotinic Agonists [therapeutic use]; Quinoxalines [therapeutic use]; Randomized Controlled Trials as Topic; Reinforcement (Psychology); Schizophrenic Psychology; Smoking [*prevention & control]; Smoking Cessation [methods]; Tobacco Use Cessation Products

MeSH check words

Adult; Humans