BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027389
Article Type:	Research
Date Submitted by the Author:	29-Oct-2018
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Keywords:	Smoking cessation, Serious mental illness, varenicline, nicotine replacement, bupropion

Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials.

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Keyword: Smoking Cessation, Smoking reduction, Serious mental illness, Physical health.

Abstract

Objective

Smoking in people with serious mental illness is a major public health problem and contributes to significant levels of morbidity and mortality. To determine the efficacy of methods used to aid smoking cessation in people with serious mental illness.

Method

Systematic review and meta-analysis of randomised controlled trials comparing interventions for smoking cessation in people with SMI.

Results

Twenty-eight randomised controlled trials were identified. Varenicline increased the likelihood of smoking cessation at both three months (RR 3.56, 95% CI 1.82-6.96, p=0.0002) and at six months (RR 3·69, 95% CI 1·08-12·60, p=0.04). Bupropion was effective at 3 months (RR 3·96, 95% CI 1·86-8·40, p=0.0003) especially at high dose, but there was no evidence of effect at 6 months (RR 2·22, 95% CI 0·52-9·47, p=0·28). In one small study nicotine therapy proved effective at increasing smoking cessation up to a period of 3 months.

Bupropion used in conjunction with NRT showed more effect than single use. Behavioural and bespoke interventions showed little overall benefit. Side-effects were found to be low.

Conclusion

The new information of this review was the effectiveness of varenicline for smoking cessation at both 3 and 6 months and the lack of evidence to support the use of both bupropion and nicotine products for sustained abstinence longer than 3 months. Overall the review found relatively few studies in this population.

Strengths and limitations of the study

- This study systematically reviewed all pharmacological and behavioural interventions to promote smoking cessation in people with serious mental illness.
- We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the strength and quality of the evidence.
- We reviewed and identified evidence that would be valuable and relevant to clinical practice.
- Research in this field was limited by a small number and low quality of randomised controlled trials.
- We recommended that studies with larger sample sizes are needed particularly to compare the relative effects of one smoking treatment versus another.

Introduction

Smoking in people with serious mental illness continues to be a major public health problem with levels of smoking remaining as high as 70% (1-3), compared to about 20% in the general population (4). Smoking contributes to the high levels of morbidity and mortality in this population (5) with mortality rates continuing to remain around twice those found in the general population, with high levels of cardiovascular and respiratory disease (1,6,7). Individuals with serious mental illness tend to have smoked for longer periods compared with other groups and are commonly classed as heavy smokers, smoking more than 25 cigarettes per day (8). They often start before the onset of their illness, are younger than non-smokers, and more of them are male (9). Generally they prefer cigarettes high in nicotine and more frequently smoke cigarettes down to the very end (10). Increased nicotine intake per cigarette is associated with more intense cigarette puffing contributing to the higher serum nicotine levels, approximately 1.3 times those in non-mentally ill controls (11,12). The effect of this greater uptake of nicotine may lead to higher than expected levels of nicotine dependence and withdrawal symptoms, even with moderate amounts of smoking (11).

There is therefore an urgent need to develop and evaluate smoking cessation interventions that work in clinical settings for people with severe mental illness who are about as likely as the general population to want to quit smoking (13). However so far the primary focus of existing smoking cessation programmes in this population has been based on the use of nicotine replacement products. There is a reluctance among some clinicians to consider new treatments that may be more effective. This may be due to lack of clarity on the effectiveness of these products or concern about side-effects (14). Early reports using medication such as varenicline had raised concerns as to its effect on the mental health of individuals (15).

The aim of this new review was to compare the effectiveness and safety of existing pharmacological and behavioural programmes for smoking cessation in people with serious mental illness. Clinicians need clear information to be able to compare the relative benefits and potential side-effects of these treatments for their patients.

Methods

Criteria for considering studies for this review.

Types of studies

All randomised controlled trials.

Types of participants

Adults with schizophrenia or other types of schizophrenia-like psychosis, schizoaffective disorders, and bipolar affective disorder, irrespective of the diagnostic criteria used, age, ethnicity and sex.

Types of interventions

All interventions where the primary aim was to promote smoking cessation. We did not include studies where smoking cessation was a secondary aim, as the focus of the intervention may not have used components such as smoking advice to achieve their outcome.

Types of outcome measures

The primary outcome determined was cessation of smoking, confirmed by biochemical quantification or, if this was not available, verbal reporting by the patient. Secondary outcome measures were changes in safety (adverse effects), mental state, general functioning, and cognitive functioning.

Search Methods, and study selection

We searched the following electronic databases: Ovid MEDLINE, Embase, CINAHL, PsycINFO, Biological Abstracts on Ovid, and The Cochrane Library (July 2018). The systematic search (Appendix A) included hand searching of journals, books, cross-referencing and bulletins (e.g brief reports/ brief statement of facts). The search filter, the Cochrane Highly Sensitive Search Strategy, was used to assist in the identification of randomised trials in MEDLINE (16). No articles were excluded on the basis of language during the search.

The abstracts of studies were examined by RP. Full text of the studies that potentially met the eligibility criteria was obtained. Selection of studies was conducted by RP and any discrepancies or difficulties were discussed with co-investigators (JG and DJS). Articles were checked for duplication of the same data. Smoking cessation was measured at 3, 6, and 12 months if possible, or the closest available data to that time point. Side-effects were measured at treatment endpoint.

Data extraction and analysis

Data was extracted by one author (RP) and checked for accuracy by the second (DJS). Data was extracted onto prepared forms to include: participants and setting, location, description of the intervention, study size, methodological issues, risk of bias, results, and general comments. All analyses were conducted using Revman Manager version 5.3. We performed a PRISMA evaluation of our meta-analysis using a standard checklist of 27 items that ensure the quality of a systematic review or meta-analysis (17).

Data from intention to treat analyses were used when available or endpoint data for participants who completed the programme. For dichotomous outcomes, the fixed effects risk ratio (RR) and its 95% confidence interval (CI) were calculated using the Mantel-Haenszel method (18). If heterogeneity was found, a random effects model was used. For continuous data, the standardized mean difference (SMD) with 95% confidence intervals was calculated as the difference in means between groups divided by the pooled standard deviation. If no standard deviations were found they were calculated from standard errors, confidence intervals, or t values (19). Authors were contacted for missing data if analyses could not be completed. Statistical heterogeneity was investigated using two methods: visual inspection of the forest plots and the I^2 test. The degree of heterogeneity was categorised as follows: 0% to

40% low level of heterogeneity; 30% to 60% moderate heterogeneity; 50% to 90% substantial heterogeneity; 75% to 100%: considerable heterogeneity (19).

Sensitivity analyses were conducted to determine the effect of dosage of medication used, and whether chemical confirmation of smoking cessation affected treatment outcomes. It was planned to use funnel plots to assess publication bias graphically and Begg and Egger tests to assess the risk of bias statistically (19,20). We performed sensitivity analyses to explore the influence of each risk of bias domain on pooled treatment effects where the risk was high.

The safety outcomes extracted from included trials were the number of patients reporting any adverse event, the number of patients reporting any serious adverse event, and number of patients withdrawn from the study because of adverse events. We contacted authors to provide further information when there were insufficient data reported in the paper. Data were pooled for the identified adverse events.

Quality Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias (19). The following recommended domains were considered: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item was rated according to the level of bias and categorised into either low, high, or unclear. The category unclear indicated unclear or unknown risk of bias (19). RevMan version 5.3.5 was used to generate figures and summaries.

The quality of evidence was rated for each pooled analysis with the GRADE (grading of recommendations assessment, development and evaluation) system (19). Outcomes of interest were ranked according to their relevance for clinical decision. The quality of evidence could be downgraded to moderate, low, or very low quality evidence, depending on the presence of five factors: limitations in the design and implementation of available studies suggesting high likelihood of bias, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision of results, and high probability of publication bias. The GRADE assessment would be downgraded by one level for each factor, up to a maximum of three

levels for all factors. If there were very severe problems for any one factor (e.g. when assessing limitations in design and implementation, all studies were unconcealed, unblinded, and lost over 50% of their patients to follow-up), randomized trial evidence may fall by two levels due to that factor alone (19).

Patient and public involvement statement

No patients or public representatives were involved in the completion of this review.

Results

The electronic search identified 1377 potentially eligible reports. Eight hundred and fifty two were excluded on the basis of the title or abstract alone. We retrieved the full text of 202 articles and excluded a further 174 studies (Fig. 1). Additional papers were found from searching, cross-referencing and bulletins.

All included studies had been published between 2000 and 2016. A total of 28 studies were identified. The studies varied in their setting, size, age, and type of intervention (Table 1). Only five studies examined individuals with bipolar affective disorder (21-25). Of these, two studies were of varenicline, one of bupropion and two using behavioural techniques in both schizophrenia and bipolar disorder.

We found eight studies comparing bupropion versus control (Table 1). Six studies used high dose bupropion (300mg) and two used buproprion 150mg/d. Seven studies examined the effect of varenicline versus control, and one study nicotine replacement therapy (NRT) versus control (Table 1). One study compared high dose versus low dose NRT. Several combinations of treatment were found including two studies using high-dose bupropion and NRT, and three studies using different types of behavioural counselling.

Two studies used contingency reinforcement (CR) in addition to either NRT (26), or bupropion (27). One study offered a bespoke smoking cessation tailored to the needs of individuals with serious mental illness (25).

Studies in this review used different types of behavioural and psychological techniques such as group therapy, psychoeducation, relaxation, and advice on possible side-effects, in addition to medication for smoking cessation. The frequency of most of these therapies was weekly, with only two studies using standardised or manualised programmes (Appendix B, Table 1).

Outcomes

The main outcome measure was smoking abstinence at three and six months. Twelve month follow-up was found in four studies (Table 1). Five studies did not confirm smoking abstinence using chemical markers (Table 1).

Meta-analyses

Bupropion

Six out of eight studies provided data to combine the effects of bupropion versus control (placebo) (Table 2). The pooled risk ratio (RR) of bupropion (150mg and 300mg per day) at three months for smoking abstinence favoured bupropion against control (N=6, n=235, RR 3·96, 95% CI 1·86-8·40, p=0·0003; heterogeneity: $Chi^2 = 1·64$, df = 5, p = 0·90; $I^2 = 0\%$)(Fig. 2).

Pooled results at six months showed no significant effect (N=3, n=104, RR 2·22, 95% CI 0·52-9·47, p=0·28; heterogeneity: $Chi^2 = 0·34$, df = 2, p = 0·85; $I^2 = 0\%$) (Fig. 3). The pooled RR showed a greater likelihood of smoking cessation using the higher dose of bupropion (300mg) at three months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). No significant effect was found using doses of 150mg or 300mg per day at six months (dose 150mg: N=1, n=19, RR 2·73, 95% CI 0·12-59·57, p=0·52, dose 300mg: N=2, n=85 RR 2·09, 95% CI 0·40-10·80, p=0·38).

Bupropion was effective for smoking cessation in individuals with a diagnosis of schizophrenia at three months (N=5, n=230, RR 3·95, 95% CI 1·81-8·62, p=0·0006). No significant effect was found in bipolar disorders in one small study (N=1, n=5, RR 4·00, 95% CI 0·24-67·71, p=0·34) (Table 2).

Varenicline

Four out of seven studies provided data comparing the effect of varenicline with placebo. The pooled RR at three months for smoking abstinence favoured varencline (N=4, n=288, RR 3.56, 95% CI 1.82-6.96, p=0·0002; heterogeneity: $Chi^2 = 1.99$, df = 3, p = 0·57; $I^2 = 0\%$) (Fig. 4). Pooled analysis at six months also favoured varenicline (N=2, n=188, RR 3·69, 95% CI 1·08-12·60, p=0·04; heterogeneity: $Chi^2 = 0·22$, df = 1, p = 0·64; $I^2 = 0\%$) (Fig. 5). Varenicline was effective for smoking cessation at three months in both schizophrenia and

bipolar disorder (Table 2) (RR 3.06 vs. 4·68). However at six months no statistically significant effect was found in either disorder.

NRT

One study (Baker et al., 2006) compared NRT versus placebo at three, six, and twelve months (Fig. 6). The RR favoured NRT at three months (N=1, n=298, RR 2·74, 95% CI 1·10-6·81, p=0·03), but not at six months (n=298, RR 2·74, 95% CI 0·74-10·12, p=0·13) or twelve months (n=298, RR 5·14, 95% CI 0·61-43·44, p=0·13). Chen et al (2013) compared high versus low dose NRT, but found no significant difference at three months (n=184, RR 0·25, 95% CI 0·03-2·19, p=0·21).

Combinations of treatment included in the meta-analyses

Several studies used combinations of treatments for smoking cessation. Data from two studies were combined comparing the effects of bupropion and NRT therapy versus control, at three and six months (28,29). The pooled RR favoured the combination of treatments at three months (N=2, n=110, RR 2·88, 95% CI 1·23-6.73, p=0·01; heterogeneity: $Chi^2 = 1.72$, df = 1, p = 0·19; $I^2 = 42\%$) but favourable at six months (N=2, n=110, RR 3·86, 95% CI 1·01-14·80, p=0·05; heterogeneity: $Chi^2 = 0·56$, df = 1, p = 0·46, $I^2 = 0\%$). Of these studies, Evins et al (2007) found no significant effect (n=51, RR 2.60, 95% CI 0·55-12.19, p=0·23).

However data from all studies of bupropion using bupropion treatment alone and 2 studies combining bupropion and NRT versus placebo were favourable at 3 months (N=8, n=345, RR 3.48, 95% CI 1.98-6.11, p=0·0001; heterogeneity: $Chi^2 = 3.77$, df = 7, p = 0·81, $I^2 = 0.\%$) and 6 months (N=5, n=214, RR 3.04, 95% CI 1·14-8.09, p=0·03; heterogeneity: $Chi^2 = 1.08$, df = 4, p = 0·90, $I^2 = 0.\%$) (Fig. 7).

Behavioural and Bespoke Programmes

No meta-analysis was used due to the heterogeneity of both intervention and comparison groups. Two studies compared the effect of NRT with different types of behavioural counselling (30,31). George et al (31) found no significant effect at three months (n=45, RR 1.01, 95% CI 0·45-2·28, p=0·98) or six months (n=45, RR 0.61, 95% CI 0·14-2.67, p=0·51). Williams et al (30) compared two behavioural counselling approaches, high intensity (TANS: Treatment of Addiction to Nicotine in Schizophrenia) versus a low intensity behavioural

counselling programme (MM: Medication Management). No significant difference in levels of smoking cessation was found in both groups at three months (15·6% TANS vs. 26·2% MM, p = 0·221).

Bennett et al (24) compared a multifaceted behavioural group intervention versus a supportive group intervention and found no difference in effect at 3 months (n=95, RR 1·13, 95% CI 0·37-3.44, p=0·83). Some individuals used medication to support smoking cessation such as bupropion or NRT.

Gilbody et al (32) offered a bespoke smoking cessation programme (SCIMITAR) to individuals with serious mental illness compared to usual care. Pharmacotherapies were prescribed by the individual's General Practitioner to aid smoking cessation (BSC group: nicotine=77, bupropion=0, varenicline= 0, E-Cigarette=3, either separately or in combination, as decided by the GP). During the trial period 48% of individuals in the intervention group received pharmacotherapies compared to 19% of the controls. The odds of quitting at 12 months was higher in the BSC (bespoke smoking cessation) intervention (36% vs. 23%) but did not reach statistical significance (OR 2.94, 95% CI 0.8-10.5, p=0.1).

Combinations and single studies not included in meta-analyses

Two studies used contingency reinforcement (CR) with either NRT (26) or bupropion (27). Gallagher et al (26) found greater levels of smoking cessation verified by carbon monoxide levels with contingent reinforcement and NRT (OR 13.73, 95% CI 3.85-49.03, p=0.001) compared to CR only (OR 11.59, 95% CI 3.23-41.61, p=0.001) at week 20. Smoking cessation with contingent reinforcement and NRT (OR 7.87, 95% CI 2.72-22.79, p=0.001) at week 36 was higher compared to CR alone (OR 4.37, 95% CI 1.49-12.81, p=0.001). Tidey et al (27) found that cotinine and carbon monoxide levels significantly decreased during the study period in participants randomized to the CR condition, but not the non-CR condition.

In single studies Weinberger et al (33) showed no significant effect of topiramate on smoking abstinence but a reduction in levels of smoking. Wing et al (34) used repetitive transcranial magnetic stimulation (rTMS) to the dorsal lateral prefrontal cortex (DLPFC). They found no effect on seven day point prevalence abstinence rates or craving scores in participants.

Sensitivity analyses

Sensitivity analyses found that bupropion in a higher dose increased the likelihood of smoking cessation at three months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). Studies that did not use chemical markers to confirm smoking cessation did not substantially affect the likelihood of cessation with bupropion (N=5, n=155, RR 3·93, 95% CI 1·48-10·40, p=0.006). Chemical verification of smoking cessation was used in all studies of varenicline and NRT included in the meta-analysis in this review.

Clinical effectiveness and numbers needed to treat

The number needed to treat (NNT) for the cessation of smoking using varenicline at 3 months was 6 patients (RD 0.19, 95% CI 0.11 to 0.27) (Table 3), and 10 patients at 6 months (RD 0.1, 95% CI 0.03 to 0.18). Varenicline resulted in 24.8% of the patients in the intervention group versus 7.3% patients in the placebo group being abstinent from smoking at 3 months (at 6 months this was 13.8% vs. 4.2% respectively).

The number needed to treat for the cessation of smoking using bupropion at 3 months was 6 patients (RD 0.19, 95% CI 0.10 to 0.28)(Table 3). NRT was the least effective, requiring 15 patients to receive treatment at 3 months (RD 0.07, 95% CI 0.01 to 0.13). Combinations proved to be the least effective of treatments to aid cessation of smoking (Table 3).

Side-Effects

Side-effects from medication were reviewed systematically to allow pooling of data where possible (Table 4). Pooled analysis found that bupropion did not significantly affect positive and negative symptoms or depressive and anxiety symptoms. Serious adverse events in individual patients were noted with bupropion. Evins et al (35) found that one participant, who was randomized to bupropion, experienced hives, urticaria, and wheezing in the first week on study medication, consistent with an allergic reaction to bupropion. Weiner et al (36) found that one participant developed a rash that resolved after medication discontinued. Another patient suffered a seizure and was found to be hyponatraemic.

Pooled analysis showed a low level of side-effects with varenicline (Table 4). The main statistically significant finding was that varenicline led to problems with nausea and vomiting, but had no other significant effects on depressive symptoms, anxiety symptoms, or suicidal ideation. Serious adverse events were noted with varenicline in individual patients. Williams et al (37) found that five patients in the treatment group and three patients in the placebo group experienced suicidal thoughts. However the authors found no clear pattern between suicidal thoughts and medication assignment. One patient with depression and suicidal thoughts took an overdose of medication, while another participant took an overdose and had a seizure. Wu et al (38) found that one patient experienced suicidal ideation but this was reported to be associated with additional situational stressors rather than a medication effect.

No significant side-effects were described for programmes using nicotine replacement therapy (Table 4).

Quality assessment

We found a total of 28 studies which varied in their methodological quality, including the method of sequence generation during randomisation, sequence allocation concealment, blinding of participants, outcome assessment, and incomplete analysis of outcome data (Appendix C, Table 1). Ten studies described using intention to treat analysis for data analysis (23,26,39-46). Participants failing to complete these studies were included as non-abstinent smokers in their analysis. Only three studies described a sample size calculation (23,37,47).

We used the Cochrane Collaboration's tool (19) for assessing the risk of bias (Fig. 8). This showed that most studies described used inadequate methods of sequence generation during randomisation, blinding of participants, analysis of outcome data, poorer methods of allocation concealment and blinding of outcome assessment. We found that Smith et al (48) showed the lowest risk of bias in all domains. It is possible that studies may have used a lower risk of study design detailed in their protocol but have not fully described their methods during publication of their study.

The quality of evidence was rated for each pooled analysis with the GRADE assessment of study quality. The GRADE clinical evidence profile graded the studies of bupropion (at 3 or 6 months) and varenicline as being of very low quality (Appendix C, Tables 2-3).

Attrition was relatively low in most of the studies of varenicline and bupropion. Chengappa et al (23) found that 24 (77%) patients randomised to varenicline completed the study, and 20 (69%) the control group. Williams et al (37) found that 61 patients (72%) completed the trial of varenicline and 37 (86%) of those taking placebo. The reasons for quitting did not highlight tolerability as an issue. In studies of bupropion (49) found similar participation with 20 patients (80%) in the intervention group completing the trial and 23 (82%) the control group. In the study by Weiner et al (36), 16 patients (67%) completed the intervention of bupropion and 16 (73%) completed the control. Five of the 8 people who dropped out of the intervention arm in this study complained of side-effects. Most were mild in nature, however one patient developed a seizure in association with hyponatraemia.

Discussion

In this review we compare up-to-date findings of programmes used to aid the cessation of smoking for people with serious mental illness, with outcomes at 3, 6, and 12 months. The primary new information of this review was the effectiveness of varenicline at 3 and 6 months but the lack of evidence to support the use of bupropion and nicotine products to achieve smoking cessation for longer than 3 months. We also found that these treatments did not significantly affect the physical or mental health of the participants, with generally low levels of side-effects. Varenicline was the most successful treatment with individuals more than three times as likely to achieve smoking cessation in both schizophrenia and bipolar disorders. Problems with side-effects from nausea and vomiting were however found with varenicline. Bupropion increased the cessation of smoking in the short term (up to 3 months) compared to control, at a dose of 300mg per day, but there was a lack of evidence to support its use in achieving sustained cessation of smoking over a longer period. Only one small study was found that used NRT and this was only effective for a period of up three months. We found that combining bupropion and NRT was only effective at 3 months. However when all studies of bupropion where pooled at 6 months, both single treatments using bupropion and those

using concurrent bupropion and nicotine, a statistically significant effect was observed. Behavioural interventions on the whole showed little benefit to achieve smoking cessation. Counselling and behavioural or specialised bespoke programmes used different types of interventions to achieve smoking cessation but no consistent effect was found. Contingency reinforcement combined with NRT was found to be beneficial for achieving smoking cessation compared to contingency reinforcement alone. Comparison of the effect of behavioural or contingency programmes versus pharmacological interventions could not be made due to the heterogeneity of the active and comparison groups used.

There are strengths and limitations to the findings we have presented. We found that effective methods are available to increase rates of smoking cessation both in schizophrenia and bipolar affective disorder. However, this evidence is based on relatively few studies. We identified all randomised trials including results available at both three months and six months, and identified studies that used chemical markers to confirm smoking abstinence. A number of limitations however need to be acknowledged. Research in this field has been so far limited by only a small number and low quality of randomised controlled trials. For example, some of the conclusions from this review are based on a single study of nicotine replacement therapy. It is possible that additional studies with negative outcomes have been conducted but remain unpublished. We found generally low levels of side-effects with both bupropion use and varenicline. However, we are aware that studies comprising of larger samples are still required to fully resolve issues of whether there are a greater potential risk of suicidality and other neuropsychiatric effects with these products used for smoking cessation.

