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Efficacy and tolerability of pharmacotherapy for smoking cessation in adults with serious mental illness: A systematic review and network meta-analysis

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Abstract

Background and aims—To assess the efficacy and tolerability of adjunctive pharmacotherapy for smoking cessation in adults with serious mental illness (SMI) by means of a systematic review and network meta-analysis.

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Declaration of Interests:

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author):

ER has nothing to disclose

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Method—We searched Embase, Medline, PsychINFO and the Cochrane Central Register of Controlled Trials, from database inception to 1 December 2014 for randomised controlled trials (RCTs) published in English. We included all studies of smokers with SMI (including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder and depressive psychoses) who were motivated to quit smoking. Pharmacotherapies included nicotine replacement therapy (NRT), bupropion and varenicline delivered as monotherapy or in combination compared with each other or placebo. The efficacy outcome was self-reported sustained smoking cessation, biochemically verified at the longest reported time point. The tolerability outcome was number of patients discontinuing the trial due to any adverse event

Results—Seventeen study reports were included which represented fourteen individual RCTs. No trials were found in patients with depressive psychoses, delusional disorder or which compared NRT monotherapy with placebo. A total of 356 and 423 participants were included in the efficacy and tolerability analyses respectively. From the network meta-analysis both bupropion and varenicline were more effective than placebo (OR 4.51 95% Credible Interval (CrI) 1.45 to 14.04 and OR 5.17 95% CrI 1.78 to 15.06 respectively). Data were insensitive to an assessment of varenicline versus bupropion (OR 1.15 95% CrI 0.24 to 5.45). There were no significant differences in tolerability. All outcomes were rated by GRADE criteria as very low quality.

Conclusions—The limited evidence available to date suggests that bupropion and varenicline are effective and tolerable for smoking cessation in adults with serious mental illnesses.

Introduction

Smoking is a leading preventable cause of illness and premature death worldwide, accounting for 20% of deaths in men over 30 years of age, and 5% in women.¹ Each year over 83,000 in the UK and 440,000 people in the US die from smoking-related illness,² with \$157 billion in health-related economic losses directly attributable to smoking.^{3–5} The global mortality toll is over 5 million annually and is increasing. Cigarette smoking has been the single largest source of preventable morbidity and mortality in the U.S. for the last 29 years.^{4–5} Fifty years after the first Surgeon General's report of an association between smoking and cancer, adult smoking in the United States has declined by 55% in the general population, to 18%.^{6–7} Comparable decreases in smoking rates have not been realised among smokers with psychiatric illness.⁸ Smoking prevalence among adults with serious mental illness (SMI) is higher today, at 53%, than it was in the general population in 1964.^{9–10} The 7.3 million adults with SMI in the US who smoke tobacco,^{11–12} make up 13% of all smokers in the US and 2.2% of the total U.S. population.¹² Recent estimates indicate that 64%–79% of those with schizophrenia spectrum disorders smoke tobacco regularly,^{11,13} as do 44–71% of those with bipolar disorder,^{10,13–15} and most state they would like to quit.^{16–18}

People with serious mental illnesses (SMI), defined as any nonorganic disorder with psychotic features that results in a substantial disability (including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder and depressive psychoses) have both higher all-cause and smoking-related mortality compared to the general population,¹⁹ and several large epidemiological studies show that people with schizophrenia and bipolar affective disorder in addition to having higher rates of smoking, have much

lower rates of former smoking and less smoking cessation treatment utilisation when compared with the general population.^{20,21,22} It is not known whether this lower rate of smoking cessation is due to lower effectiveness of smoking cessation treatments in this population or lower availability and/or utilisation of such effective treatments in this population.

