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Antidepressants for smoking cessation (Review)

Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N

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[Intervention Review]

Antidepressants for smoking cessation

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ABSTRACT

Background

Whilst the pharmacological profiles and mechanisms of antidepressants are varied, there are common reasons why they might help people to stop smoking tobacco. Firstly, nicotine withdrawal may produce depressive symptoms and antidepressants may relieve these. Additionally, some antidepressants may have a specific effect on neural pathways or receptors that underlie nicotine addiction.

Objectives

To assess the evidence for the efficacy, safety and tolerability of medications with antidepressant properties in assisting long-term tobacco smoking cessation in people who smoke cigarettes.

Search methods

We searched the Cochrane Tobacco Addiction Specialized Register, which includes reports of trials indexed in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO, clinicaltrials.gov, the ICTRP, and other reviews and meeting abstracts, in May 2019.

Selection criteria

We included randomized controlled trials (RCTs) that recruited smokers, and compared antidepressant medications with placebo or no treatment, an alternative pharmacotherapy, or the same medication used in a different way. We excluded trials with less than six months follow-up from efficacy analyses. We included trials with any follow-up length in safety analyses.

Data collection and analysis

We extracted data and assessed risk of bias using standard Cochrane methods. We also used GRADE to assess the certainty of the evidence.

The primary outcome measure was smoking cessation after at least six months follow-up, expressed as a risk ratio (RR) and 95% confidence intervals (CIs). We used the most rigorous definition of abstinence available in each trial, and biochemically validated rates if available. Where appropriate, we performed meta-analysis using a fixed-effect model.

Similarly, we presented incidence of safety and tolerance outcomes, including adverse events (AEs), serious adverse events (SAEs), psychiatric AEs, seizures, overdoses, suicide attempts, death by suicide, all-cause mortality, and trial dropout due to drug, as RRs (95% CIs).

Main results

We included 115 studies (33 new to this update) in this review; most recruited adult participants from the community or from smoking cessation clinics. We judged 28 of the studies to be at high risk of bias; however, restricting analyses only to studies at low or unclear risk did not change clinical interpretation of the results. There was high-certainty evidence that bupropion increased long-term smoking

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cessation rates (RR 1.64, 95% CI 1.52 to 1.77; I^2 = 15%; 45 studies, 17,866 participants). There was insufficient evidence to establish whether participants taking bupropion were more likely to report SAEs compared to those taking placebo. Results were imprecise and CIs encompassed no difference (RR 1.16, 95% CI 0.90 to 1.48; I^2 = 0%; 21 studies, 10,625 participants; moderate-certainty evidence, downgraded one level due to imprecision). We found high-certainty evidence that use of bupropion resulted in more trial dropouts due to adverse events of the drug than placebo (RR 1.37, 95% CI 1.21 to 1.56; I^2 = 19%; 25 studies, 12,340 participants). Participants randomized to bupropion were also more likely to report psychiatric AEs compared with those randomized to placebo (RR 1.25, 95% CI 1.15 to 1.37; I^2 = 15%; 6 studies, 4439 participants).

We also looked at the safety and efficacy of bupropion when combined with other non-antidepressant smoking cessation therapies. There was insufficient evidence to establish whether combination bupropion and nicotine replacement therapy (NRT) resulted in superior quit rates to NRT alone (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 52%; 12 studies, 3487 participants), or whether combination bupropion and varenicline resulted in superior quit rates to varenicline alone (RR 1.21, 95% CI 0.95 to 1.55; I^2 = 15%; 3 studies, 1057 participants). We judged the certainty of evidence to be low and moderate, respectively; in both cases due to imprecision, and also due to inconsistency in the former. Safety data were sparse for these comparisons, making it difficult to draw clear conclusions.

A meta-analysis of six studies provided evidence that bupropion resulted in inferior smoking cessation rates to varenicline (RR 0.71, 95% CI 0.64 to 0.79; I^2 = 0%; 6 studies, 6286 participants), whilst there was no evidence of a difference in efficacy between bupropion and NRT (RR 0.99, 95% CI 0.91 to 1.09; I^2 = 18%; 10 studies, 8230 participants).