Our findings update and review the latest evidence in this field and show that successful treatment for smoking dependence is available in people with serious mental illness. However our conclusions differ in respect of the final analysis of treatments using bupropion therapy. For example, Tsoi et al (52) in a Cochrane systematic review of patients with schizophrenia (last search November 2012), found that that bupropion was effective at both 3 and 6 months. Their final conclusions differed from our own in their summary of findings of bupropion reported at 6 months. Their final analysis of bupropion studies at 6 months incorporated both studies where bupropion was used singly as the primary treatment offered and also those using

concurrent treatments of bupropion and nicotine therapy. The pooled effect of the larger sample size found a statistically significant effect of bupropion at 6 months treatment. A recent systematic review Peckham et al similarly (53) incorporated into their findings of bupropion studies that jointly used bupropion and NRT. In our review, we have reported the outcomes of bupropion separately as, firstly, we did not think it likely that clinicians would incorporate two concurrent treatments for smoking cessation, and secondly, existing meta-analysis of studies in the general population have tended to compare one product for smoking cessation solely with another (54). In a further systematic review and network meta-analysis Roberts et al (55) assessed the efficacy and tolerability of pharmacotherapy for smoking cessation and found a favourable effect of bupropion versus placebo at an end point of 6 months (or the measured closest available data to that time point). However, they pooled studies where treatment was given to some individuals at 10 or 12 weeks, and others at 6 months. Two studies measured smoking abstinence at 10 weeks (33) and 14 weeks (36), in addition to the remaining studies at 24 weeks (35,56,57). Data was not available for cessation of smoking in these two studies (33,36) at the time point of 6 months.

The results of our review are tempered by the relatively low numbers of randomised trials in this field, most trials being underpowered, and the poor quality of evidence identified by the GRADE assessment. For example, only two studies showed the effectiveness of varenicline at 6 months, and only one study was found examining nicotine products, compared to up to 70 studies comparing NRT in the general population (50). We found low levels of side-effects, with varenicline mainly causing symptoms of nausea and vomiting. We are aware that a larger study has been recently completed (51) examining the neuropsychiatric effects of varenicline, bupropion, and NRT in individuals with or without psychiatric disorders (n=4,074), comprising unipolar and bipolar disorders, anxiety disorders, personality disorders, and psychotic illness. This study did not find a greater risk of neuropsychiatric side-effects associated with these medications. Data was not available (authors contacted) for inclusion in this review and meta-analysis. The majority of studies assessed people with schizophrenia, with only five studies including bipolar affective disorder. Studies mostly comprised head to head comparisons of treatment versus placebo. It was not possible to compare the effects of, for example, bupropion versus varenicline or NRT, or to use indirect comparison methods due

to the relatively few randomised trials available. We found that a range of counselling, behavioural and bespoke methods were offered to individuals during cessation programmes. However the exact nature, standardisation, and frequency of these interventions varied considerably in their content and frequency. The details reported by the authors were not always clear, precluding a balanced comparison. It was therefore difficult to assess the relative merits or additional benefits of these counselling sessions and whether they aided successful smoking cessation.

Implications for practice

This is a new and updated systematic review directly comparing treatments to aid cessation of smoking in people with schizophrenia and bipolar affective disorders. We found that smoking cessation was more likely to be successful using varenicline in both schizophrenia and bipolar disorders with few side-effects but there was a lack of sufficient evidence to support the use of bupropion as a single treatment in the medium and long term. Treatment with varenicline resulted in 24.8% of the patients at 3 months in the varenicline group versus 7.3% in the placebo group being abstinent from smoking (at 6 months, 13.8% vs. 4.2% respectively). However, our review is notable by the low number of studies available for each smoking cessation treatment.

Notably, the evidence for nicotine products despite their frequent use in clinical environments today, only improved the cessation of smoking up to 3 months (in one small study) in contrast to studies within the general population. We would also recommend to clinicians that the duration of treatment using pharmacological agents necessary to achieve smoking cessation should be approximately 12 weeks, which is based on the length of the most successful trials found in this review. Methods promoting longer-term abstinence from smoking are however less clear and may reflect the problems of higher dependence, chronicity, and motivation to change in this population.

Implications for Research

Further research is needed to conduct well-designed studies of adequate sample size to determine the most effective method for reducing smoking in this population. Studies so far have also achieved only relatively short-term effects on sustained smoking abstinence. Tailored or focussed programmes may be needed using single or combinations of treatments to achieve better outcomes. Similarly, clearer evidence is required to understand which type of counselling or psychological intervention is the most effective. Furthermore existing smoking cessation programmes tend to rely on evidence from general population samples. It is not clear whether these are transferrable to people with serious mental illnesses with substantially higher levels of smoking and nicotine dependence. However we also need to be realistic as to the problems of change in this population who as a result of the nature of their mental illness may be less motivated or less able to change their lifestyle (62,63).

Conclusions

This review highlighted the paucity of studies found to address the high prevalence of smoking in people with SMI and identifies a need for further randomised controlled trials. The available evidence suggested that varenicline was the most effective with low levels of side-effects but there was a lack of sufficient evidence to support the use of bupropion and NRT within this group.

Declaration of Interest

RP, and DJS declared no competing interests. JG has received research funding from MRC, ESRC, NIHR, Stanley Medical Research Institute and has received donations of drugs supplies for trials from Sanofi-Aventis and GSK. He has acted as an expert witness for Dr Reddys.

Contributors' statement

Authors: RP, DJS, and JG developed the research. RP conducted the research. RP and DJS conducted the analysis. RP drafted the manuscript. DJS and JG provided input and approved the final version.

No patients or public representatives were involved in the completion of this review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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Table 1. Characteristics of Total Included Studies

Study Name	Type of Treatment	Type of Control	Country	Diagnosis	Mean Age (yrs)	Sample Size	Sex (% male)	Ethnicity (% white)	Verification of Cessation	Duration of Intervention (wks)	Final follow-up (wks)	Results available (no. of weeks)
Evins 2001	B (150)mg	Placebo	USA	S	44·1	19	61·1	88·9	Yes	12	24	12+24
Evins 2005	B (300mg)	Placebo	USA	S	45·7	53	73·6	--	Yes	12	24	12+24
George 2002	B (300mg)	Placebo	USA	S	45·7	32	56·2	62·5	Yes	10	24	10+24
Weinberger 2008	B (300mg)	Placebo	USA	BD	57·2	5	40	100	Yes	10	10	10
Weiner 2012	B (150mg)	Placebo	USA	S	48·6	46	80·5	69·9	Yes	14	14	14
Li 2009	B (300mg)	Placebo	China	S	38·0	80	--	--	No	4	8	8
Akbarpour 2010	B (300mg)	Placebo	Iran	S	47·4	32	--	--	No	8	8	8
Bloch 2010	B (300mg)	Placebo	Israel	S	43·5	32	72	--	No	14	14	14
Weiner 2011	V	Placebo	USA	S	--	9	--	--	Yes	12	12	12
Williams 2012	V	Placebo	USA	S	41·6	128	49	37·5	Yes	12	24	12+24
Shim 2011	V	Placebo	USA	S	--	60	--	--	Yes	8	8	8
Wu 2012	V	Placebo	USA	BD	--	3	--	--	Yes	10	24	10+24
Hong 2011	V	Placebo	USA	S	--	69	--	--	No	8	8	8
Chengappa 2014	V	Placebo	USA	BD	45·9	60	31·6	68·3	Yes	12	24	12+24
Smith 2016	V	Placebo	Netherlands	S	45.1	91	37	31	Yes	12	12	12
George 2000	Behav.	Motivational, psychoeducation, prevention strategies	USA	S	39·1	45	67·4	61·5	Yes	10	24	10+24
Williams 2010	Behav.	Education counselling	USA	S	45·3	76	63·1	65·5	Yes	26	52	12+24
Gilbody 2015	Behav.	Bespoke smoking cessation service with medication	UK	S + BD	46.8	97	58	83	Yes	52	52	12+24
Bennett 2015	Behav.	Supportive Group Intervention active	USA	S + BD	54.8	178	89.3	22.5	Yes	12	12	12
Evins 2007	B(300mg) +NRT 21mg)	NRT + behavioural counselling	USA	S	44·2	23	--	--	Yes	12	52	12+24+
George 2008	B (300mg) + NRT	Group behavioural therapy.	USA	S	40·2	58	60·3	48·3	Yes	10	26	10+26
Baker 2006	NRT (21mg)	Treatment as usual	Australia	S	37·2	298	52·3	--	Yes	12	52	12+24+
Chen 2013	High vs. Low NRT	Low dose NRT	Taiwan	S	45·2	184	92·9	--	Yes	12	12	12
Gallagher 2007	CR or CR+NRT	Minimal intervention control	USA	S	42·8	180	52·3	75·7	Yes	16	36	20+36
Tidey 2011	CR	Placebo +/- Bupropion	USA	S	44·9	52	72	74	Yes	3	4	4
Weinberger 2008	Topiramate	Placebo	USA	SA	--	24	50	54	Yes	8	8	8
Szombathyne 2010	Naltrexone	Placebo	USA	S	--	--	--	--	No	12	12	12
Wing 2010	TMS	Treatment as usual	USA	S	--	13	--	--	Yes	9	9	9

Abbreviations: B=Bupropion; V=Varenicline; Behav.=Behavioural Therapy/ Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation; S=Schizophrenia: SA=Schizoaffective Disorder; BD=Bipolar Affective Disorder.

Table 2 Meta-Analysis Comparison: Risk Ratio of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies (available data)	No. of participants	Risk Ratio [95% CI]	p value
Total Meta-Analysis				
Bupropion	6	n=235	3·96 [1·86 to 8·40]	0·0003
Varenicline	4	n=288	3.56 [1.82 to 6.96]	0·0002
NRT	1	n=298	2·74 [1·10 to 6·81]	0·03
B + NRT	2	n=110	2·39 [1·14 to 5·00]	0·02
NRT/Behav.Coun.	1	n=45	0·99 [0·44 to 2·23]	0·98
High/ Low NRT	1	n=184	0·25 [0·03 to 2·19]	0·21
Schizophrenia				
Bupropion	5	n=230	3·95 [1·81 to 8·62]	0·0006
Varenicline	3	n=228	3.06 [1.32 to 7.10]	0·009
Bipolar Disorder				
Bupropion	1	n=5	4·00 [0·24 to 67·71]	0·34
Varenicline	1	n=60	4·68 [1·68 to 14·50]	0·008

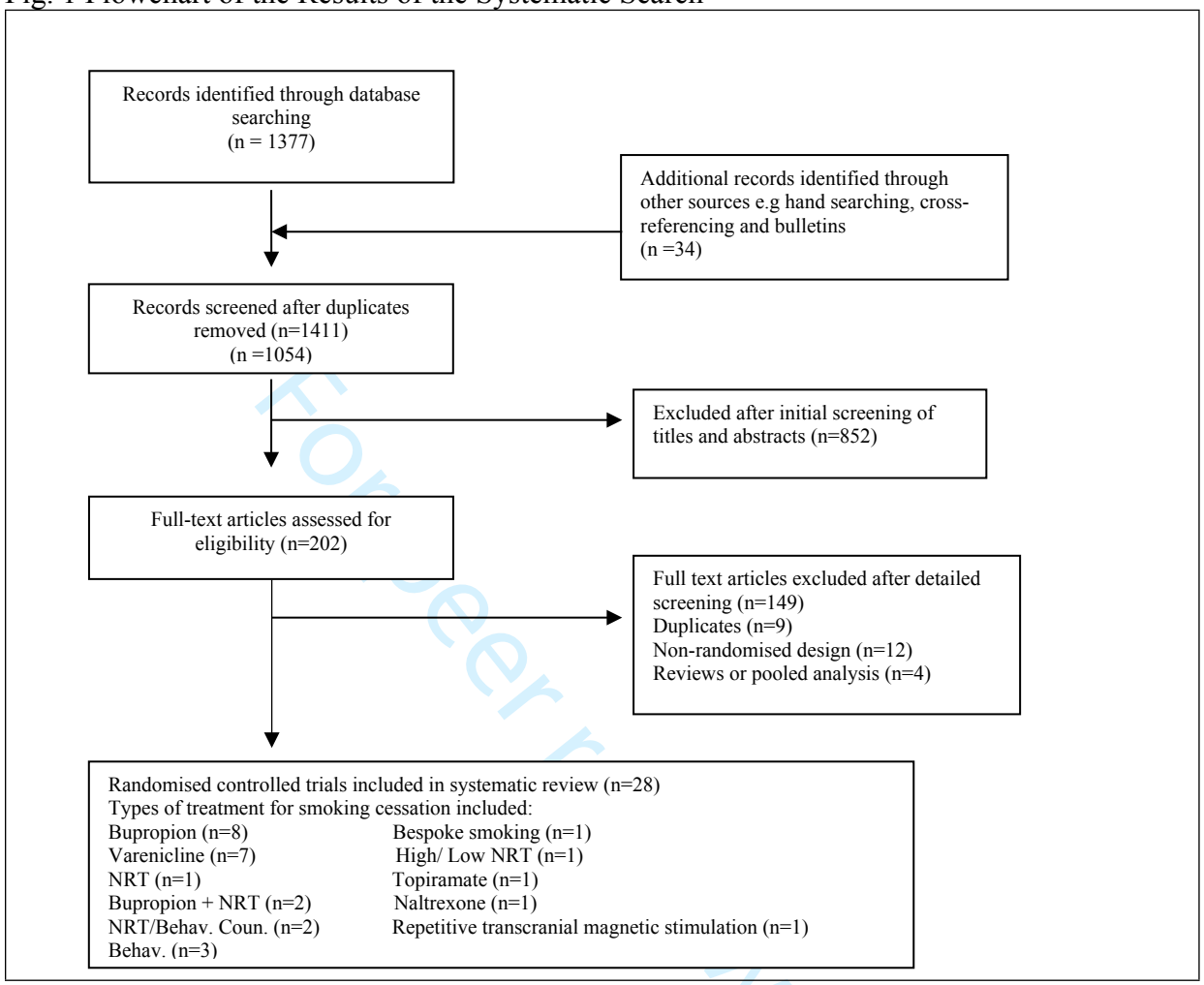
Table 3. Risk Difference (RD) and NNT of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies	No. of participants	Risk Difference (RD)	NNT	P value
Bupropion	6	235	0.19 [0.10 to 0.28]	6	<0.0001
Varenicline	4	288	0.19 [0.11 to 0.27]	6	<0.00001
NRT	1	298	0.07 [0.01 to 0.13]	15	0.02
Bupropion+NRT	2	110	0.20 [0.05 to 0.36]	5	0.006
NRT/Behav. Coun.	1	45	0.00 [-0.28 to 0.29]	--	0.98
High/ Low NRT	1	184	-0.03 [-0.08 to 0.01]	34	0.17

Table 4. Smoking Cessation Side-Effects of Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical Result	p value
Bupropion				
Positive	2	n=85	SMD -0·24 [-0·66 to -0·19]	p=0·28
Negative	2	n=85	SMD -0·15 [-0·58 to -0·27]	p=0·48
Depressive	2	n=85	SMD -0·17 [-0·59 to -0·26]	p=0·44
Anxiety	1	n=53	SMD 0·18 [-0·36 to -0·72]	p=0·52
Varenicline				
Headache	3	n=188	RR 0·71 [0·45 to 1·13]	p=0·15
Sleep Problem	4	n=288	RR 1·25 [0.77 to 2.03]	p=0·37
Nausea/ Vomiting	4	n=288	RR 1·66 [1.23 to 2.24]	p=0·0009
Diarrhoea	2	n=188	RR 1·15 [0·38 to -3·49]	p=0·80
Depression	2	n=188	RR 1·72 [0·67 to -4·45]	p=0·26
Anxiety	2	n=188	RR 0·88 [0·29 to -2·66]	p=0·82
Suicidal Ideation	2	n=188	RR 1·05 [0·33 to 3·41]	p=0·93
NRT				
Depressive	1	n=246	SMD -0·13 [-0·38 to -0·12]	p=0·31
Anxiety	1	n=212	SMD -0·05 [-0·32 to -0·22]	p=0·72

Fig. 1 Flowchart of the Results of the Systematic Search



Abbreviations: B=Bupropion; V=Varenicline; Behav.=Behavioural Therapy/ Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation

Fig. 2 Effect of Smoking Abstinence Bupropion 3 months

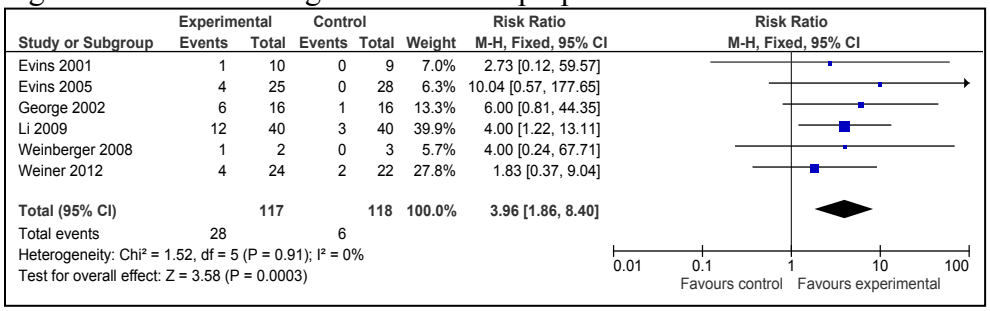


Fig. 3 Effect of Smoking Abstinence Bupropion 6 months

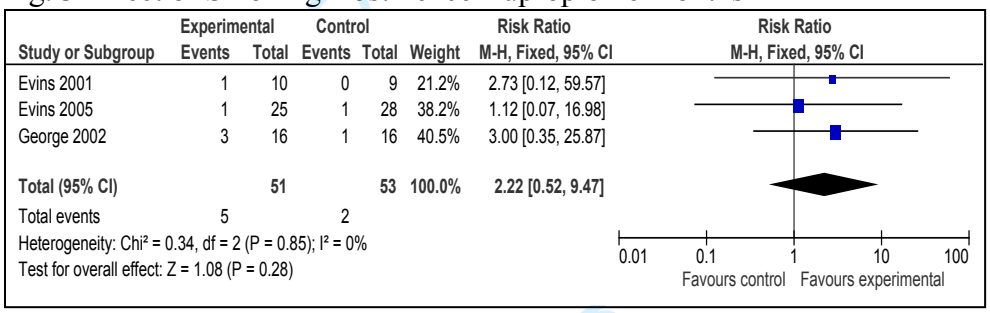


Fig. 4 Effect of Smoking Abstinence Varenicline 3 months

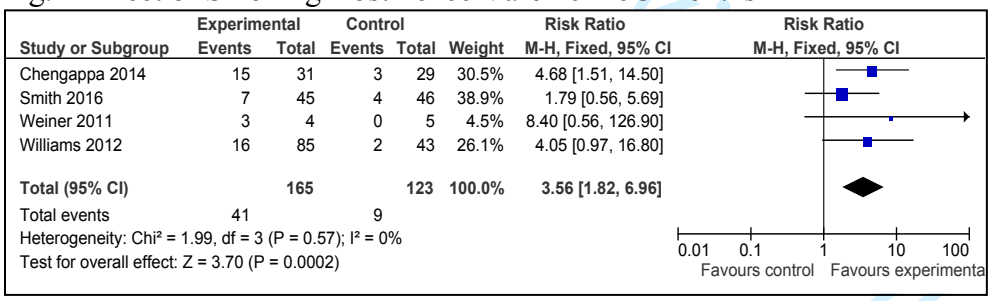


Fig. 5 Effect of Smoking Abstinence Varenicline 6 months

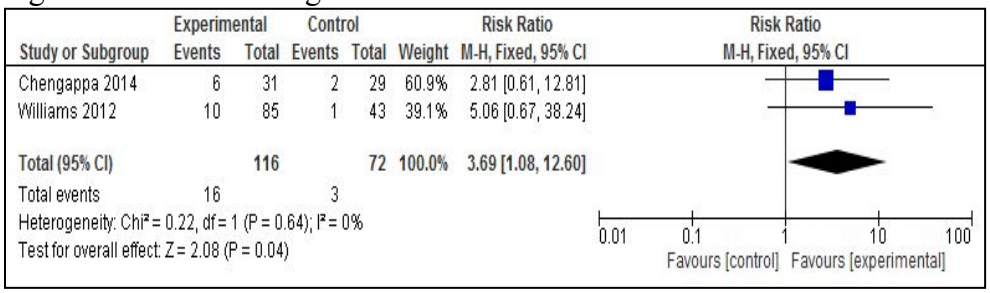


Fig. 6 Effect of Smoking Abstinence NRT 3 months

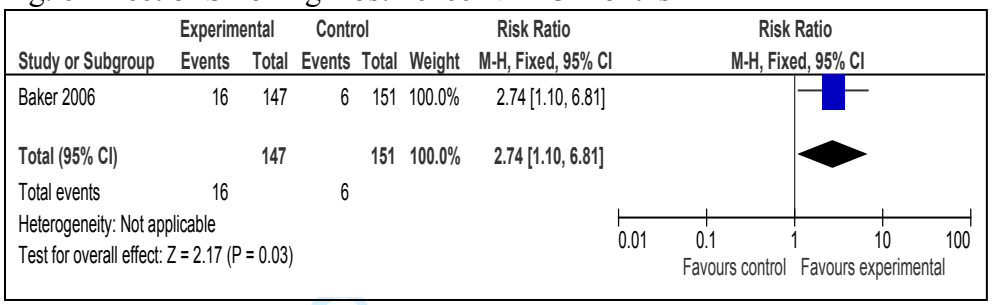
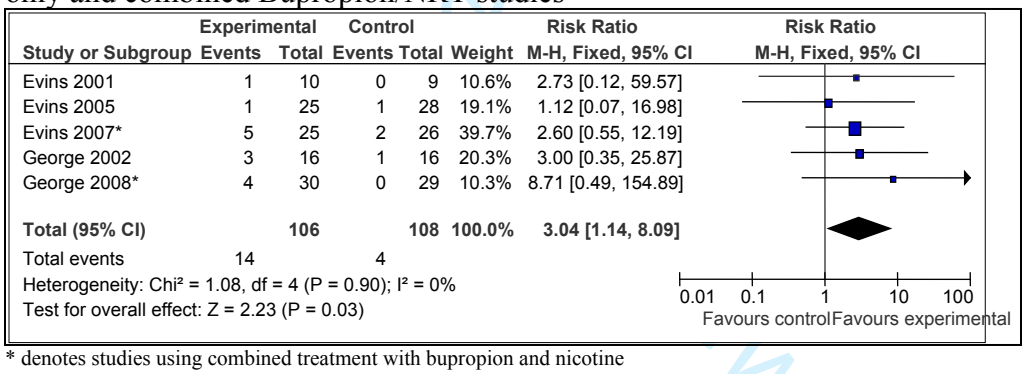
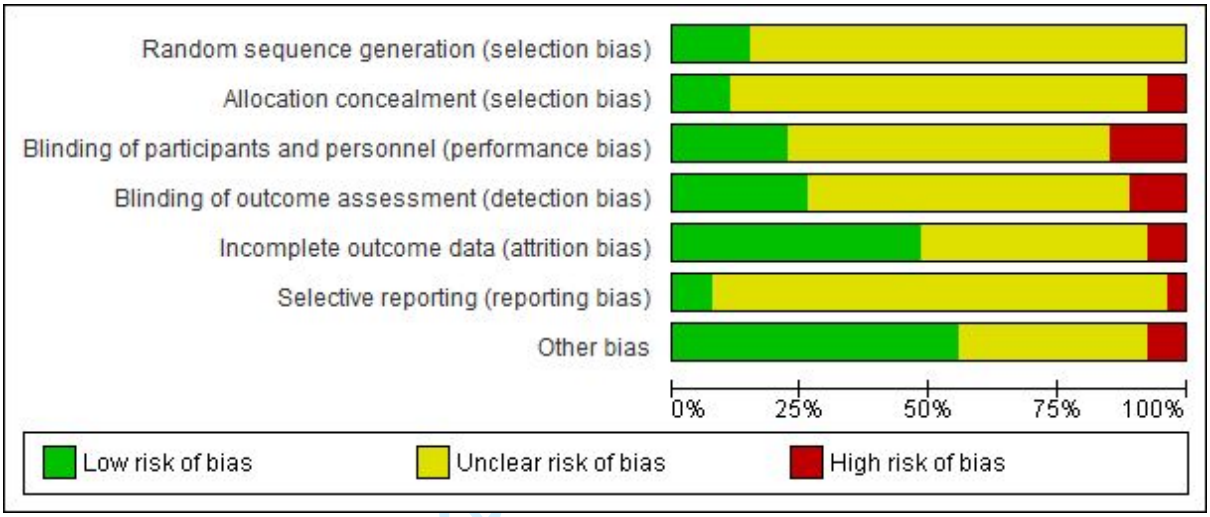