The gold standard treatment for smoking cessation is pharmacotherapy combined with individual or group behavioural support.²³ There is particular concern among health care professionals regarding psychiatric effects of both nicotine withdrawal and potential psychiatric adverse effects of pharmacotherapeutic cessation aids within this population.²⁴

Nicotine Replacement Therapy (NRT), bupropion and varenicline are licensed pharmacotherapeutic cessation aids that have been shown by network meta-analysis to be more effective than placebo in the general population, with varenicline considered superior to single forms of NRT or bupropion, and equally effective to combination NRT²⁵ however this analysis specifically excluded those patients with SMI.²⁶ We hypothesise pharmacotherapy may be an even more important component of smoking cessation treatment for smokers with SMI as placebo coupled with or without behavioural techniques for smoking cessation results in quit rates which are extremely low in this population.^{23,26} This may be due in part to nicotinic acetylcholine receptor abnormalities in the central nervous systems of those with schizophrenia spectrum disorders and could result in a differential effect of pharmacotherapy relative to behavioural therapy alone in this population.^{27,28} This underscores the importance of tolerability of these treatments to both treating health care professionals and smokers with SMI and the potential for particular benefit for maintenance treatment in this group.

Whilst varenicline and bupropion have been shown to be more effective than placebo in people with schizophrenia,²⁶ no one has previously undertaken network meta-analysis within the SMI population. Such an analysis is particularly pertinent, as these treatments appear to be underutilised in smokers with SMI, and there remain perceived concerns about the tolerability of their use, particularly surrounding concerns of alteration in mental state, and suicidal ideation.^{23,29} We report a systematic review of randomised controlled trials that compared efficacy and tolerability of adjunctive pharmacotherapy versus active or placebo control for smoking cessation in smokers with SMI who were motivated to quit. We used network meta-analysis, to allow the integration of data from direct and indirect comparisons, and provide estimates between comparisons currently unavailable in the literature, as has previously been conducted in the general population for smoking cessation pharmacotherapies.²⁵ Whilst a recent pairwise meta-analysis of smoking cessation interventions has been published in patients with a diagnosis of schizophrenia,²⁶ and whilst a comparison of available treatments prior to 2010 exists in patients with SMI,³⁰ this manuscript aims to provide an up to date and comprehensive synthesis of direct and indirect evidence through network meta-analysis to provide a clinically useful summary to guide pharmacotherapeutic smoking cessation treatment decisions for smokers with SMI. This is timely given the increasing implementation of comprehensive smoke free policies in mental health settings.³¹

Methods

Search strategy

We searched Embase, Medline, PsychINFO and the Cochrane Central Register of Controlled Trials, from database inception to December 1st 2014 for randomised controlled trials published in English. Two authors (ER and DR) initially assessed the titles and abstracts identified by the search and reviewed the full text of the remaining articles for inclusion. Any discrepancy was resolved by discussion, and where agreement could not be reached a third author (AM) was consulted. All relevant references were checked for additional citations. The full search details can be found in the online supplementary material.

Types of participants

We included all studies of adult participants with any form of severe mental illness (SMI), defined as any nonorganic disorder with psychotic features that results in a substantial disability, including schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder or depressive psychoses.¹⁹ The category excluded those with unipolar depression or with a primary diagnosis of alcohol or substance abuse, as those patients are thought to require different treatment needs.³² Participants were required to currently smoke and report being motivated to attempt to quit or reduce smoking. Studies of participants not intending to stop or significantly reduce smoking were excluded, as these groups of patients are thought to have different needs and require additional specialist support over and above standard stop smoking treatment.³³ When studies did not report the motivation to quit or reduce of participants we contacted corresponding authors of potentially includable studies and included them if they confirmed motivation to quit or reduce as a prerequisite for trial entry.

Type of Interventions

Interventions included nicotine replacement therapy (NRT), bupropion and varenicline delivered as monotherapy or in combination pharmacotherapy with or without additional psychological support. These could be compared to each other or to placebo.

Types of outcomes

We included any trial which was able to contribute data to the efficacy or tolerability outcome. The efficacy outcome is sustained smoking cessation, i.e. abstinence for six months or longer, as recommended by the Russell Standard,³⁴ an internationally recognised standard for reporting smoking cessation trials. Where multiple efficacy outcomes were reported in individual studies the preferred outcome is self-reported, biochemically verified continuous or prolonged abstinence at six months or where this was not available the longest reported time point. Where continuous or prolonged abstinence was not measured or reported, 7-day point prevalence abstinence rates at 6 months, or the longest reported time point in the study post quit-date by self-report with biochemical verification were extracted.