We also found some evidence that nortriptyline aided smoking cessation when compared with placebo (RR 2.03, 95% CI 1.48 to 2.78; I^2 = 16%; 6 studies, 975 participants), whilst there was insufficient evidence to determine whether bupropion or nortriptyline were more effective when compared with one another (RR 1.30 (favouring bupropion), 95% CI 0.93 to 1.82; I^2 = 0%; 3 studies, 417 participants). There was no evidence that any of the other antidepressants tested (including St John's Wort, selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs)) had a beneficial effect on smoking cessation. Findings were sparse and inconsistent as to whether antidepressants, primarily bupropion and nortriptyline, had a particular benefit for people with current or previous depression.

Authors' conclusions

There is high-certainty evidence that bupropion can aid long-term smoking cessation. However, bupropion also increases the number of adverse events, including psychiatric AEs, and there is high-certainty evidence that people taking bupropion are more likely to discontinue treatment compared with placebo. However, there is no clear evidence to suggest whether people taking bupropion experience more or fewer SAEs than those taking placebo (moderate certainty). Nortriptyline also appears to have a beneficial effect on smoking quit rates relative to placebo. Evidence suggests that bupropion may be as successful as NRT and nortriptyline in helping people to quit smoking, but that it is less effective than varenicline. There is insufficient evidence to determine whether the other antidepressants tested, such as SSRIs, aid smoking cessation, and when looking at safety and tolerance outcomes, in most cases, paucity of data made it difficult to draw conclusions. Due to the high-certainty evidence, further studies investigating the efficacy of bupropion versus placebo are unlikely to change our interpretation of the effect, providing no clear justification for pursuing bupropion for smoking cessation over front-line smoking cessation aids already available. However, it is important that where studies of antidepressants for smoking cessation are carried out they measure and report safety and tolerability clearly.

PLAIN LANGUAGE SUMMARY

Do medicines used to treat depression help people to quit smoking?

Background and review questions

Some medicines and supplements that have been used to treat depression (antidepressants) have also been tested to see whether they can help people to stop smoking. Two of these treatments - bupropion (sometimes called Zyban) and nortriptyline - are sometimes given to help people quit smoking. This review looks at whether using antidepressants actually helps people to stop smoking (for six months or longer), and also looks at the safety of using these medicines.

Study characteristics

This review includes 115 studies looking at how helpful and safe different antidepressants are when used to quit smoking. Most of the studies were conducted in adults. We included studies of any length when looking at safety, but studies needed to be at least six months long when assessing whether people had managed to quit smoking. The evidence is up to date to May 2019.

Key results

Using the antidepressant, bupropion, makes it 52% to 77% more likely that a person will successfully stop smoking, which is equal to five to seven more people successfully quitting for six months or more for every one hundred people who try to quit. There is evidence that people who use the antidepressant, nortriptyline, to quit smoking also improve their chances of success. There is not enough evidence to determine whether other antidepressants help people to quit smoking.

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There is evidence that bupropion increases unwanted effects, particularly those relating to mental health, and that unwanted effects may increase the chance that people stop using the medicine. However, the evidence does not suggest that bupropion is more likely to result in death, hospitalization, or life-threatening events, like seizures. There is not enough information to draw clear conclusions about the safety of nortriptyline for stopping smoking.

The evidence does not suggest that taking bupropion at the same time as other stop-smoking medicines, like varenicline (sometimes known as Champix or Chantix) or nicotine replacement therapy makes people more likely to quit smoking. People are as likely to quit smoking when using bupropion as when using nortriptyline or nicotine replacement therapy, however people using varenicline are more likely to quit than those using bupropion.

Certainty of evidence

There is high-certainty evidence that bupropion helps people to quit smoking, meaning further research is very unlikely to change this conclusion. However, there is also high-certainty evidence to suggest that people using bupropion are more likely to stop taking the medicine because of unpleasant effects than those taking a pill without medication (a placebo). The certainty of the evidence was moderate, low or very low for the other key questions we looked at. This means that the findings of those questions may change when more research is carried out. In most cases this was because there were not enough studies or studies were too small.