Fig. 7 Effect of Smoking Abstinence Bupropion 6 months with Bupropion only and combined Bupropion/NRT studies



* denotes studies using combined treatment with bupropion and nicotine

Fig. 8 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Appendix A

Summary

Search Strategy

1. exp schizophrenia/
2. psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. chronic psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp schizoaffective disorder/
5. exp bipolar affective disorder/
6. 1 or 2 or 3 or 4 or 5
7. exp smoking/
8. cigarettes.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. nicotine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. exp nicotine replacement therapy/
11. nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. nicotine inhaler.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. bupropion.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

14. exp smoking cessation/
15. transdermal nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. varenicline.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17. galantamine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18. atomoxetine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp smoking abstinence/
21. smoking reduction.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. cotinine levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23. carbon monoxide levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 20 or 21 or 22 or 23
25. 6 and 19 and 24
26. 6 and 19

Appendix B

Table 1. Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Evins 2001	CBT both groups	Nine weekly 1-h group sessions both groups
Evins 2005	CBT both groups	12-week, 12-session group of CBT. CBT program was delivered from a written manual adapted for patients with schizophrenia from American Heart Association and American Lung Association materials
George 2002	Group Session	Smoking cessation group therapy included motivational enhancement therapy (weeks 1–3) and psychoeducation, social skills training, and relapse-prevention strategies (weeks 4–10) for a total of 10 weeks. Sessions were of 60-min duration. Subjects attended weekly group therapy appointments and weekly research assessments on separate days.
Weinberger 2008	Group behavioural therapy	Participants received weekly sessions of manualised group behavioural therapy
Weiner 2012	Group Support programme	9 week structured programme increase awareness of smoking habits, relaxation, quit plan, and managing high risk situations, problems of weight gain etc.
Li 2009	Not available	Not available
Akbarpour 2010	No additional programme	No additional programme
Bloch 2010	CBT both groups	14 week, 15 session group programme. Emphasised education, motivation, encouragement, problem solving strategies, coping with triggers, behavioural tasks cognitive reconstruction. Self-esteem and self-efficacy.
Weiner 2011	Individual smoking cessation counselling	All participants received individual smoking cessation counseling based on the American Lung Association, Freedom from Smoking Program.
Williams 2012	Individual smoking cessation counselling	One to one smoking counselling. Approx. 4 weekly visits with additional phone contact.
Shim 2011	Not described	Not described
Wu 2012	Weekly meetings for verification for medication pick-up and assessment	Weekly meetings for verification for medication pick-up and assessment
Hong 2011	No counselling	Baseline, week 2,8,10 meetings. Smoking cessation counselling was also not implemented, other than encouraging smoking cessation as routine clinical practice,
Chengappa 2014	Weekly CBT	Weekly visits. 15 minutes of each visit given up for smoking counselling. CBT using published CBT for Smoking Cessation, Perkins et al,2008.
Smith 2016	Weekly counselling	All subjects received brief (5–10 minute) cigarette smoking prevention counselling at each weekly study visit using a structured program which provided different written information supplemented by verbal counselling at weekly visits.
George 2000	2 types of behavioural therapy	Group 1: The American Lung Association group participated in a standard 7-week manualized behavioural group therapy program and were seen for supportive group counselling during the remaining three weekly group sessions. Group 2: The specialized schizophrenia smoking cessation program included 3 weeks of motivational enhancement therapy (weeks 1 through 3) and seven weeks of psychoeducation, social skills training, and relapse prevention strategies (weeks 4 through 10).
Williams 2010	2 types behavioural therapy	TANS: a high-intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks. MM: a moderate intensity treatment of 9 sessions (20 minutes) over 26 weeks. MM consisted of nine sessions focused on quitting smoking that occurred over 26 weeks. Medication compliance and education about nicotine replacement therapy (NRT) are emphasized throughout, and there are

	sections on monitoring psychiatric symptoms and understanding medication interactions with tobacco.

Table 1 (contd.) Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Gilbody 2015	Bespoke smoking cessation programme and usual care	1st appointment made with Smoking Cessation practitioner, then follow-up at 1 and 6 months interview/phone/postal questionnaires by trial researchers. 12 month follow-up and study end meeting with researcher. Support sessions specifically adapted for patients with SMI.
Bennett 2015	Multifaceted behavioral group intervention or a supportive group intervention	24 twice weekly group meetings using either group therapy, goal setting, social and low financial reinforcement versus an active comparison group using supportive group, discussion of issues around smoking, barriers and confidence.
Evins 2007	NRT + behavioural counselling	Participants attended a 12-session, 1-hour, weekly smoking cessation group programme 15,17 with 3 to 7 participants led by a psychologist with tobacco treatment specialist training.
George 2008	Behavioural therapy intervention and control groups	10 weekly sessions of manualised group behavioural therapy.
Baker 2006	Treatment as usual	Eight individual 1-hour sessions of motivational interviewing and cognitive behaviour therapy plus nicotine replacement therapy, in addition to treatment as usual and provision of booklets for smoking cessation
Chen 2013	Low dose NRT + psychoeducation	6 sessions of smoking cessation psychoeducation
Gallagher 2007	Three groups, CR, CR +NRT, Self-quit. Education and motivational support to three groups	Visits were once per week for weeks 1 - 4, every other week for weeks 6-12, and once per month for weeks 16-24, with a final follow-up visit at week 36. Collective measures scheduled for each visit, offering tobacco and cessation-related education as well as motivational support.
Tidey 2011	CR with monetary reward	End of programme offered participants who expressed interest in smoking cessation were referred to local agencies and given self-help resources from the American Lung Association.
Weinberger 2008	No behavioural intervention	Visits at baseline and at Weeks 4 and 8 (end of study). No behavioural intervention.
Szombathyne 2010	Motivational enhancement therapy	3 times per week visits for 12 weeks. All patients received weekly motivational enhancement therapy addressing alcohol use.
Wing 2010	Behavioural counselling	Weekly behavioural counselling.

Abbrev. CR=Contingency Reinforcement, NRT=Nicotine Replacement Therapy

Appendix C

Table 1. Risk of bias summary by author

Study	Sequence Generation	Allocation Concealment	Blinding of personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other threats to validity
Akbarpour 2010	Unclear	High	Low	High	Unclear	Unclear	Unclear
Baker 2006	Unclear	Low	Unclear	Low	Low	Low	Low
Bennett 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bloch 2010	Unclear	High	Unclear	High	Unclear	Unclear	Low
Chen 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Chengappa 2014	Unclear	Unclear	Low	Low	Low	Unclear	Low
Evins 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Evins 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Evins 2007	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Gallagher 2007	Unclear	Unclear	High	High	Low	Unclear	Unclear
George 2000	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
George 2002	Unclear	Unclear	Low	Low	Low	Unclear	Low
George 2008	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Hong 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Li 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gilbody 2015	Low	Low	High	Unclear	Low	Unclear	Low
Shim 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Smith 2016	Low	Low	Low	Low	Low	Low	Low
Szombathyne 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Tidey 2011	Low	Unclear	Low	Low	Low	Unclear	Unclear
Weinberger 2008	Unclear	Unclear	Unclear	Unclear	High	High	High
Weinberger 2008[b]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Weiner 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Weiner 2012	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Williams 2010	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Williams 2012	Low	Unclear	Low	Low	Low	Low	Low
Wing 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wu 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Appendix C

Table 2. GRADE clinical evidence profile for bupropion compared to control at 3 and 6 months.

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion	Control	Risk Ratio (95% CI)	
6	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	28/117 (23.9%)	6/118 (5.1%)	**RR 3.96** (1.86 to 8.40)	⊕◯◯◯ VERY LOW
3	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	5/51 (9.8%)	2/53 (3.8%)	**RR 2.22** (0.52 to 9.47)	⊕◯◯◯ VERYLOW

Table 3. GRADE clinical evidence profile for varenicline compared to control at 3 and 6 months

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Control	Risk Ratio (95% CI)	
4	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	41/165 (24.8%)	9/123 (7.3%)	**RR 3.56** (1.82 to 6.96)	⊕◯◯◯ VERY LOW
2	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	16/116 (13.8%)	3/72 (4.2%)	**RR 3.69** (1.08 to 12.60)	⊕◯◯◯ VERY LOW

BMJ Open

Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027389.R1
Article Type:	Research
Date Submitted by the Author:	25-Mar-2019
Complete List of Authors:	Pearsall, Robert; Department of Psychiatry, Monklands Hospital, Smith, Daniel; University of Glasgow, Institute of Health and Wellbeing Geddes, John; University of Oxford, Department of Psychiatry
Primary Subject Heading:	Mental health
Secondary Subject Heading:	Smoking and tobacco, Mental health
Keywords:	Smoking cessation, Serious mental illness, varenicline, nicotine replacement, bupropion

Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials.

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Keyword: Smoking Cessation, Smoking reduction, Serious mental illness, Physical health.

Abstract

Objective

Smoking in people with serious mental illness is a major public health problem and contributes to significant levels of morbidity and mortality. To determine the efficacy of methods used to aid smoking cessation in people with serious mental illness.

Method

A systematic review and meta-analysis of randomised controlled trials to compare the effectiveness and safety of pharmacological and behavioural programmes for smoking cessation in people with serious mental illness.

Results

Twenty-eight randomised controlled trials were identified. Varenicline increased the likelihood of smoking cessation at both 3 months (RR 3.56, 95% CI 1.82-6.96, p=0.0002) and at 6 months (RR 3·69, 95% CI 1·08-12·60, p=0.04). Bupropion was effective at 3 months (RR 3·96, 95% CI 1·86-8·40, p=0.0003) especially at high dose, but there was no evidence of effect at 6 months (RR 2·22, 95% CI 0·52-9·47, p=0·28). In one small study nicotine therapy proved effective at increasing smoking cessation up to a period of 3 months. Bupropion used in conjunction with NRT showed more effect than single use.

Behavioural and bespoke interventions showed little overall benefit. Side-effects were found to be low.

Conclusion

The new information of this review was the effectiveness of varenicline for smoking cessation at both 3 and 6 months and the lack of evidence to support the use of both bupropion and nicotine products for sustained abstinence longer than 3 months. Overall the review found relatively few studies in this population.

Strengths and limitations of the study

- This study systematically reviewed all pharmacological and behavioural interventions to promote smoking cessation in people with serious mental illness.
- We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the strength and quality of the evidence.
- We reviewed and identified evidence that would be valuable and relevant to clinical practice.
- Research in this field was limited by a small number and low quality of randomised controlled trials.
- We recommended that studies with larger sample sizes are needed particularly to compare the relative effects of one smoking treatment versus another.

Introduction

Smoking in people with serious mental illness continues to be a major public health problem with levels of smoking remaining as high as 70% (1-3), compared to about 20% in the general population (4). Smoking contributes to the high levels of morbidity and mortality in this population (5) with mortality rates continuing to remain around twice those found in the general population, with high levels of cardiovascular and respiratory disease (1,6,7). Individuals with serious mental illness tend to have smoked for longer periods compared with other groups and are commonly classed as heavy smokers, smoking more than 25 cigarettes per day (8). They often start before the onset of their illness, are younger than non-smokers, and more of them are male (9). Generally they prefer cigarettes high in nicotine and more frequently smoke cigarettes down to the very end (10). Increased nicotine intake per cigarette is associated with more intense cigarette puffing contributing to the higher serum nicotine levels, approximately 1.3 times those in non-mentally ill controls (11,12). The effect of this greater uptake of nicotine may lead to higher than expected levels of nicotine dependence and withdrawal symptoms, even with moderate amounts of smoking (11).

There is therefore an urgent need to develop and evaluate smoking cessation interventions that work in clinical settings for people with severe mental illness who are about as likely as the general population to want to quit smoking (13). However so far the primary focus of existing smoking cessation programmes in this population has been based on the use of nicotine replacement products. There is a reluctance among some clinicians to consider new treatments that may be more effective. This may be due to lack of clarity on the effectiveness of these products or concern about side-effects (14). Early reports using medication such as varenicline had raised concerns as to its effect on the mental health of individuals (15).

The aim of this new review was to compare the effectiveness and safety of existing pharmacological and behavioural programmes for smoking cessation in people with serious mental illness. Clinicians need clear information to be able to compare the relative benefits and potential side-effects of these treatments for their patients.

Methods

Criteria for considering studies for this review.

Types of studies

All randomised controlled trials.

Types of participants

Adults with schizophrenia or other types of schizophrenia-like psychosis, schizoaffective disorders, and bipolar affective disorder, irrespective of the diagnostic criteria used, age, ethnicity and sex.

Types of interventions

We only included interventions where the primary aim of the study was to achieve smoking cessation.

Types of outcome measures

We used the strictest definition of abstinence, that is, preferring sustained over point prevalence abstinence and using biochemically validated rates where available. However if this was not available the best alternative would be used. When both outcomes were available, we considered sustained abstinence to be a superior clinical marker of abstinence. Secondary outcome measures were changes in safety (adverse effects), mental state, general functioning, and cognitive functioning.

Search Methods, and study selection

We searched the following electronic databases: Ovid MEDLINE, Embase, CINAHL, PsycINFO, Biological Abstracts on Ovid, and The Cochrane Library (last search, July 2018). The systematic search (Appendix A) included hand searching of journals, books, cross-referencing and bulletins (e.g brief reports/ brief statement of facts). The search filter, the Cochrane Highly Sensitive Search Strategy, was used to assist in the identification of randomised trials in MEDLINE (16). No articles were excluded on the basis of language during the search.

The abstracts of studies were examined by RP. Full text of the studies that potentially met the eligibility criteria was obtained. Selection of studies was conducted by RP and any discrepancies or difficulties were discussed with co-investigators (JG and DJS). Articles

were checked for duplication of the same data. Smoking cessation was measured at 3, 6, and 12 months if possible, or the closest available data to that time point. Side-effects were measured at the available data endpoints at 3, 6, and 12 months, if possible.

Data extraction and analysis

Data was extracted by one author (RP) and checked for accuracy by the second (DJS). Data was extracted onto prepared forms to include: participants and setting, location, description of the intervention, study size, methodological issues, risk of bias, results, and general comments. All analyses were conducted using Revman Manager version 5.3. We performed a PRISMA evaluation of our meta-analysis using a standard checklist of 27 items that ensure the quality of a systematic review or meta-analysis (17).

Data from intention to treat analyses were used when available or endpoint data for participants who completed the programme. For dichotomous outcomes, the fixed effects risk ratio (RR) and its 95% confidence interval (CI) were calculated using the Mantel-Haenszel method (18). If heterogeneity was found, a random effects model was used. For continuous data, the standardized mean difference (SMD) with 95% confidence intervals was calculated as the difference in means between groups divided by the pooled standard deviation. If no standard deviations were found they were calculated from standard errors, confidence intervals, or t values (19). Authors were contacted for missing data if analyses could not be completed. Statistical heterogeneity was investigated using two methods: visual inspection of the forest plots and the I^2 test. The degree of heterogeneity was categorised as follows: 0% to 40% low level of heterogeneity; 30% to 60% moderate heterogeneity; 50% to 90% substantial heterogeneity; 75% to 100%: considerable heterogeneity (19).

Sensitivity analyses were conducted to determine the effect of dosage of medication used, and whether chemical confirmation of smoking cessation affected treatment outcomes. It was planned to use funnel plots to assess publication bias graphically and Begg and Egger tests to assess the risk of bias statistically (19,20). We performed sensitivity analyses to explore the influence of each risk of bias domain on pooled treatment effects where the risk was high.

The safety outcomes extracted from included trials were the number of patients reporting any adverse event, the number of patients reporting any serious adverse event, and number of patients withdrawn from the study because of adverse events. We contacted authors to provide further information when there were insufficient data reported in the paper. Data were pooled for the identified adverse events.

Quality Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias (19). The following recommended domains were considered: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item was rated according to the level of bias and categorised into either low, high, or unclear. The category unclear indicated unclear or unknown risk of bias (19). RevMan version 5.3.5 was used to generate figures and summaries.

The quality of evidence was rated for each pooled analysis with the GRADE (grading of recommendations assessment, development and evaluation) system (19). Outcomes of interest were ranked according to their relevance for clinical decision.

Patient and public involvement statement

No patients or public representatives were involved in the completion of this review.

Results

The electronic search identified 1377 potentially eligible reports. Eight hundred and fifty two were excluded on the basis of the title or abstract alone. We retrieved the full text of 202 articles and excluded a further 174 studies (Fig. 1, Appendix B). Additional papers were found from searching, cross-referencing and bulletins.

All included studies had been published between 2000 and 2016. A total of 28 studies were identified. The studies varied in their setting, size, age, and type of intervention (Table 1). Only five studies examined individuals with bipolar affective disorder (21-25). Of these, two studies were of varenicline, one of bupropion and two using behavioural techniques in both schizophrenia and bipolar disorder. We found eight studies comparing bupropion versus placebo (Table 1).

Table 1. Characteristics of Total Included Studies

Study Name	Type of Treatment	Type of Control	Country	Diagnosis	Mean Age (yrs)	Sample Size	Sex (% male)	Ethnicity (% white)	Verification of Cessation	Duration of Intervention (wks)	Final follow-up (wks)	Results available (no. of weeks)
Evins 2001	Bupropion (150)mg	Placebo	USA	S	44·1	19	61·1	88·9	Yes	12	24	12+24
Evins 2005	Bupropion (300mg)	Placebo	USA	S	45·7	53	73·6	--	Yes	12	24	12+24
George 2002	Bupropion (300mg)	Placebo	USA	S	45·7	32	56·2	62·5	Yes	10	24	10+24
Weinberger 2008	Bupropion (300mg)	Placebo	USA	BD	57·2	5	40	100	Yes	10	10	10
Weiner 2012	Bupropion (150mg)	Placebo	USA	S	48·6	46	80·5	69·9	Yes	14	14	14
Li 2009	Bupropion (300mg)	Placebo	China	S	38·0	80	--	--	No	4	8	8
Akbarpour 2010	Bupropion (300mg)	Placebo	Iran	S	47·4	32	--	--	No	8	8	8
Bloch 2010	Bupropion (300mg)	Placebo	Israel	S	43·5	32	72	--	No	14	14	14
Weiner 2011	Varenicline	Placebo	USA	S	--	9	--	--	Yes	12	12	12
Williams 2012	Varenicline	Placebo	USA	S	41·6	128	49	37·5	Yes	12	24	12+24
Shim 2011	Varenicline	Placebo	USA	S	--	60	--	--	Yes	8	8	8
Wu 2012	Varenicline	Placebo	USA	BD	--	3	--	--	Yes	10	24	10+24
Hong 2011	Varenicline	Placebo	USA	S	--	69	--	--	No	8	8	8
Chengappa 2014	Varenicline	Placebo	USA	BD	45·9	60	31·6	68·3	Yes	12	24	12+24
Smith 2016	Varenicline	Placebo	Netherlands	S	45.1	91	37	31	Yes	12	12	12
George 2000	Behavioural Therapy	Motivational, psychoeducation, prevention strategies	USA	S	39·1	45	67·4	61·5	Yes	10	24	10+24
Williams 2010	Behavioural Therapy	Education counselling	USA	S	45·3	76	63·1	65·5	Yes	26	52	12+24 +52
Gilbody 2015	Bespoke smoking cessation service with medication	Placebo	UK	S + BD	46.8	97	58	83	Yes	52	52	12+24 +52
Bennett 2015	Behavioural Therapy	Supportive Group Intervention active	USA	S + BD	54.8	178	89.3	22.5	Yes	12	12	12
Evins 2007	Bupropion (300mg) +NRT 21mg)	NRT (21mg) + behavioural counselling	USA	S	44·2	23	--	--	Yes	12	52	12+24+52
George 2008	Bupropion (300mg) + NRT(21mg)	Group behavioural therapy.	USA	S	40·2	58	60·3	48·3	Yes	10	26	10+26
Baker 2006	NRT (21mg nicotine)	Treatment as usual	Australia	S	37·2	298	52·3	--	Yes	12	52	12+24+52
Chen 2013	High dose NRT (31.2mg nicotine)	Low dose NRT (20.8mg nicotine)	Taiwan	S	45·2	184	92·9	--	Yes	12	12	12
Gallagher 2007	CR or CR+NRT (21mg)	Minimal intervention control	USA	S	42·8	180	52·3	75·7	Yes	16	36	20+36
Tidey 2011	CR	Placebo +/- Bupropion	USA	S	44·9	52	72	74	Yes	3	4	4
Weinberger 2008	Topiramate	Placebo	USA	SA	--	24	50	54	Yes	8	8	8
Szombathyne 2010	Naltrexone	Placebo	USA	S	--	--	--	--	No	12	12	12
Wing 2010	TMS	Treatment as usual	USA	S	--	13	--	--	Yes	9	9	9

Abbreviations: B=Bupropion; Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation; S=Schizophrenia: SA=Schizoaffective Disorder; BD=Bipolar Affective Disorder.

Six studies used 300mg of bupropion per day and two used bupropion 150mg/d. Seven studies examined the effect of varenicline versus placebo, and one study nicotine replacement therapy (NRT) versus placebo (Table 1).

Outcomes

The main outcome measure was smoking abstinence at three and 6 months. Twelve month follow-up was found in four studies (Table 1). Five studies did not confirm smoking abstinence using chemical markers (Table 1).

Meta-analyses

Bupropion

Six out of eight studies provided data to combine the effects of bupropion versus placebo (Table 2). The pooled risk ratio (RR) of bupropion (150mg and 300mg per day) at 3 months for smoking abstinence favoured bupropion against placebo (N=6, n=235, RR 3·96, 95% CI 1·86-8·40, p=0·0003; heterogeneity: $Chi^2 = 1·64$, df = 5, p = 0·90; $I^2 = 0\%$)(Fig. 2).

Pooled results at 6 months of bupropion versus placebo showed no effect (N=3, n=104, RR 2·22, 95% CI 0·52-9·47, p=0·28; heterogeneity: $Chi^2 = 0·34$, df = 2, p = 0·85; $I^2 = 0\%$) (Fig. 3). The pooled RR showed a greater likelihood of smoking cessation using a dose of 300mg per day of bupropion at 3 months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). No effect was found using doses of 150mg or 300mg per day at 6 months (dose 150mg: N=1, n=19, RR 2·73, 95% CI 0·12-59·57, p=0·52, dose 300mg: N=2, n=85 RR 2·09, 95% CI 0·40-10·80, p=0·38).