The tolerability outcome was number of patients discontinuing the trial due to any adverse event, a proxy measure used commonly in both schizophrenia trials and network meta-analyses of psychotropic medication.^{35–37}

Assessment of methodological quality of included studies

Two authors (ER and DR) independently assessed the overall quality of each outcome using a modified version of Grading of Recommendations Assessment, Development and Evaluation (GRADE) for both the pairwise comparisons and the network meta-analysis. Each outcome was given a rating of high, moderate, low or very low quality based upon risk of bias (assessed using the Cochrane risk of bias tool), inconsistency (between estimates of effect across studies), indirectness (i.e. applicability of participants, interventions and outcomes to the clinical question under consideration), imprecision and the risk of publication bias. GRADE clinical evidence profiles for each outcome can be found in the online supplementary material.

Statistical Analysis

Analysis was based on all participants randomised to their original groups or those who received at least one dose of study medication (an intention-to-treat or modified intention to treat analysis). For the analysis of efficacy, outcomes for the missing participants were imputed, assuming that all missing participants were continuing smokers.

For every available pairwise comparison, the odds ratio (OR) and 95% confidence interval (CI) were calculated and pairwise meta-analysis performed by synthesising studies that compared the same interventions, using a random effects model to account for the assumption that differing studies were estimating different, but related, treatment effects. Heterogeneity was assessed by the I^2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than sampling error, and significant heterogeneity between pairwise comparisons was defined a priori as $I^2 > 50\%$. Forest plots are available in the online supplementary material.

For those interventions that had common comparators and were able to be linked within a network, we conducted a random effects network meta-analysis within a Bayesian framework;^{38,39} the model assuming a common heterogeneity across all comparisons. For trial arms in which there was a zero cell count, a continuity correction of 0.5 was applied.⁴⁰ The network plots are presented for efficacy and tolerability outcomes. The OR was calculated and presented with 95% credible interval (CrI) alongside their 95% predictive intervals (PrI) to facilitate interpretation and provide an interval within which the estimate of future studies is expected to be. To evaluate inconsistency, we calculated the difference between indirect and direct estimates whenever indirect estimates could be calculated with a common comparator. Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CrI excluding zero.

A clustered ranking plot and a plot ordering the interventions by their overall probability to be the best were constructed to depict graphically the trade-off between the efficacy and tolerability. These values are based on cluster analysis of surface under the cumulative ranking curve (SUCRA) values, (the larger the value the better the rank of treatment).

SUCRA values are conditional on the set of treatments being compared and account for the uncertainty in the estimated treatment effects.⁴¹

Two authors (ER and DR) independently extracted, checked and entered the data. Analyses and graphical representations were facilitated using the *mvmeta* command in STATA version 12.1.^{41,42}

Ethical approval was not required for this study. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Results

The search process identified 1155 records. 62 full text articles were assessed for eligibility, and 17 study reports were included, which represented 14 individual RCTs. The PRISMA flow chart for study selection can be found in the online supplementary material.

Six trials compared bupropion to placebo,^{43–50} five trials compared varenicline to placebo,^{51–55} and one trial was a three-arm trial that compared bupropion to varenicline and placebo.⁵⁶ Nine trials contributed to the efficacy network meta-analysis with a total of 356 participants,^{44–50,52–55} and ten trials contributed to the tolerability network meta-analysis with a total of 423 participants.^{43–47,49–53,55,56} Two additional trials were identified which compared bupropion plus NRT to placebo plus NRT but were unable to form part of the network due to a lack of common comparator.^{57–58} As such, the pairwise meta-analysis efficacy and tolerability odds ratios are presented with their 95% CI for this comparison. Nine trials were conducted in participants with a diagnosis of schizophrenia or schizoaffective disorder,^{43,46–50,52,55,56,58,59} two trials in participants with a diagnosis of schizophrenia^{44,45,57} and three trials were conducted in participants with a diagnosis of bipolar affective disorder.^{50,52,53} Characteristics of all included studies can be found in table one.