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SUMMARY OF FINDINGS

Summary of findings 1. Bupropion compared to placebo/no pharmacotherapy control for smoking cessation

Bupropion compared to placebo/control for smoking cessation

Population: people who smoke
Setting: any; studies conducted in Asia, Australasia, Europe, USA
Intervention: bupropion
Comparison: placebo/control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo/control	Risk with bupropion				
Smoking cessation (at least six months follow-up)	Study population		RR 1.64 (1.52 to 1.77)	17,866 (46 RCTs)	⊕⊕⊕⊕ High	
	11 per 100	18 per 100 (17 to 20)				
Serious adverse events	Study population		RR 1.16 (0.90 to 1.48)	10,625 (21 RCTs)	⊕⊕⊕⊖ Moderate[a]	
	2 per 100	3 per 100 (2 to 3)				
Dropouts due to adverse events of the drug	Study population		RR 1.37 (1.21 to 1.56)	12,340 (25 RCTs)	⊕⊕⊕⊕ High	
	7 per 100	9 per 100 (8 to 10)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to imprecision. Confidence interval encompasses no difference as well as clinically significant increase. Total number of events less than 300.

Summary of findings 2. Bupropion plus NRT compared to NRT alone for smoking cessation

Bupropion plus NRT compared to NRT alone for smoking cessation

Population: people who smoke
Setting: any; studies conducted in UK, USA
Intervention: bupropion and NRT
Comparison: NRT alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT alone	Risk with bupropion and NRT				
Smoking cessation (at least six months follow-up)	Study population		RR 1.19 (0.94 to 1.51)	3487 (12 RCTs)	⊕⊕⊝⊝ Low[a,b]	
	19 per 100	22 per 100 (17 to 28)				
Serious adverse events	Study population		RR 1.52 (0.26 to 8.89)	607 (3 RCTs)	⊕⊝⊝⊝ Very low[c,d]	
	1 per 100	1 per 100 (0 to 6)				
Dropouts due to adverse events of the drug	Study population		RR 1.67 (0.95 to 2.92)	538 (2 RCTs)	⊕⊕⊝⊝ Low[d]	
	7 per 100	11 per 100 (6 to 19)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **NRT**: nicotine replacement therapy; **RCT**: randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to inconsistency. Unexplained statistical heterogeneity (I^2 = 52%).

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[b]Downgraded one level due to imprecision. Confidence interval encompasses no difference as well as clinically significant benefit.
[c]Downgraded one level due to risk of bias. One of the three included studies judged to be at high risk of bias. Removing this study reduced the point estimate to 1.00.
[d]Downgraded two levels due to imprecision. Fewer than 100 events.

Summary of findings 3. Bupropion plus varenicline compared to varenicline alone for smoking cessation

Bupropion plus varenicline compared to varenicline alone for smoking cessation

Population: people who smoke
Setting: any; studies conducted in USA
Intervention: bupropion and varenicline
Comparison: varenicline alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with varenicline alone	Risk with bupropion and varenicline				
Smoking cessation (at least six months follow-up)	Study population		RR 1.21 (0.95 to 1.55)	1057 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	
	21 per 100	26 per 100 (20 to 33)				
Serious adverse events	Study population		RR 1.23 (0.63 to 2.42)	1268 (5 RCTs)	⊕⊕⊖⊖ Low[b]	
	2 per 100	3 per 100 (1 to 6)				
Dropouts due to adverse events of the drug	Study population		RR 0.80 (0.45 to 1.45)	1230 (4 RCTs)	⊕⊕⊖⊖ Low[b]	
	4 per 100	3 per 100 (2 to 6)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

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Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded one level due to imprecision. Fewer than 300 events overall. Confidence intervals encompass clinically significant benefit as well as no difference.
[b]Downgraded two levels due to imprecision. Fewer than 100 events overall. Confidence intervals encompass clinically significant harm as well as clinically significant benefit.

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BACKGROUND

Description of the condition

Tobacco use is one of the leading causes of preventable illness and death worldwide, accounting for over eight million deaths annually (GBD RFC 2017). Extrapolation based on current smoking trends, suggests that without widespread quitting, approximately 400 million tobacco-related deaths will occur between 2010 and 2050, mostly among current smokers (Jha 2011). Most smokers would like to stop (CDC 2017); however, quitting tobacco use is difficult. This is because users develop both a psychological and physiological dependence on smoking. The physiological dependence is caused by a component of tobacco, called nicotine (McNeill 2017).