Bupropion was effective for smoking cessation in individuals with a diagnosis of schizophrenia at 3 months (N=5, n=230, RR 3·95, 95% CI 1·81-8·62, p=0·0006). No effect was found in bipolar disorders in one small study (N=1, n=5, RR 4·00, 95% CI 0·24-67·71, p=0·34) (Table 2).

Varenicline

Four out of seven studies provided data comparing the effect of varenicline with placebo. The pooled RR at 3 months for smoking abstinence favoured varencline (N=4, n=288, RR 3.56, 95% CI 1.82-6.96, p=0·0002; heterogeneity: $Chi^2 = 1.99$, df = 3, p = 0·57; $I^2 = 0\%$) (Fig. 4). Pooled analysis at 6 months also favoured varenicline (N=2, n=188, RR 3·69,

95% CI 1·08-12·60, p=0·04; heterogeneity: Chi² = 0·22, df = 1, p = 0·64; I² = 0%) (Fig. 5). Varenicline was effective for smoking cessation at 3 months in both schizophrenia and bipolar disorder (Table 2) (RR 3.06 vs. 4·68). However at 6 months no effect was found in either disorder.

Table 2 Meta-Analysis Comparison: Risk Ratio of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies (available data)	No. of participants	Risk Ratio [95% CI]	p value
Total Meta-Analysis				
Bupropion	6	n=235	3·96 [1·86 to 8·40]	0·0003
Varenicline	4	n=288	3.56 [1.82 to 6.96]	0·0002
NRT	1	n=298	2·74 [1·10 to 6·81]	0·03
B + NRT	2	n=110	2·39 [1·14 to 5·00]	0·02
NRT/Behav.Coun.	1	n=45	0·99 [0·44 to 2·23]	0·98
High/ Low NRT	1	n=184	0·25 [0·03 to 2·19]	0·21
Schizophrenia				
Bupropion	5	n=230	3·95 [1·81 to 8·62]	0·0006
Varenicline	3	n=228	3.06 [1.32 to 7.10]	0·009
Bipolar Disorder				
Bupropion	1	n=5	4·00 [0·24 to 67·71]	0·34
Varenicline	1	n=60	4·68 [1·68 to 14·50]	0·008

NRT

One study (Baker et al., 2006) compared NRT versus placebo at three, six, and twelve months (Fig. 6). The RR favoured NRT at 3 months (N=1, n=298, RR 2·74, 95% CI 1·10-6·81, p=0·03), but not at 6 months (n=298, RR 2·74, 95% CI 0·74-10·12, p=0·13) or twelve months (n=298, RR 5·14, 95% CI 0·61-43·44, p=0·13). Chen et al (2013) compared high versus low dose NRT, but found no difference in effect at 3 months (n=184, RR 0·25, 95% CI 0·03-2·19, p=0·21).

Combinations of treatment included in the meta-analyses

Several studies used combinations of treatments for smoking cessation. Data from two studies were combined comparing the effects of bupropion and NRT therapy versus

placebo, at three and 6 months (26,27). The pooled RR favoured the combination of treatments at 3 months (N=2, n=110, RR 2·88, 95% CI 1·23-6.73, p=0·01; heterogeneity: $Chi^2 = 1.72$, df = 1, p = 0·19; $I^2 = 42\%$) and at 6 months (N=2, n=110, RR 3·86, 95% CI 1·01-14·80, p=0·05; heterogeneity: $Chi^2 = 0·56$, df = 1, p = 0·46, $I^2 = 0\%$). Of these studies, Evins et al (2007) found no effect (n=51, RR 2.60, 95% CI 0·55-12.19, p=0·23). However data from all studies of bupropion using bupropion treatment alone and 2 studies combining bupropion and NRT versus placebo were favourable at 3 months (N=8, n=345, RR 3.48, 95% CI 1.98-6.11, p=0·0001; heterogeneity: $Chi^2 = 3.77$, df = 7, p = 0·81, $I^2 = 0.\%$) and 6 months (N=5, n=214, RR 3.04, 95% CI 1·14-8.09, p=0·03; heterogeneity: $Chi^2 = 1.08$, df = 4, p = 0·90, $I^2 = 0.\%$) (Fig. 7).

Behavioural and Bespoke Programmes

No meta-analysis was used due to the heterogeneity of both intervention and comparison groups (Appendix C, Table 1). Two studies compared the effect of NRT with different types of behavioural counselling (28,29). George et al (29) found no effect at 3 months (n=45, RR 1.01, 95% CI 0·45-2·28, p=0·98) or 6 months (n=45, RR 0.61, 95% CI 0·14-2.67, p=0·51). Williams et al (28) compared two behavioural counselling approaches, high intensity (TANS: Treatment of Addiction to Nicotine in Schizophrenia) versus a low intensity behavioural counselling programme (MM: Medication Management). No difference in levels of smoking cessation was found in both groups at 3 months (15·6% TANS vs. 26·2% MM, p = 0·221).

Bennett et al (24) compared a multifaceted behavioural group intervention versus a supportive group intervention and found no difference in effect at 3 months (n=95, RR 1·13, 95% CI 0·37-3.44, p=0·83). Some individuals used medication to support smoking cessation such as bupropion or NRT.

Gilbody et al (30) offered a bespoke smoking cessation programme (SCIMITAR) to individuals with serious mental illness compared to usual care. Pharmacotherapies were prescribed by the individual's General Practitioner to aid smoking cessation (BSC group: nicotine=77, bupropion=0, varenicline= 0, E-Cigarette=3, either separately or in combination, as decided by the GP). During the trial period 48% of individuals in the intervention group received pharmacotherapies compared to 19% of the placebo group. The odds of quitting at 12 months was higher in the BSC (bespoke smoking cessation)

intervention (36% vs. 23%) but did not reach statistical significance (OR 2.94, 95% CI 0.8-10.5, p=0.1).

Sensitivity analyses

Sensitivity analyses found that bupropion at a dose of 300mg per day increased the likelihood of smoking cessation at 3 months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). Studies that did not use chemical markers to confirm smoking cessation did not substantially affect the likelihood of cessation with bupropion (N=5, n=155, RR 3·93, 95% CI 1·48-10·40, p=0.006). Chemical verification of smoking cessation was used in all studies of varenicline and NRT included in the meta-analysis in this review.

Clinical effectiveness and numbers needed to treat

The number needed to treat (NNT) for the cessation of smoking using varenicline at 3 months was 6 patients (RD 0.19, 95% CI 0.11 to 0.27) (Table 3), and 10 patients at 6 months (RD 0.1, 95% CI 0.03 to 0.18). Varenicline resulted in 24.8% of the patients in the intervention group versus 7.3% patients in the placebo group being abstinent from smoking at 3 months (at 6 months this was 13.8% vs. 4.2% respectively).

The number needed to treat for the cessation of smoking using bupropion at 3 months was 6 patients (RD 0.19, 95% CI 0.10 to 0.28)(Table 3). NRT was the least effective, requiring 15 patients to receive treatment at 3 months (RD 0.07, 95% CI 0.01 to 0.13). Combinations proved to be the least effective of treatments to aid cessation of smoking (Table 3).

Side-Effects

Side-effects from medication were reviewed systematically to allow pooling of data where possible (Table 4). Pooled analysis found that bupropion did not affect positive and negative symptoms or depressive and anxiety symptoms. Serious adverse events in individual patients were noted with bupropion. Evins et al (31) found that one participant, who was randomized to bupropion, experienced hives, urticaria, and wheezing in the first week on study medication, consistent with an allergic reaction to bupropion. Weiner et al (32) found that one participant developed a rash that resolved after medication discontinued. Another patient suffered a seizure and was found to be hyponatraemic.

Table 3. Risk Difference (RD) and NNT of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies	No. of participants	Risk Difference (RD)	NNT	P value
Bupropion	6	235	0.19 [0.10 to 0.28]	6	<0.0001
Varenicline	4	288	0.19 [0.11 to 0.27]	6	<0.00001
NRT	1	298	0.07 [0.01 to 0.13]	15	0.02
Bupropion+NRT	2	110	0.20 [0.05 to 0.36]	5	0.006
NRT/Behav. Coun.	1	45	0.00 [-0.28 to 0.29]	--	0.98
High/ Low NRT	1	184	-0.03 [-0.08 to 0.01]	34	0.17

Pooled analysis showed a low level of side-effects with varenicline (Table 4). The main finding was that varenicline led to problems with nausea and vomiting, but had no other effects on depressive symptoms, anxiety symptoms, or suicidal ideation. Serious adverse events were noted with varenicline in individual patients. Williams et al (33) found that five patients in the treatment group and three patients in the placebo group experienced suicidal thoughts. However the authors found no clear pattern between suicidal thoughts and medication assignment. One patient with depression and suicidal thoughts took an overdose of medication, while another participant took an overdose and had a seizure. Wu et al (34) found that one patient experienced suicidal ideation but this was reported to be associated with additional situational stressors rather than a medication effect.

No notable side-effects were described for programmes using nicotine replacement therapy (Table 4).

Quality assessment

We found a total of 28 studies which varied in their methodological quality, including the method of sequence generation during randomisation, sequence allocation concealment, blinding of participants, outcome assessment, and incomplete analysis of outcome data (Appendix D, Table 1). Ten studies described using intention to treat analysis for data analysis (23,35-43). Participants failing to complete these studies were included as non-abstinent smokers in their analysis. Only three studies described a sample size calculation (23,33,44). The interpretation of funnel plots (Fig. 8) was limited due to the small number

of pooled results in this analysis, and similarly Egger tests were not preformed due to the low number of available studies.

Table 4. Smoking Cessation Side-Effects of Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical Result	p value
Bupropion				
Positive	2	n=85	SMD -0·24 [-0·66 to -0·19]	p=0·28
Negative	2	n=85	SMD -0·15 [-0·58 to -0·27]	p=0·48
Depressive	2	n=85	SMD -0·17 [-0·59 to -0·26]	p=0·44
Anxiety	1	n=53	SMD 0·18 [-0·36 to -0·72]	p=0·52
Varenicline				
Headache	3	n=188	RR 0·71 [0·45 to 1·13]	p=0·15
Sleep Problem	4	n=288	RR 1·25 [0.77 to 2.03]	p=0·37
Nausea/ Vomiting	4	n=288	RR 1·66 [1.23 to 2.24]	p=0·0009
Diarrhoea	2	n=188	RR 1·15 [0·38 to -3·49]	p=0·80
Depression	2	n=188	RR 1·72 [0·67 to -4·45]	p=0·26
Anxiety	2	n=188	RR 0·88 [0·29 to -2·66]	p=0·82
Suicidal Ideation	2	n=188	RR 1·05 [0·33 to 3·41]	p=0·93
NRT				
Depressive	1	n=246	SMD -0·13 [-0·38 to -0·12]	p=0·31
Anxiety	1	n=212	SMD -0·05 [-0·32 to -0·22]	p=0·72

We used the Cochrane Collaboration's tool (19) for assessing the risk of bias (Fig. 9). This showed that most studies described used inadequate methods of sequence generation during randomisation, blinding of participants, analysis of outcome data, poorer methods of allocation concealment and blinding of outcome assessment. We found that Smith et al (45) showed the lowest risk of bias in all domains.

The quality of evidence was rated for each pooled analysis with the GRADE assessment of study quality. The GRADE clinical evidence profile graded the studies of bupropion (at 3 or 6 months) and varenicline as being of very low quality (Appendix D, Tables 2-3).

Discussion

In this review we compare up-to-date findings of programmes used to aid the cessation of smoking for people with serious mental illness, with outcomes at 3, 6, and 12 months. The primary new information of this review was the effectiveness of varenicline at 3 and 6 months but the lack of evidence to support the use of bupropion and nicotine products to achieve smoking cessation for longer than 3 months. We also found that these treatments did not notably affect the physical or mental health of the participants, with generally low levels of side-effects. Varenicline was the most successful treatment with individuals more than three times as likely to achieve smoking cessation in both schizophrenia and bipolar disorders. Problems with side-effects from nausea and vomiting were however found with varenicline. Bupropion increased the cessation of smoking in the short term (up to 3 months) compared to placebo, at a dose of 300mg per day, but there was a lack of evidence to support its use in achieving sustained cessation of smoking over a longer period. Only one small study was found that used NRT and this was only effective for a period of up 3 months. We found that combining bupropion and NRT was only effective at 3 months. However when all studies of bupropion where pooled at 6 months, both single treatments using bupropion and those using concurrent bupropion and nicotine, stronger evidence was observed. Behavioural interventions on the whole showed little benefit to achieve smoking cessation. Counselling and behavioural or specialised bespoke programmes used different types of interventions to achieve smoking cessation but no consistent effect was found. Contingency reinforcement combined with NRT was found to be beneficial for achieving smoking cessation compared to contingency reinforcement alone. Comparison of the effect of behavioural or contingency programmes versus pharmacological interventions could not be made due to the heterogeneity of the active and comparison groups used.

There are strengths and limitations to the findings we have presented. We found that effective methods are available to increase rates of smoking cessation both in schizophrenia and bipolar affective disorder. However, this evidence is based on relatively few studies. We identified all randomised trials including results available at both 3 months and 6 months, and identified studies that used chemical markers to confirm smoking abstinence. A number of limitations however need to be acknowledged. Research in this field has been so far limited by only a small number and low quality of randomised controlled trials. For example, some of the conclusions from this review are based on a single study of nicotine replacement therapy. It is possible that additional studies with

negative outcomes have been conducted but remain unpublished. We found generally low levels of side-effects with both bupropion use and varenicline. However, we are aware that studies comprising of larger samples are still required to fully resolve issues of whether there are a greater potential risk of suicidality and other neuropsychiatric effects with these products used for smoking cessation.

Our findings update and review the latest evidence in this field and show that successful treatment for smoking dependence is available in people with serious mental illness. However our conclusions differ in respect of the final analysis of treatments using bupropion therapy. For example, Tsoi et al (46) in a Cochrane systematic review of patients with schizophrenia (last search November 2012), found that that bupropion was effective at both 3 and 6 months. Their final conclusions differed from our own in their summary of findings of bupropion reported at 6 months. Their final analysis of bupropion studies at 6 months incorporated both studies where bupropion was used singly as the primary treatment offered and also those using concurrent treatments of bupropion and nicotine therapy. The pooled effect of the larger sample size found stronger evidence to support the use of bupropion at 6 months treatment. A recent systematic review Peckham et al similarly (47) incorporated into their findings of bupropion studies that jointly used bupropion and NRT. In our review, we have reported the outcomes of bupropion separately as, firstly, we did not think it likely that clinicians would incorporate two concurrent treatments for smoking cessation, and secondly, existing meta-analysis of studies in the general population have tended to compare one product for smoking cessation solely with another (48).

The results of our review are tempered by the relatively low numbers of randomised trials in this field, most trials being underpowered, and the poor quality of evidence identified by the GRADE assessment. For example, only two studies showed the effectiveness of varenicline at 6 months, and only one study was found examining nicotine products, compared to up to 70 studies comparing NRT in the general population (49). We found low levels of side-effects, with varenicline mainly causing symptoms of nausea and vomiting. We are aware that a larger study has been recently completed (50) examining the neuropsychiatric effects of varenicline, bupropion, and NRT in individuals with or without psychiatric disorders (n=4,074), comprising unipolar and bipolar disorders, anxiety disorders, personality disorders, and psychotic illness. This study did not find a greater risk

of neuropsychiatric side-effects associated with these medications. Data was not available (authors contacted) for inclusion in this review and meta-analysis.

Implications for practice

This is a new and updated systematic review directly comparing treatments to aid cessation of smoking in people with schizophrenia and bipolar affective disorders. We found that smoking cessation was more likely to be successful using varenicline in both schizophrenia and bipolar disorders with few side-effects but there was a lack of sufficient evidence to support the use of bupropion as a single treatment in the medium and long term. Treatment with varenicline resulted in 24.8% of the patients at 3 months in the varenicline group versus 7.3% in the placebo group being abstinent from smoking (at 6 months, 13.8% vs. 4.2% respectively). However, our review is notable by the low number of studies available for each smoking cessation treatment.

Implications for Research

Further research is needed to conduct well-designed studies of adequate sample size to determine the most effective method for reducing smoking in this population. Studies so far have also achieved only relatively short-term effects on sustained smoking abstinence. Tailored or focussed programmes may be needed using single or combinations of treatments to achieve better outcomes. Similarly, clearer evidence is required to understand which type of counselling or psychological intervention is the most effective. Furthermore existing smoking cessation programmes tend to rely on evidence from general population samples. It is not clear whether these are transferrable to people with serious mental illnesses with substantially higher levels of smoking and nicotine dependence. However we also need to be realistic as to the problems of change in this population who as a result of the nature of their mental illness may be less motivated or less able to change their lifestyle (51,52).

Conclusions

This review highlighted the paucity of studies found to address the high prevalence of smoking in people with SMI and identifies a need for further randomised controlled trials. The available evidence suggested that varenicline was the most effective with low levels of side-effects but there was a lack of sufficient evidence to support the use of bupropion and NRT within this group.

Declaration of Interest

RP, and DJS declared no competing interests. JG has received research funding from MRC, ESRC, NIHR, Stanley Medical Research Institute and has received donations of drugs supplies for trials from Sanofi-Aventis and GSK. He has acted as an expert witness for Dr Reddys.

Contributors' statement

Authors: RP, DJS, and JG developed the research. RP conducted the research. RP and DJS conducted the analysis. RP drafted the manuscript. DJS and JG provided input and approved the final version.

No patients or public representatives were involved in the completion of this review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability statement

The data is pooled results from a systematic review and meta-analysis of treatments for smoking cessation. The pooled results are available in our paper as a supplementary file and are available for review with details of the included studies.

Summary of Figures:

Fig. 1 Flowchart of the Results of the Systematic Search

Fig. 2 Pooled effect of bupropion versus placebo for smoking cessation at 3 months

Fig. 3 Pooled effect of bupropion versus placebo for smoking cessation at 6 months

Fig. 4 Pooled effect of varenicline versus placebo for smoking cessation at 3 months

Fig. 5 Pooled effect of varenicline versus placebo for smoking cessation at 6 months

Fig. 6 Pooled effect of NRT versus placebo for smoking cessation at 3 months

Fig. 7 Pooled effect of bupropion only and combined bupropion/NRT studies versus placebo for smoking cessation at 6 months

Fig. 8 Funnel Plots of Smoking Cessation studies.

Fig. 9 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix A: Summary Search Strategy

Appendix B: Excluded Studies

Appendix C: Types of Counselling in Smoking Cessation Programme

Appendix D: Table 1. Risk of bias summary by author

Appendix D: Table 2. GRADE clinical evidence profile for bupropion compared to control at 3 and 6 months.

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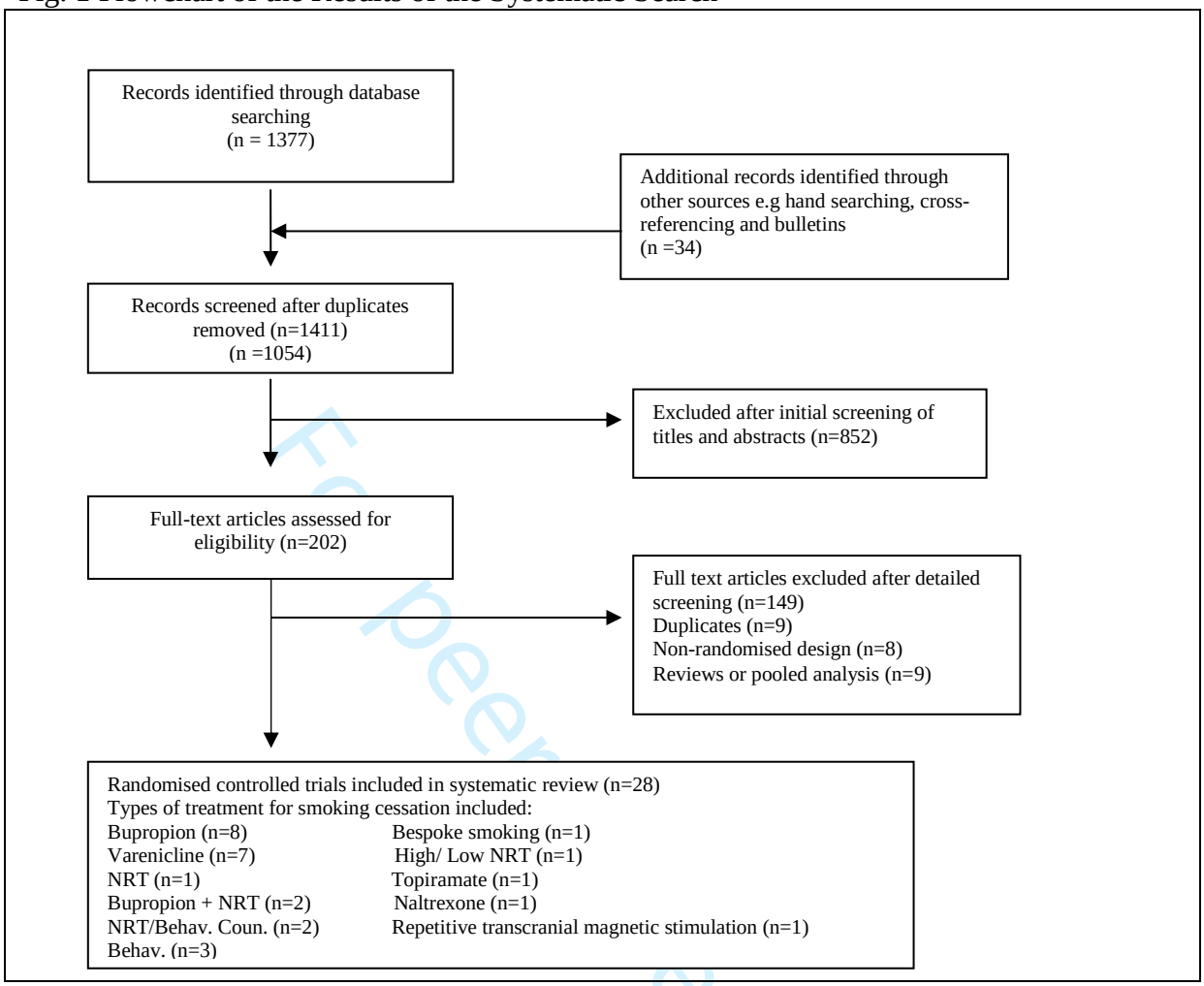
Fig. 1 Flowchart of the Results of the Systematic Search



Abbreviations: B=Bupropion; V=Varenicline; Behav.=Behavioural Therapy/ Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation

Fig. 2 Pooled effect of bupropion versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

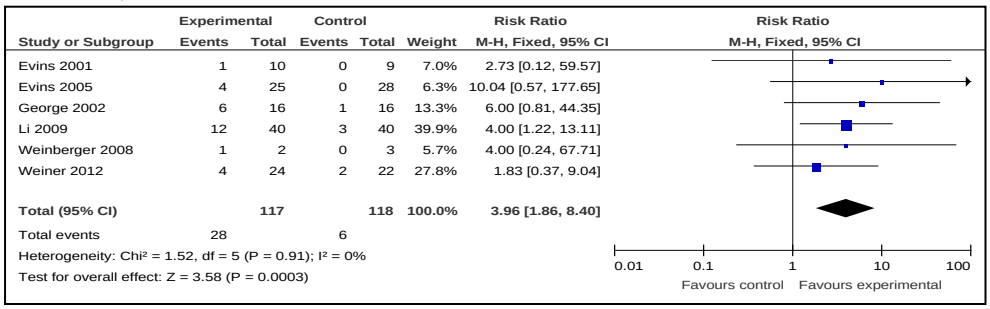


Fig. 3 Pooled effect of bupropion versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval

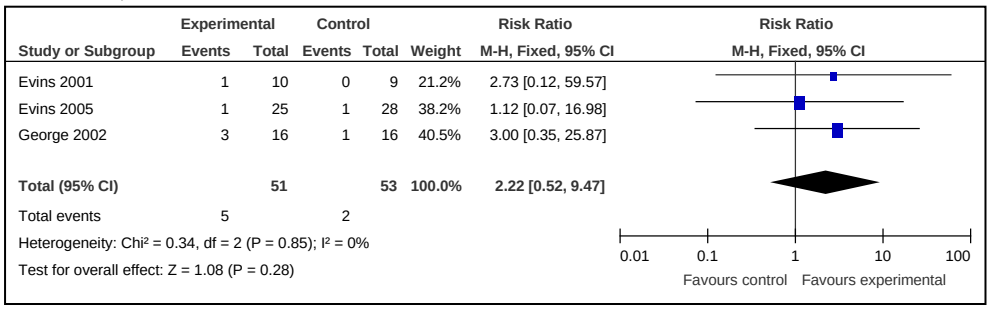


Fig. 4 Pooled effect of varenicline versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

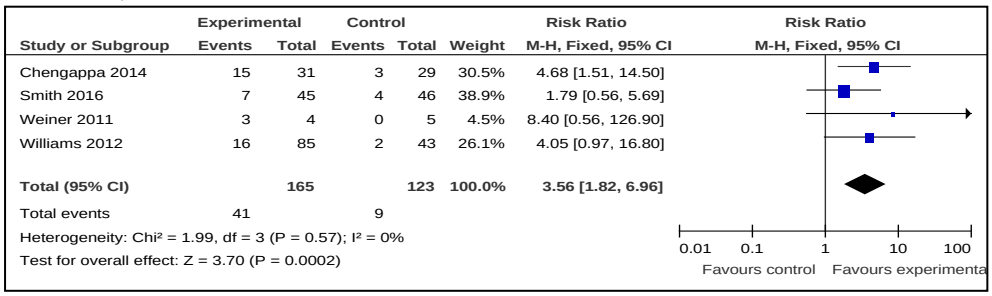


Fig. 5 Pooled effect of varenicline versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval

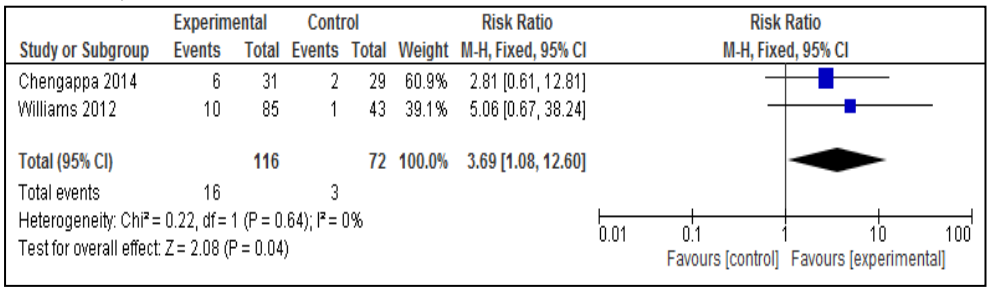


Fig. 6 Pooled effect of NRT versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

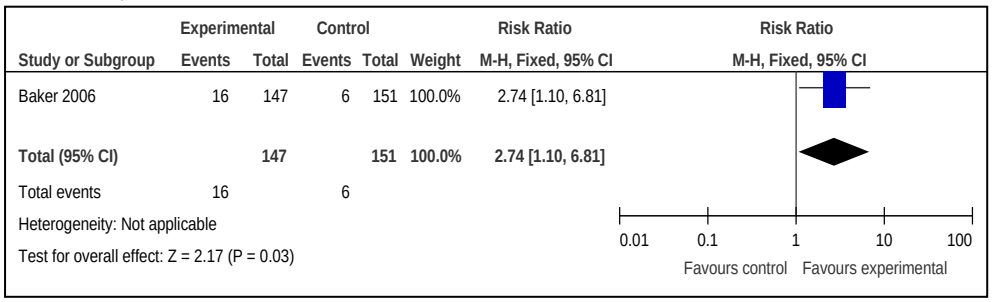
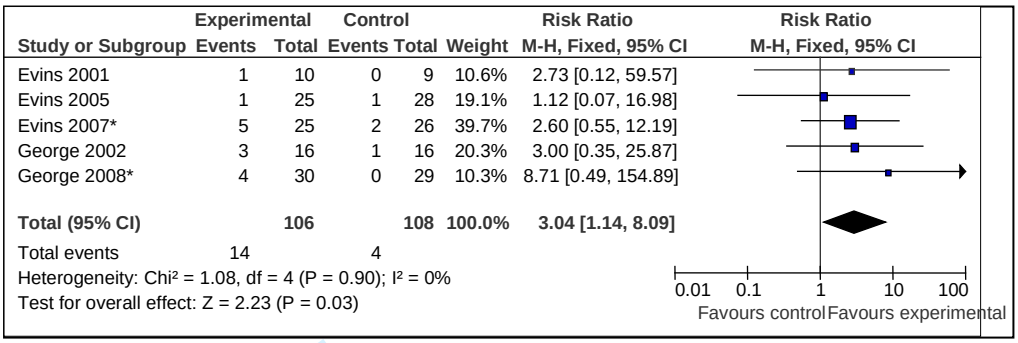


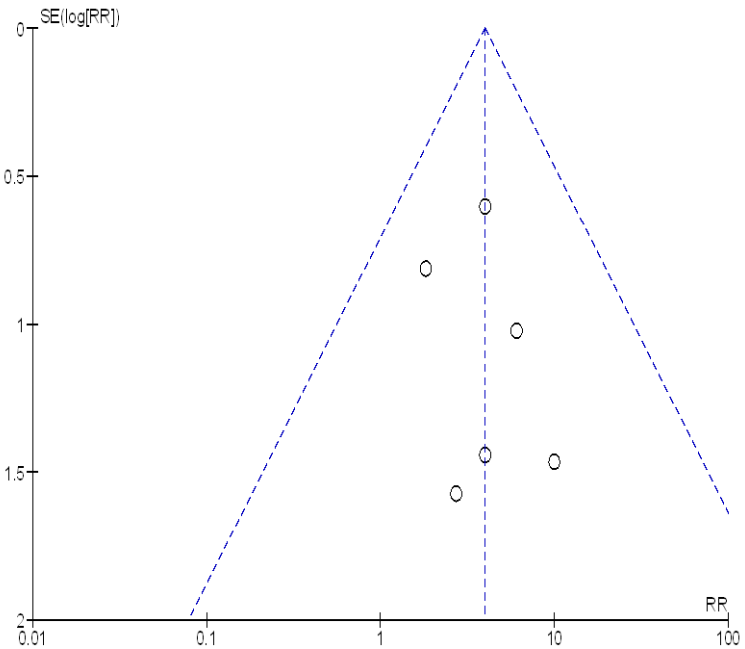
Fig. 7 Pooled effect of bupropion only and combined bupropion/NRT studies versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval



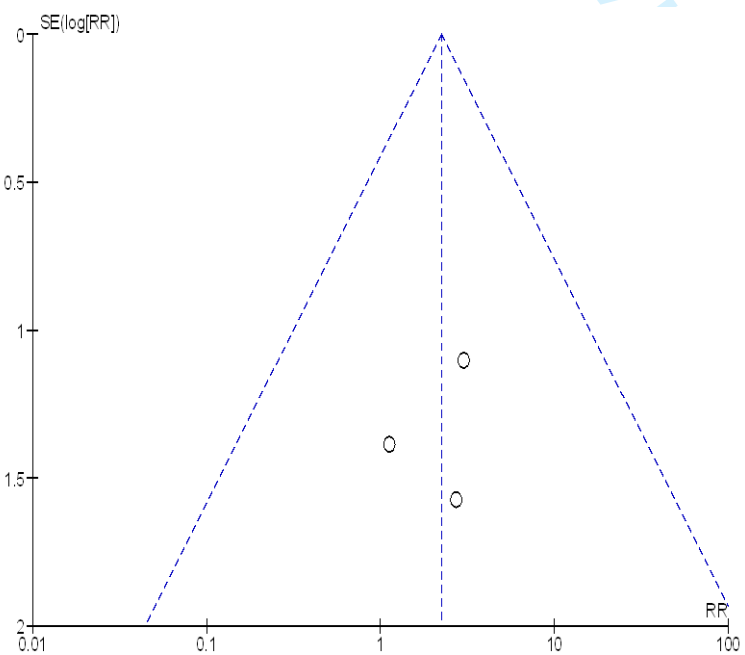
* denotes studies using combined treatment with bupropion and nicotine

Fig. 8 Funnel Plots of Smoking Cessation studies.

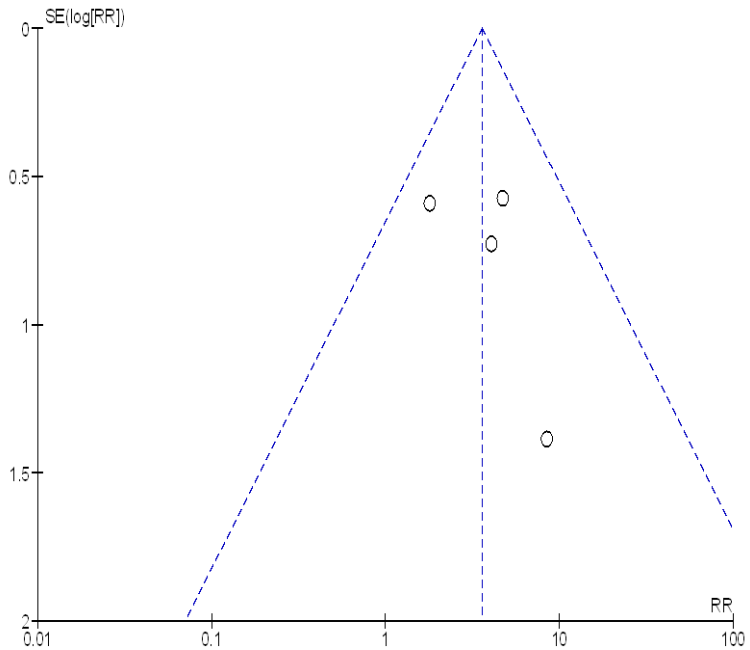
(i) Funnel plot of comparison: Bupropion 3 months.



(ii) Funnel plot of comparison: Bupropion 6 months



(iii) Funnel plot of comparison: Varenicline 3 months



(iv) Funnel plot of comparison: Varenicline 6 months

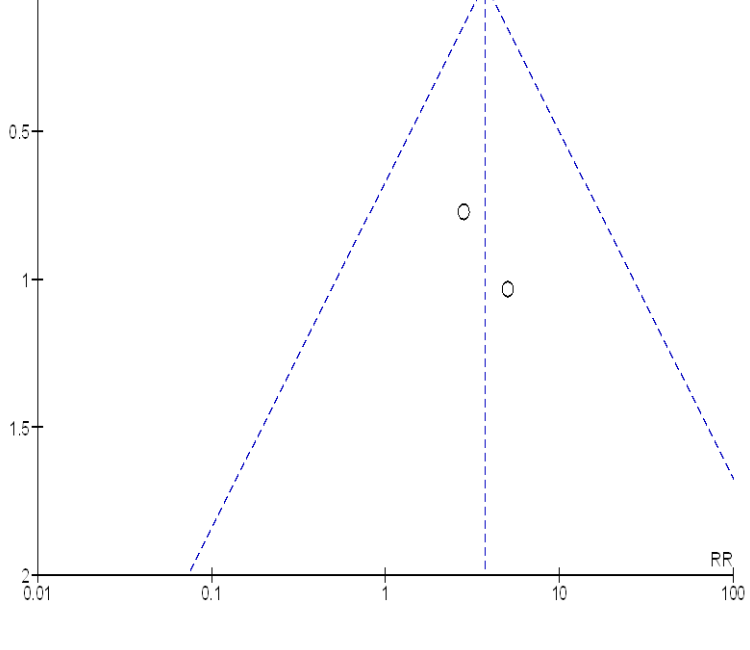
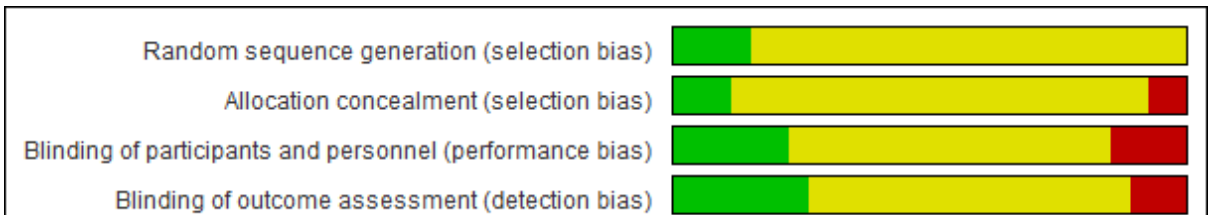


Fig. 9 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Appendix A

Summary

Search Strategy

1. exp schizophrenia/
2. psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. chronic psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp schizoaffective disorder/
5. exp bipolar affective disorder/
6. 1 or 2 or 3 or 4 or 5
7. exp smoking/
8. cigarettes.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. nicotine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. exp nicotine replacement therapy/
11. nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. nicotine inhaler.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. bupropion.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. exp smoking cessation/

15. transdermal nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. varenicline.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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18. atomoxetine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
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20. exp smoking abstinence/
21. smoking reduction.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. cotinine levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23. carbon monoxide levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 20 or 21 or 22 or 23
25. 6 and 19 and 24
26. 6 and 19

Appendix B Excluded Studies

Study Details	Reason for Exclusion
Baker 2018	Additional health interventions
Peckham 2107	Study Protocol
Baker 2011	Study Protocol
Baker 2011	Health lifestyle intervention
Aschbrenner 2018	Feasibility Study
Manhapra 2017	Non randomised
Sharma 2017	Non randomised
Brunette 2018	Web based intervention
Jimenez-Ruiz 2018	Cohort Study
Baker 2018	Healthy Living Intervention
Rogers 2017	Follow-up study non randomised
Clark 2017	Non randomised
Bakhai 2017	Non randomised
Garcia-Portilla	Non randomised
Nash 2016	Electronic health record tool
Schieder 2016	Descriptive report
Thorndike 2016	Subgroup analysis reporting weight gain
Burke 2016	Descriptive review
Wu 2016	Systematic review
Peckham 2016	Qualitative study exploration of smoking cessation problems
Roberts 2016	Systematic Review
Molero 2015	Varenicline Cohort Study
Stubbs 2015	Clinical review
Molero 2015	Varenicline Cohort Study
Thomas 2015	Varenicline Systematic Review
Bradshaw 2014	Review/ descriptive paper on smoking cessation
Howard 2013	Cohort study pregant women with mental health disorders
Filia 2014	Secondary analysis (non smoking) of intervention study
Ward 2018	Review article
Okoli 2018	Intention to engage study in smoking
Khadjesari 2017	Retrospective cohort study
Andrews 2106	Healthy living intervention
Roberts 2016	Systematic review and meta-analysis
Hamilton 2016	Before and after study
Gardner-Sood 2015	Baseline data only
Takahashi 2014	Pharmacokinetics study, secondary analysis
Dickens 2014	Smoking behaviour/ motives to quit, non-randomised
Filia 2014	Risks and benefits, non-randomised
Szatkowski 2013	Non-randomised
Brown 2013	General study
Meszaros 2013	Varenicline and alcohol addiction
Okali 2012	Smoking/ Substance misuse

Hardy 2012	Descriptive
Murray 2012	Review
Lydall 2011	Genetic factors
Brown 2011	Descriptive
Kisely 2011	Systematic review and meta-analysis
Sawa 2011	Cohort study
Prebble 2011	Case study
Brown 2011	Report
Kisely 2011	Non smoking
Pinto 2010	Smoking and general factors
Bergen 2009	Summary conference
Alhatem 2009	Varenicline side-effects. no intervention
Tait 2009	Smoking and cognitive change
Hilton 2007	Smoking and substance misuse
Dratcu 2007	Smoking clozapine and caffeine report
Doolan 2006	Review article
Prochaska 2006	Motivation in smoking
Himelhoch 2004	Smoking/ COPD prevalence
Aubin 2004	Non psychosis RCT
Li 2003	Genetics smoking
Ziedonis 2003	Discussion article
Brunette 2018	Additional diagnoses in mental illness
Baker 2018	Healthy living intervention
Travelli 2017	Cohort study
Taylor 2017	Discussion article
Schuster 2017	Cohort varenicline and CBT
Peckham 2017	Protocol
Garcia-Portilla 2016	Non-randomised
Tedeschi 2016	Mental health screening non- intervention
Cunningham 2016	Neuropsychiatric adverse events varenicline or nicotine
McGinty 2016	Discussion/ review article
Tidey 2015	Electronic cigarettes and chronic mental illness
Jackson 2015	Non-intervention
Evins 2015	Review article
Filia 2014	No comparison group
Yargic 2013	Non-English
Castle 2012	No comparison group
Hardy 2012	Diabetes risk factors
Newaz 2012	Smoking beliefs non randomised
Baker 2011	Study protocol
QOF Clinical indicators x4 2009 duplicates	No comparison
Lowe 2010	Smoking cessation on clozapine/ olanzapine treatment review
Kotov 2010	Smoking and schizophrenia association no comparison
Lawn 2002	Qualitative study
Anfang 1997	Case report
Tejedor 2018	Smoking cessation, psychosis and substance use
Roson 2017	Open label study

Manettis 2018	Nicotine receptor subtypes
Zou 2018	Cohort study
Sharma 2017	Review electronic cigarettes
Ahmed 2018	Systematic review and meta-analysis
Ignacio 2018	Cohort study
Baker 2018	Healthy living intervention in smokers
Brunette 2018	Smoking Cessation in anxiety, major depression as well as psychotic illness
Meernik 2018	No comparative group
Europena Public Health Conference	Report
Ayeyard 2018	Non mental illness RCT nicotine
Politis 2018	Open label study
Davies 2018	Varenicline cohort study
Roson 2017	Open label study
Sharma 2017	Review article
Jimenez-Ruiz 2018	Varenicline general mental health
Evins 2017	RCT but initial open label treatment Varenicline
Schuster 2017	No comparison group
Garcia-Portilla 2016	Qualitative study
Schroeder 2016	Discussion article
Thorndike 2016	Secondary analysis weight gain and CVS risk
Burke 2016	Narrative review
Kiski 2015	Systematic review and meta-analysis
Kaduri 2015	Cohort study and all psychiatric disorders
Hoeppner 2015	Pooled analysis of 2 RCTs
Evins 2014	RCT but initial open label phase
Kale 2014	Non mental illness
MacKowick 2012	Discussion article/ Review
Castle 2012	Varenicline Non comparison group health intervention
Benes 2012	Nicotinic receptors
Roberts 2016	Systematic review and network meta-analysis
Gonzalez-Blanco 2014	Open label study varenicline and nicotine patches
Englisch 2013	Systematic review and meta-analysis
Aguiar 2009	Follow-up study
Tidey 2015	Systematic review and meta-analysis
McClure 2010	Non SMI diagnosis
Weiner 2001	No comparison group
Shiina 2010	Primary effects on cognitive function
Garcia-Portilla 2013	Protocol
Sharma 2018	Practices and attitudes
Okali 2017	Retrospective analysis
Laude 2017	Non mental illness
Wu 2016	Systematic review and meta-analysis
Cunningham 2016	Retrospective cohort
Pachas 2012	Non randomisation
Tidey 2020	Before after study
Weinberger 2016	Descriptive/ Discussion

Baker 2016	RCT but initial open label Nicotine/ Varenicline/ Combined
Molero 2015	Not serious mental illness
Roberts 2018	Effect on cognitive function
Zawertailo 2017	Smoking predictors
Das 2017	Comorbid substance misuse
Laude 2017	Non mental health population
Aubin 2012	Non-randomised
McEvoy 1999	Before and after
Pachas 2012	Before and after
Gold 2018	Comorbid substance misuse
Compton 2018	Discussion
Das 2017	Comorbid substance misuse

Appendix C

Table 1. Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Evins 2001	CBT both groups	Nine weekly 1-h group sessions both groups
Evins 2005	CBT both groups	12-week, 12-session group of CBT. CBT program was delivered from a written manual adapted for patients with schizophrenia from American Heart Association and American Lung Association materials
George 2002	Group Session	Smoking cessation group therapy included motivational enhancement therapy (weeks 1–3) and psychoeducation, social skills training, and relapse-prevention strategies (weeks 4–10) for a total of 10 weeks. Sessions were of 60-min duration. Subjects attended weekly group therapy appointments and weekly research assessments on separate days.
Weinberger 2008	Group behavioural therapy	Participants received weekly sessions of manualised group behavioural therapy
Weiner 2012	Group Support programme	9 week structured programme increase awareness of smoking habits, relaxation, quit plan, and managing high risk situations, problems of weight gain etc.
Li 2009	Not available	Not available
Akbarpour 2010	No additional programme	No additional programme
Bloch 2010	CBT both groups	14 week, 15 session group programme. Emphasised education, motivation, encouragement, problem solving strategies, coping with triggers, behavioural tasks cognitive reconstruction. Self-esteem and self-efficacy.
Weiner 2011	Individual smoking cessation counselling	All participants received individual smoking cessation counseling based on the American Lung Association, Freedom from Smoking Program.
Williams 2012	Individual smoking cessation counselling	One to one smoking counselling. Approx. 4 weekly visits with additional phone contact.
Shim 2011	Not described	Not described
Wu 2012	Weekly meetings for verification for medication pick-up and assessment	Weekly meetings for verification for medication pick-up and assessment
Hong 2011	No counselling	Baseline, week 2,8,10 meetings. Smoking cessation counselling was also not implemented, other than encouraging smoking cessation as routine clinical practice,
Chengappa 2014	Weekly CBT	Weekly visits. 15 minutes of each visit given up for smoking counselling. CBT using published CBT for Smoking Cessation, Perkins et al,2008.
Smith 2016	Weekly counselling	All subjects received brief (5–10 minute) cigarette smoking prevention counselling at each weekly study visit using a structured program which provided different written information supplemented by verbal counselling at weekly visits.
George 2000	2 types of behavioural therapy	Group 1: The American Lung Association group participated in a standard 7-week manualized behavioural group therapy program and were seen for supportive group counselling during the remaining three weekly group sessions. Group 2: The specialized schizophrenia smoking cessation program included 3 weeks of motivational enhancement therapy (weeks 1 through 3) and seven weeks of psychoeducation, social skills training, and relapse prevention strategies (weeks 4 through 10).
Williams 2010	2 types behavioural therapy	TANS: a high-intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks. MM: a moderate intensity treatment of 9 sessions (20 minutes) over 26 weeks. MM consisted of nine sessions focused on quitting smoking that occurred over 26 weeks. Medication compliance and education about nicotine replacement therapy (NRT) are emphasized throughout, and there are sections on monitoring psychiatric symptoms and understanding medication interactions with tobacco.