The overall quality of all outcomes was rated as very low with most studies not reporting details about randomisation and allocation concealment. There was no significant heterogeneity demonstrated for any pairwise comparison (all I^2 values <30%) and no evidence of inconsistency within the network, however there were no closed loops within the network and whilst no heterogeneity was demonstrated the extent to which this is a true representation within this population is limited by small number of trials and participants. Further details can be found in the GRADE tables and footnotes in the online supplementary material.

Direct pairwise meta-analysis results are available in the online supplementary material. For those interventions that had common comparators network meta-analysis demonstrated both bupropion and varenicline to be significantly more effective for smoking cessation than placebo, OR 4.51 95% CrI (1.45 to 14.04) and OR 5.17 95% CrI (1.78 to 15.06) respectively. When comparing varenicline with bupropion in terms of treatment efficacy there was no significant advantage for one treatment over the other, OR 1.15 95% CrI (0.24 to 5.45) (Figure 2a). There were no significant differences in tolerability between any

comparison. Neither active treatment differed from the other or from placebo in terms of the drop out rate (Figure 2b). Figure two shows the summary estimates and predictive interval of the odds ratios for efficacy and tolerability. Figure three shows the interventions ordered by their overall probability to be the best treatment, and figure four shows their clustered rankings in terms of both efficacy and tolerability. Differences between bupropion and varenicline depicted in figures 3 and 4 are not significant.

In direct pairwise meta-analysis comparing bupropion plus NRT compared to placebo plus NRT we were unable to demonstrate a statistically significant difference between the interventions OR 4.13 95% CI (0.92 to 18.57), due to small sample size the estimate is imprecise with a wide CI. There was no significant difference in tolerability, OR 1.04 95% CI (0.14 to 8.04). Forest plots for these comparisons can be found in the online supplementary material.

Discussion

Bupropion and varenicline are effective and tolerable for smoking cessation in adults with SMI. Both varenicline and bupropion had superior treatment efficacy to placebo and were not different from each other. There were no significant differences in drop outs due to any adverse event including any changes in mental state or expressed suicidal ideation, and no deaths reported that were deemed to be related to study medication across all trials. This review supports the finding that, as in the general population,²⁵ bupropion and varenicline are more effective than placebo in people with SMI, however it also exposes gaps in the smoking cessation treatment literature within the SMI population. Notably there are no available data to date upon which to assess efficacy and tolerability of NRT monotherapy in this population versus placebo, or versus other monotherapies. Though bupropion ranks higher than varenicline for combined efficacy and tolerability this is statistically insignificant as such there is inconclusive evidence it should be recommended over varenicline as first line treatment, or that short term treatment with either results in effects that are durable and sustained long term.

There were several limitations including the small number of trials and participants, resulting in imprecise estimates with wide credible intervals. The methodological quality of the included trials also contributed to all outcomes being graded as very low quality. No comparison was available for NRT versus placebo in this population, and due to limited number of available comparators we were unable to connect the trials of bupropion plus NRT versus NRT plus placebo into the network. Due to the small number of participants in a sparse network with low numbers of events we chose to apply continuity corrections to cells with zero event count, which has the potential to bias towards no difference between interventions and produce large variances. Of eleven trials reporting efficacy data eight reported biochemically verified continuous or prolonged abstinence of which only three reported at or later than six months. This necessitated the use of earlier than six month continuous abstinence data for five trials. Point prevalence efficacy data were used from the remaining three trials. . Whilst there has been evidence that cytisine, which is licensed for use in Russia and some of the former socialist economy countries, and non-licensed therapies including nortriptyline and clonidine increased chances of quitting in the general

population this review didn't formally evaluate their evidence base but the authors are not aware of any trials conducted with these agents in the SMI population.²⁵ It should also be highlighted that this review only focussed on those trials which included a pharmacotherapy intervention for smoking cessation compared to other pharmacotherapies or to placebo.

The study has several strengths in that the review methods were systematic and comprehensive. The network is also able to comment on indirect estimates of varenicline compared to bupropion, not previously available in the literature. Although there were no closed loops within the developed network we demonstrated no significant heterogeneity between pairwise comparisons or between comparable direct and indirect estimates in the network.