Table 1 (contd.) Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Gilbody 2015	Bespoke smoking cessation programme and usual care	1st appointment made with Smoking Cessation practitioner, then follow-up at 1 and 6 months interview/phone/postal questionnaires by trial researchers. 12 month follow-up and study end meeting with researcher. Support sessions specifically adapted for patients with SMI.
Bennett 2015	Multifaceted behavioral group intervention or a supportive group intervention	24 twice weekly group meetings using either group therapy, goal setting, social and low financial reinforcement versus an active comparison group using supportive group, discussion of issues around smoking, barriers and confidence.
Evins 2007	NRT + behavioural counselling	Participants attended a 12-session, 1-hour, weekly smoking cessation group programme 15,17 with 3 to 7 participants led by a psychologist with tobacco treatment specialist training.
George 2008	Behavioural therapy intervention and control groups	10 weekly sessions of manualised group behavioural therapy.
Baker 2006	Treatment as usual	Eight individual 1-hour sessions of motivational interviewing and cognitive behaviour therapy plus nicotine replacement therapy, in addition to treatment as usual and provision of booklets for smoking cessation
Chen 2013	Low dose NRT + psychoeducation	6 sessions of smoking cessation psychoeducation
Gallagher 2007	Three groups, CR, CR +NRT, Self-quit. Education and motivational support to three groups	Visits were once per week for weeks 1 - 4, every other week for weeks 6-12, and once per month for weeks 16-24, with a final follow-up visit at week 36. Collective measures scheduled for each visit, offering tobacco and cessation-related education as well as motivational support.
Tidey 2011	CR with monetary reward	End of programme offered participants who expressed interest in smoking cessation were referred to local agencies and given self-help resources from the American Lung Association.
Weinberger 2008	No behavioural intervention	Visits at baseline and at Weeks 4 and 8 (end of study). No behavioural intervention.
Szombathyne 2010	Motivational enhancement therapy	3 times per week visits for 12 weeks. All patients received weekly motivational enhancement therapy addressing alcohol use.
Wing 2010	Behavioural counselling	Weekly behavioural counselling.

Abbrev. CR=Contingency Reinforcement, NRT=Nicotine Replacement Therapy

Appendix D

Table 1. Risk of bias summary by author

Study	Sequence Generation	Allocation Concealment	Blinding of personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other threats to validity
Akbarpour 2010	Unclear	High	Low	High	Unclear	Unclear	Unclear
Baker 2006	Unclear	Low	Unclear	Low	Low	Low	Low
Bennett 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bloch 2010	Unclear	High	Unclear	High	Unclear	Unclear	Low
Chen 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Chengappa 2014	Unclear	Unclear	Low	Low	Low	Unclear	Low
Evins 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Evins 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Evins 2007	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Gallagher 2007	Unclear	Unclear	High	High	Low	Unclear	Unclear
George 2000	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
George 2002	Unclear	Unclear	Low	Low	Low	Unclear	Low
George 2008	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Hong 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Li 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gilbody 2015	Low	Low	High	Unclear	Low	Unclear	Low
Shim 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Smith 2016	Low	Low	Low	Low	Low	Low	Low
Szombathyne 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Tidey 2011	Low	Unclear	Low	Low	Low	Unclear	Unclear
Weinberger 2008	Unclear	Unclear	Unclear	Unclear	High	High	High
Weinberger 2008[b]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Weiner 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Weiner 2012	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Williams 2010	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Williams 2012	Low	Unclear	Low	Low	Low	Low	Low
Wing 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wu 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Appendix D

Table 2. GRADE clinical evidence profile for bupropion compared to control at 3 and 6 months.

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion	Control	Risk Ratio (95% CI)	
6	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	28/117 (23.9%)	6/118 (5.1%)	**RR 3.96** (1.86 to 8.40)	⊕◯◯◯ VERY LOW
3	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	5/51 (9.8%)	2/53 (3.8%)	**RR 2.22** (0.52 to 9.47)	⊕◯◯◯ VERYLOW

Table 3. GRADE clinical evidence profile for varenicline compared to control at 3 and 6 months

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Control	Risk Ratio (95% CI)	
4	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	41/165 (24.8%)	9/123 (7.3%)	**RR 3.56** (1.82 to 6.96)	⊕◯◯◯ VERY LOW
2	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	16/116 (13.8%)	3/72 (4.2%)	**RR 3.69** (1.08 to 12.60)	⊕◯◯◯ VERY LOW

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7/8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7/8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

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Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-027389.R2
Article Type:	Research
Date Submitted by the Author:	23-May-2019
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Primary Subject Heading:	Mental health
Secondary Subject Heading:	Smoking and tobacco, Mental health
Keywords:	Smoking cessation, Serious mental illness, varenicline, nicotine replacement, bupropion

Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials.

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Keyword: Smoking Cessation, Smoking reduction, Serious mental illness, Physical health.

Abstract

Objective

Smoking in people with serious mental illness is a major public health problem and contributes to significant levels of morbidity and mortality. The aim of the review was to systematically examine the efficacy of methods used to aid smoking cessation in people with serious mental illness.

Method

A systematic review and meta-analysis of randomised controlled trials to compare the effectiveness and safety of pharmacological and behavioural programmes for smoking cessation in people with serious mental illness. Electronic databases were searched for trials to July 2018. We used the Cochrane Collaboration's tool for assessing the risk of bias.

Results

Twenty-eight randomised controlled trials were identified. Varenicline increased the likelihood of smoking cessation at both 3 months (RR 3.56, 95% CI 1.82-6.96, p=0.0002) and at 6 months (RR 3·69, 95% CI 1·08-12·60, p=0.04). Bupropion was effective at 3 months (RR 3·96, 95% CI 1·86-8·40, p=0.0003) especially at a dose of 300mg per day, but there was no evidence of effect at 6 months (RR 2·22, 95% CI 0·52-9·47, p=0·28). In one small study nicotine therapy proved effective at increasing smoking cessation up to a period

of 3 months. Bupropion used in conjunction with NRT showed more effect than single use. Behavioural and bespoke interventions showed little overall benefit. Side-effects were found to be low.

Conclusion

The new information of this review was the effectiveness of varenicline for smoking cessation at both 3 and 6 months and the lack of evidence to support the use of both bupropion and nicotine products for sustained abstinence longer than 3 months. Overall the review found relatively few studies in this population.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Strengths and limitations of the study

- This study systematically reviewed all pharmacological and behavioural interventions to promote smoking cessation in people with serious mental illness.
- We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to evaluate the strength and quality of the evidence.
- We reviewed and identified evidence that would be valuable and relevant to clinical practice.
- Research in this field was limited by a small number and low quality of randomised controlled trials.
- We recommended that studies with larger sample sizes are needed particularly to compare the relative effects of one smoking treatment versus another.

Introduction

Smoking in people with serious mental illness continues to be a major public health problem with levels of smoking remaining as high as 70% (1-3), compared to about 20% in the general population (4). Smoking contributes to the high levels of morbidity and mortality in this population (5) with mortality rates continuing to remain around twice those found in the general population, with high levels of cardiovascular and respiratory disease (1,6,7). Individuals with serious mental illness tend to have smoked for longer periods compared with other groups and are commonly classed as heavy smokers, smoking more than 25 cigarettes per day (8). They often start before the onset of their illness, are younger than non-smokers, and more of them are male (9). Generally they prefer cigarettes high in nicotine and more frequently smoke cigarettes down to the very end (10). Increased nicotine intake per cigarette is associated with more intense cigarette puffing contributing to the higher serum nicotine levels, approximately 1.3 times those in non-mentally ill controls (11,12). The effect of this greater uptake of nicotine may lead to higher than expected levels of nicotine dependence and withdrawal symptoms, even with moderate amounts of smoking (11).

There is therefore an urgent need to develop and evaluate smoking cessation interventions that work in clinical settings for people with severe mental illness who are about as likely as the general population to want to quit smoking (13). However so far the primary focus of existing smoking cessation programmes in this population has been based on the use of nicotine replacement products. There is a reluctance among some clinicians to consider new treatments that may be more effective. This may be due to lack of clarity on the effectiveness of these products or concern about side-effects (14). Early reports using medication such as varenicline had raised concerns as to its effect on the mental health of individuals (15).

The aim of this new review was to compare the effectiveness and safety of existing pharmacological and behavioural programmes for smoking cessation in people with serious mental illness. Clinicians need clear information to be able to compare the relative benefits and potential side-effects of these treatments for their patients.

Methods

Criteria for considering studies for this review.

Types of studies

All randomised controlled trials.

Types of participants

Adults with schizophrenia or other types of schizophrenia-like psychosis, schizoaffective disorders, and bipolar affective disorder, irrespective of the diagnostic criteria used, age, ethnicity and sex.

Types of interventions

We only included interventions where the primary aim of the study was to achieve smoking cessation.

Types of outcome measures

We used the strictest definition of abstinence, that is, preferring sustained over point prevalence abstinence and using biochemically validated rates where available. However if this was not available the best alternative would be used. When both outcomes were available, we considered sustained abstinence to be a superior clinical marker of abstinence. Secondary outcome measures were changes in safety (adverse effects), mental state, general functioning, and cognitive functioning.

Search Methods, and study selection

We searched the following electronic databases: Ovid MEDLINE, Embase, CINAHL, PsycINFO, Biological Abstracts on Ovid, and The Cochrane Library (start January 2017, last search July 2018). The systematic search (Appendix A) included hand searching of journals, books, cross-referencing and bulletins (e.g brief reports/ brief statement of facts). The search filter, the Cochrane Highly Sensitive Search Strategy, was used to assist in the identification of randomised trials in MEDLINE (16). No articles were excluded on the basis of language during the search.

The abstracts of studies were examined by RP. Full text of the studies that potentially met the eligibility criteria was obtained. Selection of studies was conducted by RP and any discrepancies or difficulties were discussed with co-investigators (JG and DJS). Articles were checked for duplication of the same data. Smoking cessation was measured at 3, 6, and

12 months if possible, or the closest available data to that time point. Side-effects were measured at the available data endpoints at 3, 6, and 12 months, if possible.

Data extraction and analysis

Data was extracted by one author (RP) and checked for accuracy by the second (DJS). Data was extracted onto prepared forms to include: participants and setting, location, description of the intervention, study size, methodological issues, risk of bias, results, and general comments. All analyses were conducted using Revman Manager version 5.3. We performed a PRISMA evaluation of our meta-analysis using a standard checklist of 27 items that ensure the quality of a systematic review or meta-analysis (17).

Data from intention to treat analyses were used when available or endpoint data for participants who completed the programme. For dichotomous outcomes, the fixed effects risk ratio (RR) and its 95% confidence interval (CI) were calculated using the Mantel-Haenszel method (18). If heterogeneity was found, a random effects model was used. For continuous data, the standardized mean difference (SMD) with 95% confidence intervals was calculated as the difference in means between groups divided by the pooled standard deviation. If no standard deviations were found they were calculated from standard errors, confidence intervals, or t values (19). Authors were contacted for missing data if analyses could not be completed. Statistical heterogeneity was investigated using two methods: visual inspection of the forest plots and the I^2 test. The degree of heterogeneity was categorised as follows: 0% to 40% low level of heterogeneity; 30% to 60% moderate heterogeneity; 50% to 90% substantial heterogeneity; 75% to 100%: considerable heterogeneity (19).

Sensitivity analyses were conducted to determine the effect of dosage of medication used, and whether chemical confirmation of smoking cessation affected treatment outcomes. It was planned to use funnel plots to assess publication bias graphically and Begg and Egger tests to assess the risk of bias statistically (19,20). We performed sensitivity analyses to explore the influence of each risk of bias domain on pooled treatment effects where the risk was high.

The safety outcomes extracted from included trials were the number of patients reporting any adverse event, the number of patients reporting any serious adverse event, and number of patients withdrawn from the study because of adverse events. We contacted authors to

provide further information when there were insufficient data reported in the paper. Data were pooled for the identified adverse events.

Quality Assessment

We used the Cochrane Collaboration's tool for assessing the risk of bias (19). The following recommended domains were considered: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias. Each item was rated according to the level of bias and categorised into either low, high, or unclear. The category unclear indicated unclear or unknown risk of bias (19). RevMan version 5.3.5 was used to generate figures and summaries.

The quality of evidence was rated for each pooled analysis with the GRADE (grading of recommendations assessment, development and evaluation) system (19). Outcomes of interest were ranked according to their relevance for clinical decision.

Patient and public involvement statement

No patients or public representatives were involved in the completion of this review.

Results

The electronic search identified 1377 potentially eligible reports. Eight hundred and fifty two were excluded on the basis of the title or abstract alone. We retrieved the full text of 202 articles and excluded a further 174 studies (Fig. 1, Appendix B). Additional papers were found from searching, cross-referencing and bulletins.

All included studies had been published between 2000 and 2016. A total of 28 studies were identified. The studies varied in their setting, size, age, and type of intervention (Table 1). Only five studies examined individuals with bipolar affective disorder (21-25). Of these, two studies were of varenicline, one of bupropion and two using behavioural techniques in both schizophrenia and bipolar disorder. We found eight studies comparing bupropion versus placebo (Table 1).

Table 1. Characteristics of Total Included Studies

Study Name	Type of Treatment	Type of Control	Country	Diagnosis	Mean Age (yrs)	Sample Size	(female %) Sex	Ethnicity (% white)	Verification of Cessation	Duration of Intervention (wks)	Final follow-up (wks)	Results available (no. of weeks)
Evins 2001	Bupropion (150)mg	Placebo	USA	S	44·1	19	61·1	88·9	Yes	12	24	12+24
Evins 2005	Bupropion (300mg)	Placebo	USA	S	45·7	53	73·6	--	Yes	12	24	12+24
George 2002	Bupropion (300mg)	Placebo	USA	S	45·7	32	56·2	62·5	Yes	10	24	10+24
Weinberger 2008	Bupropion (300mg)	Placebo	USA	BD	57·2	5	40	100	Yes	10	10	10
Weiner 2012	Bupropion (150mg)	Placebo	USA	S	48·6	46	80·4	69·9	Yes	14	14	14
Li 2009	Bupropion (300mg)	Placebo	China	S	38·0	80	--	--	No	4	8	8
Akbarpour 2010	Bupropion (300mg)	Placebo	Iran	S	47·4	32	--	--	No	8	8	8
Bloch 2010	Bupropion (300mg)	Placebo	Israel	S	43·5	32	72	--	No	14	14	14
Weiner 2011	Varenicline	Placebo	USA	S	--	9	--	--	Yes	12	12	12
Williams 2012	Varenicline	Placebo	USA	S	41·6	128	49	37·5	Yes	12	24	12+24
Shim 2011	Varenicline	Placebo	USA	S	--	60	--	--	Yes	8	8	8
Wu 2012	Varenicline	Placebo	USA	BD	--	3	--	--	Yes	10	24	10+24
Hong 2011	Varenicline	Placebo	USA	S	--	69	--	--	No	8	8	8
Chengappa 2014	Varenicline	Placebo	USA	BD	45·9	60	31·6	68·3	Yes	12	24	12+24
Smith 2016	Varenicline	Placebo	Netherlands	S	45.1	91	37	31	Yes	12	12	12
George 2000	Behavioural Therapy	Motivational, psychoeducation, prevention strategies	USA	S	39·1	45	67·4	61·5	Yes	10	24	10+24
Williams 2010	Behavioural Therapy	Education counselling	USA	S	45·3	76	63·1	65·5	Yes	26	52	12+24 +52
Gilbody 2015	Bespoke smoking cessation service with medication	Placebo	UK	S + BD	46.8	97	58	83	Yes	52	52	12+24 +52
Bennett 2015	Behavioural Therapy	Supportive Group Intervention active	USA	S + BD	54.8	178	89.3	22.5	Yes	12	12	12
Evins 2007	Bupropion (300mg) +NRT 21mg)	NRT (21mg) + behavioural counselling	USA	S	44·2	23	--	--	Yes	12	52	12+24+52
George 2008	Bupropion (300mg) + NRT(21mg)	Group behavioural therapy.	USA	S	40·2	58	60·4	48·3	Yes	10	26	10+26
Baker 2006	NRT (21mg nicotine)	Treatment as usual	Australia	S	37·2	298	52·3	--	Yes	12	52	12+24+52
Chen 2013	High dose NRT (31.2mg nicotine)	Low dose NRT (20.8mg nicotine)	Taiwan	S	45·2	184	92·9	--	Yes	12	12	12
Gallagher 2007	CR or CR+NRT (21mg)	Minimal intervention control	USA	S	42·8	180	52·4	75·7	Yes	16	36	20+36
Tidey 2011	CR	Placebo +/- Bupropion	USA	S	44·9	52	72	74	Yes	3	4	4
Weinberger 2008	Topiramate	Placebo	USA	SA	--	24	50	54	Yes	8	8	8
Szombathyne 2010	Naltrexone	Placebo	USA	S	--	--	--	--	No	12	12	12
Wing 2010	TMS	Treatment as usual	USA	S	--	13	--	--	Yes	9	9	9

Abbreviations: B=Bupropion; Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation; S=Schizophrenia: SA=Schizoaffective Disorder; BD=Bipolar Affective Disorder.

Six studies used 300mg of bupropion per day and two used bupropion 150mg/d. Seven studies examined the effect of varenicline versus placebo, and one study nicotine replacement therapy (NRT) versus placebo (Table 1).

Outcomes

The main outcome measure was smoking abstinence at three and 6 months. Twelve month follow-up was found in four studies (Table 1). Five studies did not confirm smoking abstinence using chemical markers (Table 1).

Meta-analyses

Bupropion

Six out of eight studies provided data to combine the effects of bupropion versus placebo (Table 2). The pooled risk ratio (RR) of bupropion (150mg and 300mg per day) at 3 months for smoking abstinence favoured bupropion against placebo (N=6, n=235, RR 3·96, 95% CI 1·86-8·40, p=0·0003; heterogeneity: $Chi^2 = 1·64$, df = 5, p = 0·90; $I^2 = 0\%$)(Fig. 2).

Pooled results at 6 months of bupropion versus placebo showed no effect (N=3, n=104, RR 2·22, 95% CI 0·52-9·47, p=0·28; heterogeneity: $Chi^2 = 0·34$, df = 2, p = 0·85; $I^2 = 0\%$) (Fig. 3). The pooled RR showed a greater likelihood of smoking cessation using a dose of 300mg per day of bupropion at 3 months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). No effect was found using doses of 150mg or 300mg per day at 6 months (dose 150mg: N=1, n=19, RR 2·73, 95% CI 0·12-59·57, p=0·52, dose 300mg: N=2, n=85 RR 2·09, 95% CI 0·40-10·80, p=0·38).

Bupropion was effective for smoking cessation in individuals with a diagnosis of schizophrenia at 3 months (N=5, n=230, RR 3·95, 95% CI 1·81-8·62, p=0·0006). No effect was found in bipolar disorders in one small study (N=1, n=5, RR 4·00, 95% CI 0·24-67·71, p=0·34) (Table 2).

Varenicline

Four out of seven studies provided data comparing the effect of varenicline with placebo. The pooled RR at 3 months for smoking abstinence favoured varencline (N=4, n=288, RR 3.56, 95% CI 1.82-6.96, p=0·0002; heterogeneity: $Chi^2 = 1.99$, df = 3, p = 0·57; $I^2 = 0\%$) (Fig. 4). Pooled analysis at 6 months also favoured varenicline (N=2, n=188, RR 3·69, 95% CI 1·08-12·60, p=0·04; heterogeneity: $Chi^2 = 0·22$, df = 1, p = 0·64; $I^2 = 0\%$) (Fig. 5).

Varenicline was effective for smoking cessation at 3 months in both schizophrenia and bipolar disorder (Table 2) (RR 3.06 vs. 4·68). However at 6 months no effect was found in either disorder.

Table 2 Meta-Analysis Comparison: Risk Ratio of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies (available data)	No. of participants	Risk Ratio [95% CI]	p value
Total Meta-Analysis				
Bupropion	6	n=235	3·96 [1·86 to 8·40]	0·0003
Varenicline	4	n=288	3.56 [1.82 to 6.96]	0·0002
NRT	1	n=298	2·74 [1·10 to 6·81]	0·03
B + NRT	2	n=110	2·39 [1·14 to 5·00]	0·02
NRT/Behav.Coun.	1	n=45	0·99 [0·44 to 2·23]	0·98
High/ Low NRT	1	n=184	0·25 [0·03 to 2·19]	0·21
Schizophrenia				
Bupropion	5	n=230	3·95 [1·81 to 8·62]	0·0006
Varenicline	3	n=228	3.06 [1.32 to 7.10]	0·009
Bipolar Disorder				
Bupropion	1	n=5	4·00 [0·24 to 67·71]	0·34
Varenicline	1	n=60	4·68 [1·68 to 14·50]	0·008

NRT

One study (Baker et al., 2006) compared NRT versus placebo at three, six, and twelve months (Fig. 6). The RR favoured NRT at 3 months (N=1, n=298, RR 2·74, 95% CI 1·10-6·81, p=0·03), but not at 6 months (n=298, RR 2·74, 95% CI 0·74-10·12, p=0·13) or twelve months (n=298, RR 5·14, 95% CI 0·61-43·44, p=0·13). Chen et al (2013) compared high versus low dose NRT, but found no difference in effect at 3 months (n=184, RR 0·25, 95% CI 0·03-2·19, p=0·21).

Combinations of treatment included in the meta-analyses

Several studies used combinations of treatments for smoking cessation. Data from two studies were combined comparing the effects of bupropion and NRT therapy versus placebo, at three and 6 months (26,27). The pooled RR favoured the combination of treatments at 3

months (N=2, n=110, RR 2·88, 95% CI 1·23-6.73, p=0·01; heterogeneity: Chi² = 1.72, df = 1, p = 0·19; I² = 42%) and at 6 months (N=2, n=110, RR 3·86, 95% CI 1·01-14·80, p=0·05; heterogeneity: Chi² = 0·56, df = 1, p = 0·46, I² = 0%). Of these studies, Evins et al (2007) found no effect (n=51, RR 2.60, 95% CI 0·55-12.19, p=0·23).

However data from all studies of bupropion using bupropion treatment alone and 2 studies combining bupropion and NRT versus placebo were favourable at 3 months (N=8, n=345, RR 3.48, 95% CI 1.98-6.11, p=0·0001; heterogeneity: Chi² = 3.77, df = 7, p = 0·81, I² = 0.%) and 6 months (N=5, n=214, RR 3.04, 95% CI 1·14-8.09, p=0·03; heterogeneity: Chi² = 1.08, df = 4, p = 0·90, I² = 0.%) (Fig. 7).

Behavioural and Bespoke Programmes

No meta-analysis was used due to the heterogeneity of both intervention and comparison groups (Appendix C, Table 1). Two studies compared the effect of NRT with different types of behavioural counselling (28,29). George et al (29) found no effect at 3 months (n=45, RR 1.01, 95% CI 0·45-2·28, p=0·98) or 6 months (n=45, RR 0.61, 95% CI 0·14-2.67, p=0·51). Williams et al (28) compared two behavioural counselling approaches, high intensity (TANS: Treatment of Addiction to Nicotine in Schizophrenia) versus a low intensity behavioural counselling programme (MM: Medication Management). No difference in levels of smoking cessation was found in both groups at 3 months (15·6% TANS vs. 26·2% MM, p = 0·221).

Bennett et al (24) compared a multifaceted behavioural group intervention versus a supportive group intervention and found no difference in effect at 3 months (n=95, RR 1·13, 95% CI 0·37-3.44, p=0·83). Some individuals used medication to support smoking cessation such as bupropion or NRT.