Most studies were conducted in people with schizophrenia and or schizoaffective disorder, whilst only three studies with 70 participants were conducted in bipolar affective disorder.^{50,52,53} We found no studies conducted in those patients with depressive psychoses or delusional disorder. Five studies were deemed eligible but did not report if recruited patients were motivated to quit smoking.^{50,54,55,60,61} We contacted all corresponding authors, all replied and three trials were confirmed to have recruited motivated to quit smokers and were included,^{50,54,55} two trials were confirmed to have recruited non-motivated smokers and were excluded^{60,61}.

Whilst our study shows that bupropion and varenicline are both effective and tolerable in terms of smoking cessation adjunctive pharmacotherapy, and that there is a higher probability that bupropion outranks varenicline when both outcomes are combined the quality of the data prevents firm conclusions being drawn as to recommended first line therapy, as such individual preferences should determine which treatment to use first. Whilst evidence suggests that smokers with schizophrenia smoke more heavily and extract more nicotine from each cigarette^{23,62} the lack of available randomised data for any NRT monotherapy versus placebo comparison in this group prevents us commenting on the efficacy and tolerability of this pharmacological strategy despite its more frequent prescription compared to other pharmacological adjuncts.^{20,23} This prompts the need for future research, particularly for placebo-controlled trials of NRT in an SMI population, and trials which report outcomes beyond the end of treatment, so that longer-term effects of the intervention can be better evaluated. We would hypothesise triallists may have thought the efficacy of NRT to have been proven in over a hundred placebo-controlled RCTs in a variety of populations, and as such the necessity to do this in another population may not have been thought appropriate. However quit rates are low in the SMI population^{23,26} potentially due to neurobiological factors and differential utilisation of smoking cessation products. Whilst our study shows no difference in tolerability of pharmacotherapy compared to placebo, we acknowledge there exists concern regarding perceived neuropsychiatric side effects of varenicline. Recent studies have found no significant difference between varenicline and comparison groups in terms of neuropsychiatric events in general population or SMI smokers. Gibbons and Mann analysed data from 17 placebo controlled trials to compare the effects in patients with (n=1,004) and without (n=7,023) psychiatric disorders, and also the rates of neuropsychiatric adverse events in patients receiving varenicline or NRT (n=35,800).⁶³ They found no evidence of risk of serious neuropsychiatric adverse

events, in individuals with and without a recent history of a psychiatric disorder. Rates of neuropsychiatric disorders were significantly lower for varenicline than for NRT. Similarly, in a meta-analysis of 39 RCTs including n=10,761 participants, there was no evidence of an increased risk of suicide or attempted suicide in patients with or without a mental illness.⁶⁴

It should be remembered that the gold standard intervention for smoking cessation is pharmacotherapy coupled with individual or group behavioural support and as such pharmacotherapy intervention estimates of efficacy should be always be taken in the context of behavioural support interventions. However given the high prevalence of regular tobacco smoking, and low rates of former smoking in the SMI population,²³ coupled with the recent opportunity for intervention with implementation of universal smoke free policies there is a need to maximise the provision of effective smoking cessation therapies,³¹ including the prescription of proven efficacious and tolerable pharmacotherapies such as varenicline and bupropion on a much broader scale than is currently practiced

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Network plot of the efficacy and tolerability of pharmacological intervention for smoking cessation in patients with serious mental illness who are motivated to quit (efficacy and tolerability outcomes).

Figure 2.

Figure 2 A and B: Predictive interval plots for A. efficacy and B. Tolerability of pharmacological intervention for smoking cessation in patients with serious mental illness. The black solid lines represent the confidence intervals for summary odds ratios for each comparison and the red dashed lines the respective predictive intervals. The blue line is the line of no effect (odds ratio equal to 1).

Figure 3.

Interventions ordered by their overall probability to be the best treatment in terms of both efficacy and tolerability, showing the contributions to the overall scores of efficacy and tolerability. The cumulative percentages after normalisation (0–100) are shown in the key. Every drug was scored with points up to a maximum of 50 for efficacy and 50 for tolerability (overall maximum score 100), with data from rankograms and SUCRAs. No significant difference was demonstrated between bupropion and varenicline.