Gilbody et al (30) offered a bespoke smoking cessation programme (SCIMITAR) to individuals with serious mental illness compared to usual care. Pharmacotherapies were prescribed by the individual's General Practitioner to aid smoking cessation (BSC group: nicotine=77, bupropion=0, varenicline= 0, E-Cigarette=3, either separately or in combination, as decided by the GP). During the trial period 48% of individuals in the intervention group received pharmacotherapies compared to 19% of the placebo group. The odds of quitting at 12 months was higher in the BSC (bespoke smoking cessation)

intervention (36% vs. 23%) but did not reach statistical significance (OR 2.94, 95% CI 0.8-10.5, p=0.1).

Sensitivity analyses

Sensitivity analyses found that bupropion at a dose of 300mg per day increased the likelihood of smoking cessation at 3 months (dose 150mg: N=2, n=65, RR 2·01, 95% CI 0·49-8·28, p=0·33, dose 300mg: N=4, n=170 RR 4·99, 95% CI 2·01-12·39, p=0·0005). Studies that did not use chemical markers to confirm smoking cessation did not substantially affect the likelihood of cessation with bupropion (N=5, n=155, RR 3·93, 95% CI 1·48-10·40, p=0.006). Chemical verification of smoking cessation was used in all studies of varenicline and NRT included in the meta-analysis in this review.

Clinical effectiveness and numbers needed to treat

The number needed to treat (NNT) for the cessation of smoking using varenicline at 3 months was 6 patients (RD 0.19, 95% CI 0.11 to 0.27) (Table 3), and 10 patients at 6 months (RD 0.1, 95% CI 0.03 to 0.18). Varenicline resulted in 24.8% of the patients in the intervention group versus 7.3% patients in the placebo group being abstinent from smoking at 3 months (at 6 months this was 13.8% vs. 4.2% respectively).

The number needed to treat for the cessation of smoking using bupropion at 3 months was 6 patients (RD 0.19, 95% CI 0.10 to 0.28)(Table 3). NRT was the least effective, requiring 15 patients to receive treatment at 3 months (RD 0.07, 95% CI 0.01 to 0.13). Combinations proved to be the least effective of treatments to aid cessation of smoking (Table 3).

Side-Effects

Side-effects from medication were reviewed systematically to allow pooling of data where possible (Table 4). Pooled analysis found that bupropion did not affect positive and negative symptoms or depressive and anxiety symptoms. Serious adverse events in individual patients were noted with bupropion. Evins et al (31) found that one participant, who was randomized to bupropion, experienced hives, urticaria, and wheezing in the first week on study medication, consistent with an allergic reaction to bupropion. Weiner et al (32) found that one participant developed a rash that resolved after medication discontinued. Another patient suffered a seizure and was found to be hyponatraemic.

Table 3. Risk Difference (RD) and NNT of Smoking Cessation at 3 months

Outcome or subgroup title	No. of studies	No. of participants	Risk Difference (RD)	NNT	P value
Bupropion	6	235	0.19 [0.10 to 0.28]	6	<0.0001
Varenicline	4	288	0.19 [0.11 to 0.27]	6	<0.00001
NRT	1	298	0.07 [0.01 to 0.13]	15	0.02
Bupropion+NRT	2	110	0.20 [0.05 to 0.36]	5	0.006
NRT/Behav. Coun.	1	45	0.00 [-0.28 to 0.29]	--	0.98
High/ Low NRT	1	184	-0.03 [-0.08 to 0.01]	34	0.17

Pooled analysis showed a low level of side-effects with varenicline (Table 4). The main finding was that varenicline led to problems with nausea and vomiting, but had no other effects on depressive symptoms, anxiety symptoms, or suicidal ideation. Serious adverse events were noted with varenicline in individual patients. Williams et al (33) found that five patients in the treatment group and three patients in the placebo group experienced suicidal thoughts. However the authors found no clear pattern between suicidal thoughts and medication assignment. One patient with depression and suicidal thoughts took an overdose of medication, while another participant took an overdose and had a seizure. Wu et al (34) found that one patient experienced suicidal ideation but this was reported to be associated with additional situational stressors rather than a medication effect.

No notable side-effects were described for programmes using nicotine replacement therapy (Table 4).

Quality assessment

We found a total of 28 studies which varied in their methodological quality, including the method of sequence generation during randomisation, sequence allocation concealment, blinding of participants, outcome assessment, and incomplete analysis of outcome data (Appendix D, Table 1). Ten studies described using intention to treat analysis for data analysis (23,35-43). Participants failing to complete these studies were included as non-abstinent smokers in their analysis. Only three studies described a sample size calculation (23,33,44). The interpretation of funnel plots (Fig. 8) was limited due to the small number of

pooled results in this analysis, and similarly Egger tests were not preformed due to the low number of available studies.

Table 4. Smoking Cessation Side-Effects of Treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical Result	p value
Bupropion				
Positive	2	n=85	SMD -0·24 [-0·66 to -0·19]	p=0·28
Negative	2	n=85	SMD -0·15 [-0·58 to -0·27]	p=0·48
Depressive	2	n=85	SMD -0·17 [-0·59 to -0·26]	p=0·44
Anxiety	1	n=53	SMD 0·18 [-0·36 to -0·72]	p=0·52
Varenicline				
Headache	3	n=188	RR 0·71 [0·45 to 1·13]	p=0·15
Sleep Problem	4	n=288	RR 1·25 [0.77 to 2.03]	p=0·37
Nausea/ Vomiting	4	n=288	RR 1·66 [1.23 to 2.24]	p=0·0009
Diarrhoea	2	n=188	RR 1·15 [0·38 to -3·49]	p=0·80
Depression	2	n=188	RR 1·72 [0·67 to -4·45]	p=0·26
Anxiety	2	n=188	RR 0·88 [0·29 to -2·66]	p=0·82
Suicidal Ideation	2	n=188	RR 1·05 [0·33 to 3·41]	p=0·93
NRT				
Depressive	1	n=246	SMD -0·13 [-0·38 to -0·12]	p=0·31
Anxiety	1	n=212	SMD -0·05 [-0·32 to -0·22]	p=0·72

We used the Cochrane Collaboration's tool (19) for assessing the risk of bias (Fig. 9). This showed that most studies described used inadequate methods of sequence generation during randomisation, blinding of participants, analysis of outcome data, poorer methods of allocation concealment and blinding of outcome assessment. We found that Smith et al (45) showed the lowest risk of bias in all domains.

The quality of evidence was rated for each pooled analysis with the GRADE assessment of study quality. The GRADE clinical evidence profile graded the studies of bupropion (at 3 or 6 months) and varenicline as being of very low quality (Appendix D, Tables 2-3).

Discussion

In this review we compare up-to-date findings of programmes used to aid the cessation of smoking for people with serious mental illness, with outcomes at 3, 6, and 12 months. The primary new information of this review was the effectiveness of varenicline at 3 and 6 months but the lack of evidence to support the use of bupropion and nicotine products to achieve smoking cessation for longer than 3 months. We also found that these treatments did not notably affect the physical or mental health of the participants, with generally low levels of side-effects. Varenicline was the most successful treatment with individuals more than three times as likely to achieve smoking cessation in both schizophrenia and bipolar disorders. Problems with side-effects from nausea and vomiting were however found with varenicline. Bupropion increased the cessation of smoking in the short term (up to 3 months) compared to placebo, at a dose of 300mg per day, but there was a lack of evidence to support its use in achieving sustained cessation of smoking over a longer period. Only one small study was found that used NRT and this was only effective for a period of up 3 months. We found that combining bupropion and NRT was only effective at 3 months. However when all studies of bupropion where pooled at 6 months, both single treatments using bupropion and those using concurrent bupropion and nicotine, stronger evidence was observed. Behavioural interventions on the whole showed little benefit to achieve smoking cessation. Counselling and behavioural or specialised bespoke programmes used different types of interventions to achieve smoking cessation but no consistent effect was found. Contingency reinforcement combined with NRT was found to be beneficial for achieving smoking cessation compared to contingency reinforcement alone. Comparison of the effect of behavioural or contingency programmes versus pharmacological interventions could not be made due to the heterogeneity of the active and comparison groups used.

There are strengths and limitations to the findings we have presented. We found that effective methods are available to increase rates of smoking cessation both in schizophrenia and bipolar affective disorder. However, this evidence is based on relatively few studies. We identified all randomised trials including results available at both 3 months and 6 months, and identified studies that used chemical markers to confirm smoking abstinence. A number of limitations however need to be acknowledged. Research in this field has been so far limited by only a small number and low quality of randomised controlled trials. For example, some of the conclusions from this review are based on a single study of nicotine replacement therapy. It is possible that additional studies with negative outcomes have been conducted

but remain unpublished. We found generally low levels of side-effects with both bupropion use and varenicline. However, we are aware that studies comprising of larger samples are still required to fully resolve issues of whether there are a greater potential risk of suicidality and other neuropsychiatric effects with these products used for smoking cessation.

Our findings update and review the latest evidence in this field and show that successful treatment for smoking dependence is available in people with serious mental illness. However our conclusions differ in respect of the final analysis of treatments using bupropion therapy. For example, Tsoi et al (46) in a Cochrane systematic review of patients with schizophrenia (last search November 2012), found that that bupropion was effective at both 3 and 6 months. Their final conclusions differed from our own in their summary of findings of bupropion reported at 6 months. Their final analysis of bupropion studies at 6 months incorporated both studies where bupropion was used singly as the primary treatment offered and also those using concurrent treatments of bupropion and nicotine therapy. The pooled effect of the larger sample size found stronger evidence to support the use of bupropion at 6 months treatment. A recent systematic review Peckham et al similarly (47) incorporated into their findings of bupropion studies that jointly used bupropion and NRT. In our review, we have reported the outcomes of bupropion separately as, firstly, we did not think it likely that clinicians would incorporate two concurrent treatments for smoking cessation, and secondly, existing meta-analysis of studies in the general population have tended to compare one product for smoking cessation solely with another (48).

The results of our review are tempered by the relatively low numbers of randomised trials in this field, most trials being underpowered, and the poor quality of evidence identified by the GRADE assessment. For example, only two studies showed the effectiveness of varenicline at 6 months, and only one study was found examining nicotine products, compared to up to 70 studies comparing NRT in the general population (49). We found low levels of side-effects, with varenicline mainly causing symptoms of nausea and vomiting. We are aware that a larger study has been recently completed (50) examining the neuropsychiatric effects of varenicline, bupropion, and NRT in individuals with or without psychiatric disorders (n=4,074), comprising unipolar and bipolar disorders, anxiety disorders, personality disorders, and psychotic illness. This study did not find a greater risk of neuropsychiatric side-effects associated with these medications. Data was not available (authors contacted) for inclusion in this review and meta-analysis.

Implications for practice

This is a new and updated systematic review directly comparing treatments to aid cessation of smoking in people with schizophrenia and bipolar affective disorders. We found that smoking cessation was more likely to be successful using varenicline in both schizophrenia and bipolar disorders with few side-effects but there was a lack of sufficient evidence to support the use of bupropion as a single treatment in the medium and long term. Treatment with varenicline resulted in 24.8% of the patients at 3 months in the varenicline group versus 7.3% in the placebo group being abstinent from smoking (at 6 months, 13.8% vs. 4.2% respectively). However, our review is notable by the low number of studies available for each smoking cessation treatment.

Implications for Research

Further research is needed to conduct well-designed studies of adequate sample size to determine the most effective method for reducing smoking in this population. Studies so far have also achieved only relatively short-term effects on sustained smoking abstinence. Tailored or focussed programmes may be needed using single or combinations of treatments to achieve better outcomes. Similarly, clearer evidence is required to understand which type of counselling or psychological intervention is the most effective. Furthermore existing smoking cessation programmes tend to rely on evidence from general population samples. It is not clear whether these are transferrable to people with serious mental illnesses with substantially higher levels of smoking and nicotine dependence. However we also need to be realistic as to the problems of change in this population who as a result of the nature of their mental illness may be less motivated or less able to change their lifestyle (51,52).

Conclusions

This review highlighted the paucity of studies found to address the high prevalence of smoking in people with SMI and identifies a need for further randomised controlled trials. The available evidence suggested that varenicline was the most effective with low levels of side-effects but there was a lack of sufficient evidence to support the use of bupropion and NRT within this group.

Declaration of Interest

RP, and DJS declared no competing interests. JG has received research funding from MRC, ESRC, NIHR, Stanley Medical Research Institute and has received donations of drugs supplies for trials from Sanofi-Aventis and GSK. He has acted as an expert witness for Dr Reddys.

Contributors' statement

Authors: RP, DJS, and JG developed the research. RP conducted the research. RP and DJS conducted the analysis. RP drafted the manuscript. DJS and JG provided input and approved the final version.

No patients or public representatives were involved in the completion of this review.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Data availability statement

The data is pooled results from a systematic review and meta-analysis of treatments for smoking cessation. The pooled results are available in our paper as a supplementary file and are available for review with details of the included studies.

Summary of Figures:

Fig. 9 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Appendix A: Summary Search Strategy

Appendix B: Excluded Studies

Appendix C: Types of Counselling in Smoking Cessation Programme

Appendix D: Table 1. Risk of bias summary by author

Appendix D: Table 2. GRADE clinical evidence profile for bupropion compared to control at 3 and 6 months.

Appendix D: Table 3. GRADE clinical evidence profile for varenicline compared to control at 3 and 6 months.

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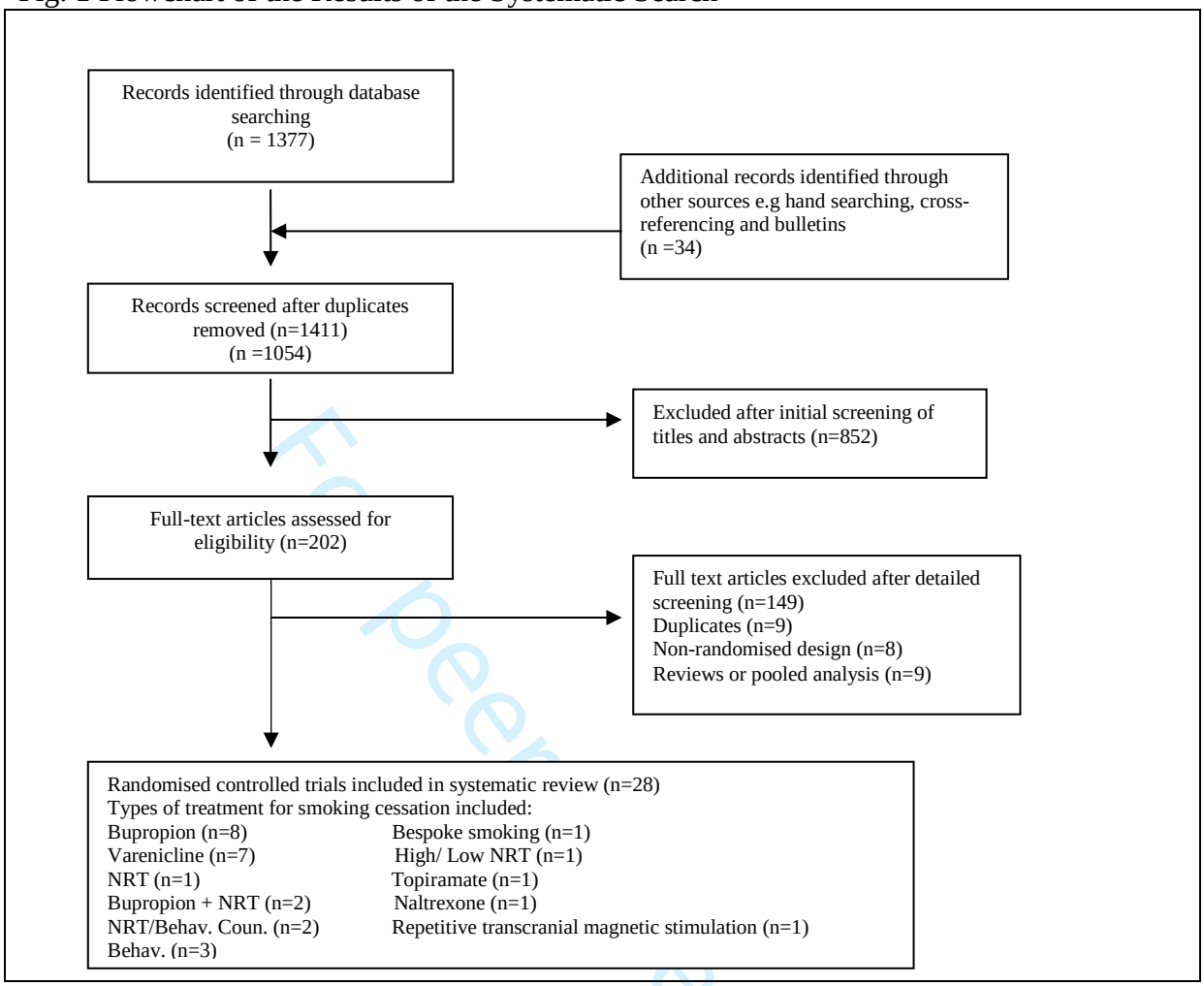
Fig. 1 Flowchart of the Results of the Systematic Search



Abbreviations: B=Bupropion; V=Varenicline; Behav.=Behavioural Therapy/ Counselling; B+NRT=Bupropion and NRT; NRT=Nicotine Replacement Therapy; High vs. Low dose NRT; CR= Contingent Reinforcement; TMS=Transcranial Magnetic Stimulation

Fig. 2 Pooled effect of bupropion versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

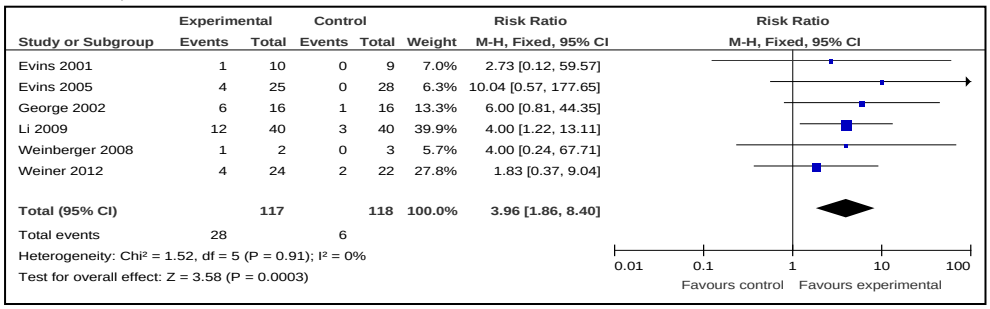


Fig. 3 Pooled effect of bupropion versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval

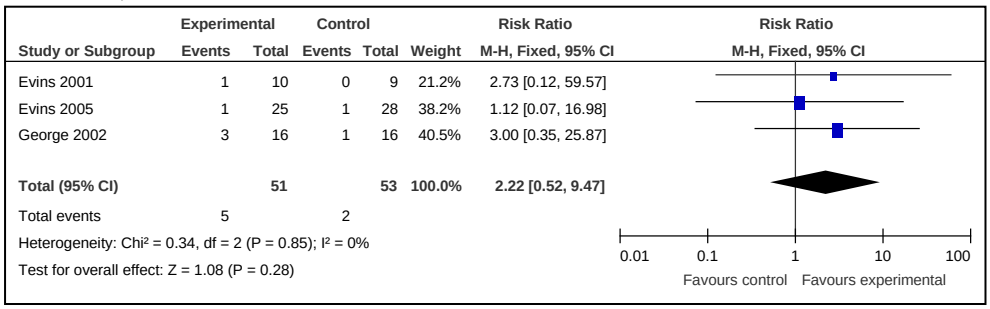


Fig. 4 Pooled effect of varenicline versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

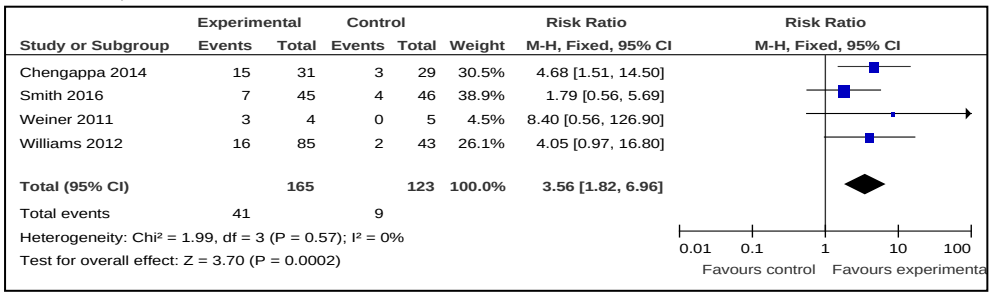


Fig. 5 Pooled effect of varenicline versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval

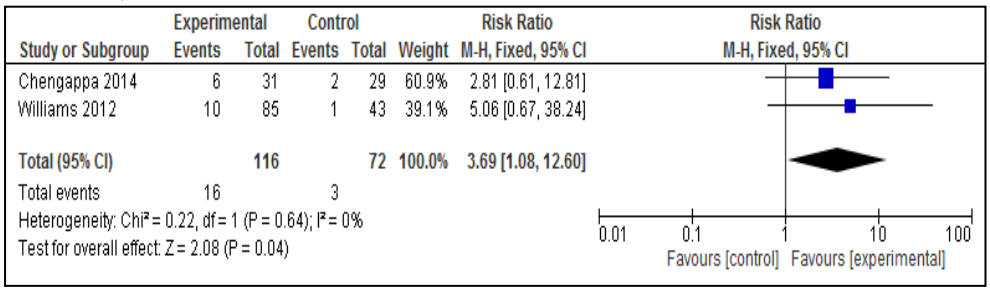


Fig. 6 Pooled effect of NRT versus placebo for smoking cessation at 3 months, with risk ratio and 95% confidence interval

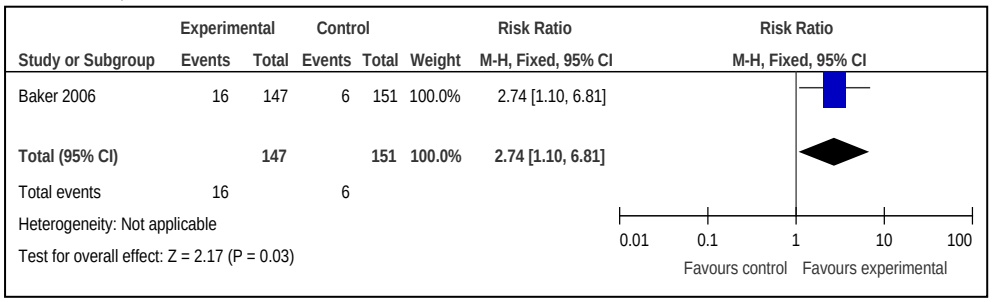
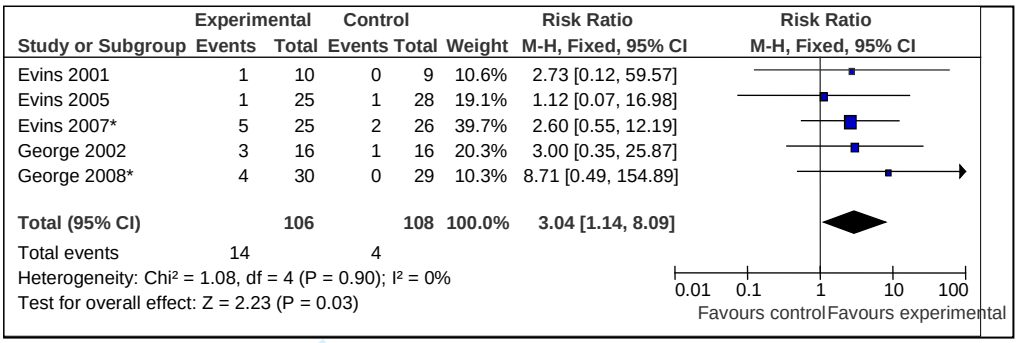