Figure 4.

Clustered ranking plot of the pharmacological intervention for smoking cessation in patients with serious mental illness network based on cluster analysis of SUCRA values for two different outcomes: efficacy and tolerability. Treatments lying in the upper right corner are more effective and tolerable than the other treatments.

Table 1

Characteristics of Included Studies

	Population	Inclusion and Exclusion Criteria	n	Trial Duration	Intervention	Comparison	Reported Outcomes
Bupropion versus placebo							
Bloch 2010	Israeli smokers who met DSM-IV-TR for schizophrenia or schizoaffective disorder recruited from the community All patients were interested in quitting or at least reduce significantly the number of cigarettes per day	Judged by their psychiatrists to be clinically stable Had a stable dose of antipsychotic medication for at least one month. Were in stable physical health.	61	14 weeks	Bupropion 150mg PO od for 3/7 then 300mg PO od thereafter + 15 sessions group CBT	Placebo	Abstinence not defined or measured Number of participants who discontinued the trial because of adverse events.
Evins 2001	American smokers with a DSM-IV diagnosis of schizophrenia recruited from the community All patients were interested in quitting.	All patients were on stable dose of antipsychotic medications for at least 4 wks. Patients were excluded if they had co-morbid substance misuse, bulimia, a history of seizure disorder or current major depressive episode.	19	12 weeks	Bupropion 150mg PO od + 9 sessions group CBT	Placebo	Sustained abstinence (self-report verified by expired CO level < 9 ppm or serum cotinine < 14 ng/ml at last 4 weeks of therapy) at weeks 12 and 24. Follow-up study also reported point prevalence abstinence after 2 years Number of participants who discontinued the trial because of adverse events
Evins 2005	American smokers with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, depressed type recruited from the community All patients were interested in quitting.	All patients were on antipsychotic medication for more than 30 days and had stable psychiatric symptoms. Patients excluded with substance use disorder (other than nicotine or caffeine) within 6 months, or with a history of seizure disorder, bulimia, mania or current major depressive episode	57	12 weeks	Bupropion 150 mg PO od for 7/7 then 300mg PO od thereafter + 12 sessions group CBT	Placebo	Sustained abstinence (self-report verified by expired CO level < 9 ppm at last four study visits) at week 12. Number of participants who discontinued the trial because of adverse events
George 2002	American smokers with DSM-IV diagnosis of schizophrenia or schizoaffective disorder recruited from the community All patients were interested in quitting.	Patients fulfilled the following criteria: (1) FTND score ≥ 5 ; (2) expired CO level ≥ 10 ppm; (3) plasma cotinine level ≥ 150 ng/ml. Patients were excluded if they had (1) a history of epilepsy or seizure; (2) history of alcohol or drug abuse 6 months before the study; (3) a change of dose of antipsychotic for symptom control or side effect in the past 6 months.	32	10 weeks	Bupropion 150mg PO od for 3/7 then 300 mg PO od thereafter + 10 sessions of group therapy for motivational enhancement, psychoeducation and relapse prevention	Placebo	Sustained abstinence (self-report verified by expired CO level < 10 ppm at last four weeks therapy session) at week 10.

	Population	Inclusion and Exclusion Criteria	n	Trial Duration	Intervention	Comparison	Reported Outcomes
Weiner 2012	American smokers with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder recruited from the community. All patients were interested in decreasing smoking.	All patients had an FTND score of 4 and no change in their usual medication regimen. Patients were excluded with current depressive episode, substance misuse other than nicotine in the past 3 months, substance dependence other than nicotine in the past 6 months, or neurological diagnosis or unstable medical condition.	46	14 weeks	Bupropion 300 mg PO od for 12 weeks (weeks 2 to 14) + 9 sessions of group therapy according to American Cancer Society Fresh Start Program (modified for people with schizophrenia)	Placebo	Sustained abstinence (self-report for last four study visits verified by CO < 10ppm for 4 weeks) at week 14 Number of participants who discontinued the trial because of adverse events.
Weinberger 2008	American smokers with a DSM-IV diagnosis of Bipolar I disorder recruited from the community	Patients were excluded with current antidepressant medication, not taking or not being stabilised on a mood stabiliser, current drug use or medical conditions.	5	10 weeks	Bupropion IR 75mg PO od for 3/7 increasing to 150mg SR PO od for 4/7 increased to 150mg SR PO bd thereafter until week 10 as tolerated + weekly manualised group behavioural therapy for smoking cessation	Placebo	Point prevalence abstinence (self-report verified by CO < 10ppm) at week 10 Number of participants who discontinued the trial because of adverse events.
Bupropion versus varenicline versus placebo							
Fatemi 2013	American smoker with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder Expressed a motivation to either quit or reduce smoking.	Patients were clinically stable, have no substance misuse within the previous three months, did not use other nicotine products, not currently taking bupropion or varenicline.	24	12 weeks	Varenicline 1mg PO bd + 20 minutes of antismoking counselling at each visit	Bupropion SR 150mg PO bd Placebo	Abstinence not defined or measured Number of participants who discontinued the trial because of adverse events.
Varenicline versus placebo							
Meszaros 2013	American smokers with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder recruited from the community. All consented patients expressed a desire to quit drinking and smoking.	Patients took antipsychotic medication for at least 4 weeks Exclusion criteria included: (1) unable to give informed consent; (2) currently receiving any pharmacological smoking cessation treatment including bupropion; (3) currently taking naltrexone, Campral or Anabuse; (4) history of suicide attempt in the past yr; (5) suicidal ideation at baseline; (6) female of childbearing potential without contraception; (7) pregnancy; (8) unstable medical or psychiatric disorder; (9) positive urine drug screen for cocaine, opioids or amphetamine at baseline, or current DSM-IV diagnosis of cocaine, opioid or	10	9 weeks	Varenicline 0.5mg PO od for 3/7, then 0.5mg PO bd for 4/7, then 1mg PO bd for 7 weeks Varenicline 0.5mg PO od for 3/7, then 0.5mg PO bd for 4/7, then 1mg PO bd for 7 weeks	Placebo	Abstinence not defined or measured Number of participants who discontinued the trial because of adverse events. Abstinence not defined or measured Number of participants who discontinued the trial because of adverse events.

	Population	Inclusion and Exclusion Criteria	n	Trial Duration	Intervention	Comparison	Reported Outcomes
		cannabis dependence (1 month prior to enrolment) cannabis dependence (1 month prior to enrolment)					
Williams 2012	American and Canadian smokers with a DSM-IV-TR diagnosis of schizophrenia or schizoaffective disorder recruited from the community All patients scored at least 7 on the baseline motivation to quit score of the contemplation ladder.	All were clinically stable (without hospitalisation or acute exacerbation and receiving psychiatric treatment for the past six months with a total PANSS score of <70. Female participants required a negative pregnancy test. Exclusion criteria included serious suicidal ideation/behaviour, history of drug/alcohol abuse or dependence, clinically significant cerebrovascular or cardiovascular disease in the last six months, serious unstable medical disease, uncontrolled hypertension, previous use of varenicline, BMI <15 or >38, use of other smoking cessation aids, use of marijuana or other tobacco products during study.	128	12 weeks	Varenicline 0.5mg PO bid for 3/7, then 1mg PO bid for 11 weeks + Weekly group counselling (less than 30 minutes)	Placebo PO bid for 3/7, then 0.5mg PO bid for 4/7, then 1mg PO bid for 11 weeks	7 day point prevalence abstinence (self-report verified by CO < 10 ppm) at week 12 and 24. Number of participants who discontinued the trial because of adverse events.
Chengappa 2014	American smokers with a DSM-IV diagnosis of bipolar disorder (I, II or NOS) recruited from the community. Willingness to quit smoking in the next 30 days.	All patients had a MADRS and YMRS 8. Maintenance medication for bipolar disorder used for at least 8 weeks in six months prior to enrolment no history of hospitalisation, suicide attempts or aggressive or violent acts. Bupropion was only exclusionary if being used as a smoking cessation aid, females required a negative pregnancy test. Exclusion criteria were uncontrolled seizure disorder, current or past (3 months) alcohol or drug dependence, unstable medical conditions, moderate to severe renal failure.	60	12 weeks	Varenicline 0.5mg PO od for 3/7, then 0.5mg PO bid for 4/7, then 1mg PO bid for 11 weeks + 15 minutes of smoking cessation counselling at each visit	Placebo	Sustained abstinence (self-report and verified by expired CO < 10 ppm for last 4 weeks) at week 12. Number of participants who discontinued the trial because of adverse events.
Wu 2012	Canadian smokers with a SCID derived DSM-IV diagnosis of bipolar disorder I or II *From author correspondence "Motivated to quit at baseline based on a contemplation ladder score of 7 or higher"	All patients were on a stable dose of mood stabiliser for at least a month and deemed psychiatrically stable through clinical evaluation. Patients were excluded with major medical conditions or drug abuse or dependence in the last three months.	5	10 weeks	Varenicline 0.5mg PO od for 3/7, then 0.5mg PO bid for 4/7, then 1mg PO bid for 9 weeks + weekly manualised smoking cessation group behavioural therapy	Placebo	7 day point prevalence abstinence (self-report verified by CO < 10 ppm) at week 10 and 24.
Weiner 2011	American smokers with a DSM-IV-TR diagnosis	All patients were clinically stable and on a stable dose of	9	14 weeks	Varenicline 1mg PO bid	Placebo	Sustained abstinence (self-report confirmed by expired