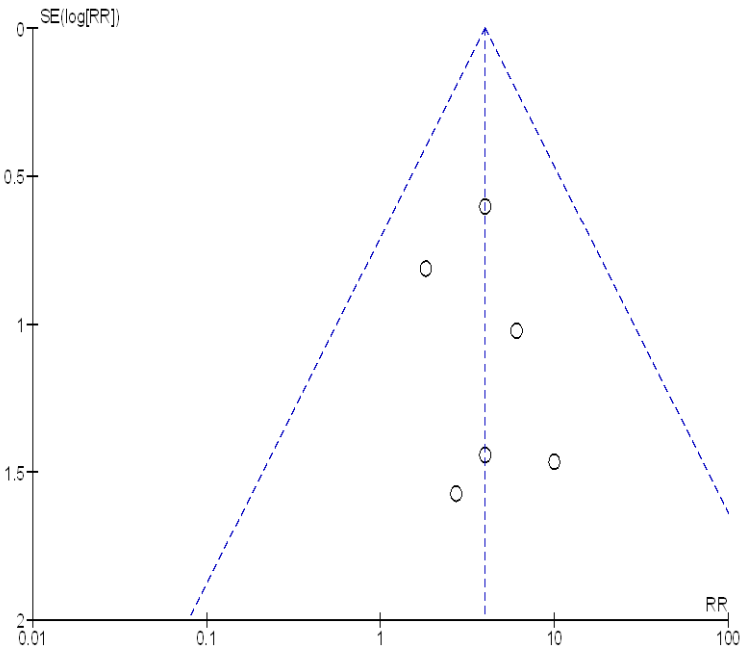
Fig. 7 Pooled effect of bupropion only and combined bupropion/NRT studies versus placebo for smoking cessation at 6 months, with risk ratio and 95% confidence interval



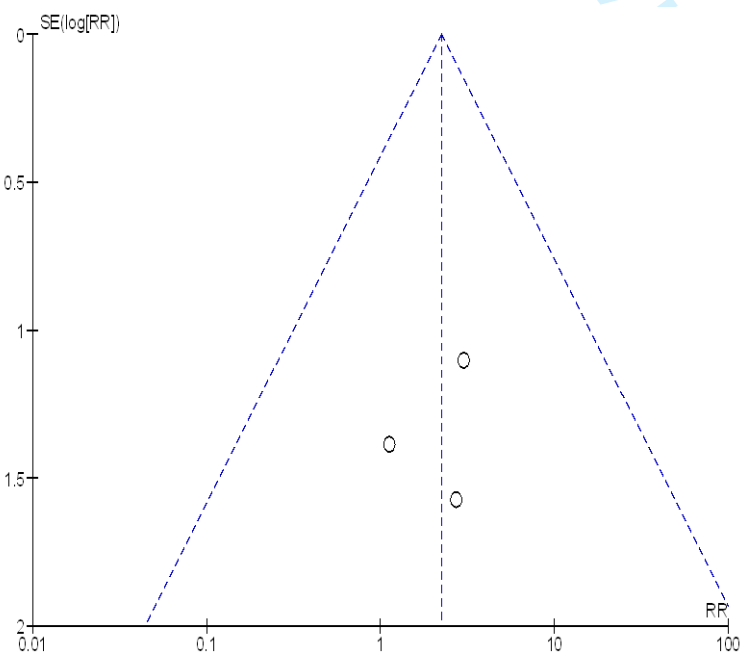
* denotes studies using combined treatment with bupropion and nicotine

Fig. 8 Funnel Plots of Smoking Cessation studies.

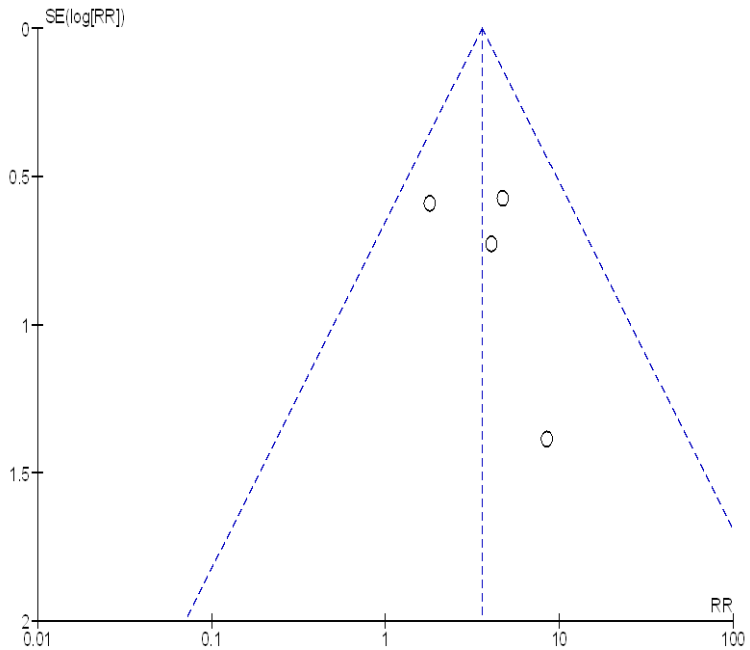
(i) Funnel plot of comparison: Bupropion 3 months.



(ii) Funnel plot of comparison: Bupropion 6 months



(iii) Funnel plot of comparison: Varenicline 3 months



(iv) Funnel plot of comparison: Varenicline 6 months

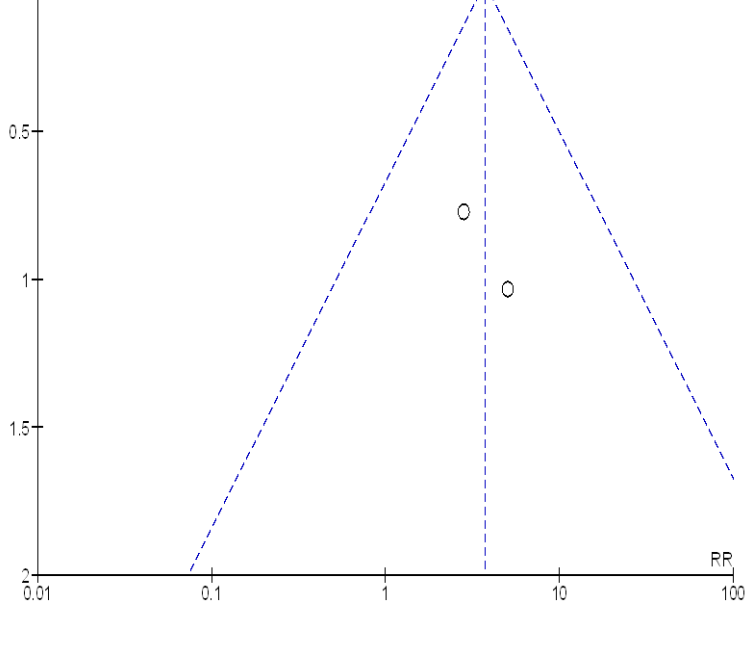
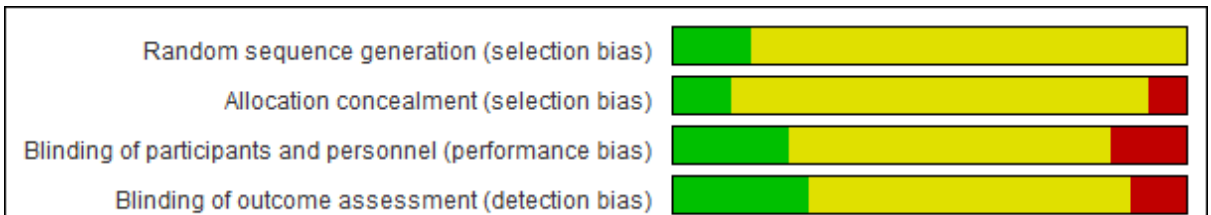


Fig. 9 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Appendix A

Summary

Search Strategy

1. exp schizophrenia/
2. psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. chronic psychosis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. exp schizoaffective disorder/
5. exp bipolar affective disorder/
6. 1 or 2 or 3 or 4 or 5
7. exp smoking/
8. cigarettes.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. nicotine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
10. exp nicotine replacement therapy/
11. nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
12. nicotine inhaler.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
13. bupropion.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. exp smoking cessation/

15. transdermal nicotine patch.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
16. varenicline.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
17. galantamine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18. atomoxetine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
19. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20. exp smoking abstinence/
21. smoking reduction.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
22. cotinine levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
23. carbon monoxide levels.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
24. 20 or 21 or 22 or 23
25. 6 and 19 and 24
26. 6 and 19

Appendix B Excluded Studies

Study Details	Reason for Exclusion
Baker 2018	Additional health interventions
Peckham 2107	Study Protocol
Baker 2011	Study Protocol
Baker 2011	Health lifestyle intervention
Aschbrenner 2018	Feasibility Study
Manhapra 2017	Non randomised
Sharma 2017	Non randomised
Brunette 2018	Web based intervention
Jimenez-Ruiz 2018	Cohort Study
Baker 2018	Healthy Living Intervention
Rogers 2017	Follow-up study non randomised
Clark 2017	Non randomised
Bakhai 2017	Non randomised
Garcia-Portilla	Non randomised
Nash 2016	Electronic health record tool
Schieder 2016	Descriptive report
Thorndike 2016	Subgroup analysis reporting weight gain
Burke 2016	Descriptive review
Wu 2016	Systematic review
Peckham 2016	Qualitative study exploration of smoking cessation problems
Roberts 2016	Systematic Review
Molero 2015	Varenicline Cohort Study
Stubbs 2015	Clinical review
Molero 2015	Varenicline Cohort Study
Thomas 2015	Varenicline Systematic Review
Bradshaw 2014	Review/ descriptive paper on smoking cessation
Howard 2013	Cohort study pregant women with mental health disorders
Filia 2014	Secondary analysis (non smoking) of intervention study
Ward 2018	Review article
Okoli 2018	Intention to engage study in smoking
Khadjesari 2017	Retrospective cohort study
Andrews 2106	Healthy living intervention
Roberts 2016	Systematic review and meta-analysis
Hamilton 2016	Before and after study
Gardner-Sood 2015	Baseline data only
Takahashi 2014	Pharmacokinetics study, secondary analysis
Dickens 2014	Smoking behaviour/ motives to quit, non-randomised
Filia 2014	Risks and benefits, non-randomised
Szatkowski 2013	Non-randomised
Brown 2013	General study
Meszaros 2013	Varenicline and alcohol addiction
Okali 2012	Smoking/ Substance misuse

Hardy 2012	Descriptive
Murray 2012	Review
Lydall 2011	Genetic factors
Brown 2011	Descriptive
Kisely 2011	Systematic review and meta-analysis
Sawa 2011	Cohort study
Prebble 2011	Case study
Brown 2011	Report
Kisely 2011	Non smoking
Pinto 2010	Smoking and general factors
Bergen 2009	Summary conference
Alhatem 2009	Varenicline side-effects. no intervention
Tait 2009	Smoking and cognitive change
Hilton 2007	Smoking and substance misuse
Dratcu 2007	Smoking clozapine and caffeine report
Doolan 2006	Review article
Prochaska 2006	Motivation in smoking
Himelhoch 2004	Smoking/ COPD prevalence
Aubin 2004	Non psychosis RCT
Li 2003	Genetics smoking
Ziedonis 2003	Discussion article
Brunette 2018	Additional diagnoses in mental illness
Baker 2018	Healthy living intervention
Travelli 2017	Cohort study
Taylor 2017	Discussion article
Schuster 2017	Cohort varenicline and CBT
Peckham 2017	Protocol
Garcia-Portilla 2016	Non-randomised
Tedeschi 2016	Mental health screening non- intervention
Cunningham 2016	Neuropsychiatric adverse events varenicline or nicotine
McGinty 2016	Discussion/ review article
Tidey 2015	Electronic cigarettes and chronic mental illness
Jackson 2015	Non-intervention
Evins 2015	Review article
Filia 2014	No comparison group
Yargic 2013	Non-English
Castle 2012	No comparison group
Hardy 2012	Diabetes risk factors
Newaz 2012	Smoking beliefs non randomised
Baker 2011	Study protocol
QOF Clinical indicators x4 2009 duplicates	No comparison
Lowe 2010	Smoking cessation on clozapine/ olanzapine treatment review
Kotov 2010	Smoking and schizophrenia association no comparison
Lawn 2002	Qualitative study
Anfang 1997	Case report
Tejedor 2018	Smoking cessation, psychosis and substance use
Roson 2017	Open label study

Manettis 2018	Nicotine receptor subtypes
Zou 2018	Cohort study
Sharma 2017	Review electronic cigarettes
Ahmed 2018	Systematic review and meta-analysis
Ignacio 2018	Cohort study
Baker 2018	Healthy living intervention in smokers
Brunette 2018	Smoking Cessation in anxiety, major depression as well as psychotic illness
Meernik 2018	No comparative group
Europena Public Health Conference	Report
Ayeyard 2018	Non mental illness RCT nicotine
Politis 2018	Open label study
Davies 2018	Varenicline cohort study
Roson 2017	Open label study
Sharma 2017	Review article
Jimenez-Ruiz 2018	Varenicline general mental health
Evins 2017	RCT but initial open label treatment Varenicline
Schuster 2017	No comparison group
Garcia-Portilla 2016	Qualitative study
Schroeder 2016	Discussion article
Thorndike 2016	Secondary analysis weight gain and CVS risk
Burke 2016	Narrative review
Kiski 2015	Systematic review and meta-analysis
Kaduri 2015	Cohort study and all psychiatric disorders
Hoeppner 2015	Pooled analysis of 2 RCTs
Evins 2014	RCT but initial open label phase
Kale 2014	Non mental illness
MacKowick 2012	Discussion article/ Review
Castle 2012	Varenicline Non comparison group health intervention
Benes 2012	Nicotinic receptors
Roberts 2016	Systematic review and network meta-analysis
Gonzalez-Blanco 2014	Open label study varenicline and nicotine patches
Englisch 2013	Systematic review and meta-analysis
Aguiar 2009	Follow-up study
Tidey 2015	Systematic review and meta-analysis
McClure 2010	Non SMI diagnosis
Weiner 2001	No comparison group
Shiina 2010	Primary effects on cognitive function
Garcia-Portilla 2013	Protocol
Sharma 2018	Practices and attitudes
Okali 2017	Retrospective analysis
Laude 2017	Non mental illness
Wu 2016	Systematic review and meta-analysis
Cunningham 2016	Retrospective cohort
Pachas 2012	Non randomisation
Tidey 2020	Before after study
Weinberger 2016	Descriptive/ Discussion

Baker 2016	RCT but initial open label Nicotine/ Varenicline/ Combined
Molero 2015	Not serious mental illness
Roberts 2018	Effect on cognitive function
Zawertailo 2017	Smoking predictors
Das 2017	Comorbid substance misuse
Laude 2017	Non mental health population
Aubin 2012	Non-randomised
McEvoy 1999	Before and after
Pachas 2012	Before and after
Gold 2018	Comorbid substance misuse
Compton 2018	Discussion
Das 2017	Comorbid substance misuse

Appendix C

Table 1. Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Evins 2001	CBT both groups	Nine weekly 1-h group sessions both groups
Evins 2005	CBT both groups	12-week, 12-session group of CBT. CBT program was delivered from a written manual adapted for patients with schizophrenia from American Heart Association and American Lung Association materials
George 2002	Group Session	Smoking cessation group therapy included motivational enhancement therapy (weeks 1–3) and psychoeducation, social skills training, and relapse-prevention strategies (weeks 4–10) for a total of 10 weeks. Sessions were of 60-min duration. Subjects attended weekly group therapy appointments and weekly research assessments on separate days.
Weinberger 2008	Group behavioural therapy	Participants received weekly sessions of manualised group behavioural therapy
Weiner 2012	Group Support programme	9 week structured programme increase awareness of smoking habits, relaxation, quit plan, and managing high risk situations, problems of weight gain etc.
Li 2009	Not available	Not available
Akbarpour 2010	No additional programme	No additional programme
Bloch 2010	CBT both groups	14 week, 15 session group programme. Emphasised education, motivation, encouragement, problem solving strategies, coping with triggers, behavioural tasks cognitive reconstruction. Self-esteem and self-efficacy.
Weiner 2011	Individual smoking cessation counselling	All participants received individual smoking cessation counseling based on the American Lung Association, Freedom from Smoking Program.
Williams 2012	Individual smoking cessation counselling	One to one smoking counselling. Approx. 4 weekly visits with additional phone contact.
Shim 2011	Not described	Not described
Wu 2012	Weekly meetings for verification for medication pick-up and assessment	Weekly meetings for verification for medication pick-up and assessment
Hong 2011	No counselling	Baseline, week 2,8,10 meetings. Smoking cessation counselling was also not implemented, other than encouraging smoking cessation as routine clinical practice,
Chengappa 2014	Weekly CBT	Weekly visits. 15 minutes of each visit given up for smoking counselling. CBT using published CBT for Smoking Cessation, Perkins et al,2008.
Smith 2016	Weekly counselling	All subjects received brief (5–10 minute) cigarette smoking prevention counselling at each weekly study visit using a structured program which provided different written information supplemented by verbal counselling at weekly visits.
George 2000	2 types of behavioural therapy	Group 1: The American Lung Association group participated in a standard 7-week manualized behavioural group therapy program and were seen for supportive group counselling during the remaining three weekly group sessions. Group 2: The specialized schizophrenia smoking cessation program included 3 weeks of motivational enhancement therapy (weeks 1 through 3) and seven weeks of psychoeducation, social skills training, and relapse prevention strategies (weeks 4 through 10).
Williams 2010	2 types behavioural therapy	TANS: a high-intensity treatment of 24 sessions (45 minutes) delivered over 26 weeks. MM: a moderate intensity treatment of 9 sessions (20 minutes) over 26 weeks. MM consisted of nine sessions focused on quitting smoking that occurred over 26 weeks. Medication compliance and education about nicotine replacement therapy (NRT) are emphasized throughout, and there are sections on monitoring psychiatric symptoms and understanding medication interactions with tobacco.

Table 1 (contd.) Types of Counselling in Smoking Cessation Programme

Study	Behavioural or Counselling in studies	Smoking Cessation Therapy
Gilbody 2015	Bespoke smoking cessation programme and usual care	1st appointment made with Smoking Cessation practitioner, then follow-up at 1 and 6 months interview/phone/postal questionnaires by trial researchers. 12 month follow-up and study end meeting with researcher. Support sessions specifically adapted for patients with SMI.
Bennett 2015	Multifaceted behavioral group intervention or a supportive group intervention	24 twice weekly group meetings using either group therapy, goal setting, social and low financial reinforcement versus an active comparison group using supportive group, discussion of issues around smoking, barriers and confidence.
Evins 2007	NRT + behavioural counselling	Participants attended a 12-session, 1-hour, weekly smoking cessation group programme 15,17 with 3 to 7 participants led by a psychologist with tobacco treatment specialist training.
George 2008	Behavioural therapy intervention and control groups	10 weekly sessions of manualised group behavioural therapy.
Baker 2006	Treatment as usual	Eight individual 1-hour sessions of motivational interviewing and cognitive behaviour therapy plus nicotine replacement therapy, in addition to treatment as usual and provision of booklets for smoking cessation
Chen 2013	Low dose NRT + psychoeducation	6 sessions of smoking cessation psychoeducation
Gallagher 2007	Three groups, CR, CR +NRT, Self-quit. Education and motivational support to three groups	Visits were once per week for weeks 1 - 4, every other week for weeks 6-12, and once per month for weeks 16-24, with a final follow-up visit at week 36. Collective measures scheduled for each visit, offering tobacco and cessation-related education as well as motivational support.
Tidey 2011	CR with monetary reward	End of programme offered participants who expressed interest in smoking cessation were referred to local agencies and given self-help resources from the American Lung Association.
Weinberger 2008	No behavioural intervention	Visits at baseline and at Weeks 4 and 8 (end of study). No behavioural intervention.
Szombathyne 2010	Motivational enhancement therapy	3 times per week visits for 12 weeks. All patients received weekly motivational enhancement therapy addressing alcohol use.
Wing 2010	Behavioural counselling	Weekly behavioural counselling.

Abbrev. CR=Contingency Reinforcement, NRT=Nicotine Replacement Therapy

Appendix D

Table 1. Risk of bias summary by author

Study	Sequence Generation	Allocation Concealment	Blinding of personnel	Blinding of outcome	Incomplete outcome data	Selective reporting	Other threats to validity
Akbarpour 2010	Unclear	High	Low	High	Unclear	Unclear	Unclear
Baker 2006	Unclear	Low	Unclear	Low	Low	Low	Low
Bennett 2015	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Bloch 2010	Unclear	High	Unclear	High	Unclear	Unclear	Low
Chen 2013	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Chengappa 2014	Unclear	Unclear	Low	Low	Low	Unclear	Low
Evins 2001	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Evins 2005	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Evins 2007	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Low
Gallagher 2007	Unclear	Unclear	High	High	Low	Unclear	Unclear
George 2000	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
George 2002	Unclear	Unclear	Low	Low	Low	Unclear	Low
George 2008	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Hong 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Li 2009	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Gilbody 2015	Low	Low	High	Unclear	Low	Unclear	Low
Shim 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low
Smith 2016	Low	Low	Low	Low	Low	Low	Low
Szombathyne 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Tidey 2011	Low	Unclear	Low	Low	Low	Unclear	Unclear
Weinberger 2008	Unclear	Unclear	Unclear	Unclear	High	High	High
Weinberger 2008[b]	Unclear	Unclear	Unclear	Unclear	High	Unclear	Low
Weiner 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Weiner 2012	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Low
Williams 2010	Low	Unclear	High	Unclear	Low	Unclear	Unclear
Williams 2012	Low	Unclear	Low	Low	Low	Low	Low
Wing 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wu 2012	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Appendix D

Table 2. GRADE clinical evidence profile for bupropion compared to control at 3 and 6 months.

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bupropion	Control	Risk Ratio (95% CI)	
6	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	28/117 (23.9%)	6/118 (5.1%)	**RR 3.96** (1.86 to 8.40)	⊕◯◯◯ VERY LOW
3	randomised trials	very serious	no serious inconsistency	no serious indirectness	very serious imprecision	none	5/51 (9.8%)	2/53 (3.8%)	**RR 2.22** (0.52 to 9.47)	⊕◯◯◯ VERYLOW

Table 3. GRADE clinical evidence profile for varenicline compared to control at 3 and 6 months

Quality assessment							№ of patients		Effect	Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Varenicline	Control	Risk Ratio (95% CI)	
4	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	41/165 (24.8%)	9/123 (7.3%)	**RR 3.56** (1.82 to 6.96)	⊕◯◯◯ VERY LOW
2	randomised trials	very serious [1]	no serious inconsistency	no serious indirectness	very serious imprecision	none	16/116 (13.8%)	3/72 (4.2%)	**RR 3.69** (1.08 to 12.60)	⊕◯◯◯ VERY LOW

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7/8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7/8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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