	Population	Inclusion and Exclusion Criteria	n	Trial Duration	Intervention	Comparison	Reported Outcomes
	of schizophrenia or schizoaffective disorder of schizophrenia or schizoaffective disorder of schizophrenia or schizoaffective disorder *From author correspondence "Yes to quit at some point-but some did say they really just wanted to cut down."	Patients were recruited from the community. Patients were included if they (1) had any lifetime history of suicide attempt; (2) had psychiatric hospitalisation within the past 6 ms; (3) had suicidal ideation or were currently depressed; (4) were taking bupropion.			+ Individual smoking cessation counselling based on American Lung Association Freedom from smoking program.		CO < 10ppm for last four study visits) Number of participants who discontinued the trial because of adverse events.
Bupropion + NRT versus placebo + NRT							
Evins 2007	American smokers with a DSM-IV diagnosis of schizophrenia recruited from the community. All pts were interested in quitting.	All patients were on antipsychotic medication for > 30 days and had stable psychiatric symptoms. Patients excluded with substance use disorder (other than nicotine or caffeine) within 6 months, or with a history of seizure disorder, bulimia, mania or current major depressive episode.	51	12 weeks	Bupropion S/R 150mg PO od for 7/7 and bupropion S/R 300 mg PO od thereafter + 1) 12 sessions group CBT and (2) Transdermal nicotine patch (from week 4) 21 mg/day for 4 weeks, then 14 mg/day for 2 weeks, 7 mg/day for 2 weeks + up to 18 mg per day nicotine gum as required	Placebo	Sustained abstinence (defined by meeting 7-day point prevalence abstinence by self-report at every assessment after target quit date at the time point, verified by expired CO level < 8 ppm) at weeks 8, 12, 24 and 52. Number of participants who discontinued the trial because of adverse events.
George 2008	American smokers with a SCID-IV diagnosis of schizophrenia or schizoaffective disorder recruited from the community. All pts were interested in quitting.	All patients were clinically stable and on a stable dose of antipsychotic for at least 1 month before randomisation. Patients with alcohol or substance misuse or dependence 3 months before study or a history of seizure disorder were excluded.	59	10 weeks	Bupropion S/R 150mg PO od for 3/7 and bupropion S/R 300 mg PO od thereafter + 10 weekly 50-minute sessions of group behavioural therapy and Transdermal Nicotine patch (21 mg per 24 hours) from day 15 to day 70	Placebo	Sustained abstinence (self-report verified by expired CO < 10 ppm for last 4 weeks of trial and 6 months post target quit date) at weeks 10 and 24.