Description of the intervention

Whilst antidepressant medications are primarily used for the treatment of depression and disorders of negative affect, they have also been used to help individuals stop smoking. They offer an alternative to other frontline smoking cessation therapies, such as nicotine replacement therapy (NRT), and nicotine agonists, such as varenicline.

The following medications and substances, regarded as having antidepressant properties, have been investigated for their effect on smoking cessation in at least one study.

- Tricyclic antidepressants (TCAs): doxepin, imipramine and nortriptyline
- Monoamine oxidase inhibitors (MAOIs): moclobemide, selegiline, lazabemide, and EVT302
- Selective serotonin reuptake inhibitors (SSRIs): fluoxetine, paroxetine, sertraline, citalopram, and zimeledine
- Atypical antidepressants: bupropion, tryptophan, venlafaxine
- Extracts of St. John's wort (*Hypericum perforatum* L)
- Dietary supplement: S-Adenosyl-L-Methionine (SAMe)

Of the antidepressant medications indicated for smoking cessation, the most commonly used is bupropion. It has both dopaminergic and adrenergic actions, and appears to be an antagonist at the nicotinic acetylcholinergic receptor (Fryer 1999). It has been licensed as a prescription aid to smoking cessation in many countries. The usual dose for smoking cessation is 150 mg once a day for three days, increasing to 150 mg twice a day continued for 7 to 12 weeks, and quit attempts are generally initiated one week after starting pharmacotherapy.

Following bupropion, the second most commonly tested medication for smoking cessation is the TCA, nortriptyline. It enhances noradrenergic and serotonergic activity by blocking reuptake of these neurotransmitters (Benowitz 2000). It is licensed for smoking cessation in New Zealand. The recommended regimen is 10 to 28 days of titration before the quit attempt, followed by a 12-week dose of 75 mg to 100 mg daily (Cahill 2013).

No other antidepressants are currently licensed for use as smoking cessation aids, although others have been tested for possible use.

How the intervention might work

Multiple observations have provided a rationale for studying the effects of antidepressant medications for smoking cessation: a history of depression is found more frequently amongst smokers than nonsmokers, nicotine may have antidepressant effects, and antidepressants influence the neurotransmitters and receptors involved in nicotine addiction (Benowitz 2000; Kotlyar 2001). It has also been hypothesized that cessation may precipitate depression, however evidence suggests that this is unlikely to be the case, and that cessation may actually reduce the likelihood of depression (Taylor 2014).

The diverse pharmacological targets of antidepressants means their mechanisms of action are varied. Evidence suggests bupropion may aid smoking cessation by blocking nicotine effects, relieving withdrawal (Cryan 2003; West 2008), and reducing depressed mood (Lerman 2002a). Monoamine oxidase-A (MOA-A) inhibitors may aid smoking cessation by substituting the ability of smoking to act as a MOA inhibitor (Lewis 2007). It has been hypothesized that SSRIs might be helpful because they increase serotonin, which is also associated with improving negative affect (Benowitz 2000). The mechanisms of other antidepressants for smoking cessation remain unstudied.

Although there is an evident relationship between alleviating negative affect and antidepressant pharmacology, it is unclear whether antidepressants work mostly due to reducing negative affect, reducing urges to smoke or withdrawal symptoms, or by acting as nicotine blockers.

Why it is important to do this review

The ongoing impact of smoking on global morbidity and mortality necessitates effective and safe treatments to aid smoking cessation. Since the last update of this review was published in 2014 (Hughes 2014), a substantial amount of new evidence has emerged to assess antidepressants as smoking cessation aids. This has the potential to change or strengthen our conclusions regarding the efficacy of some of these antidepressants when compared with no treatment, whilst also strengthening the evidence regarding the safety of those antidepressant currently being used to help people quit smoking (bupropion and nortriptyline). Further evidence on safety outcomes may help to clarify the potential interaction between bupropion and seizures, as well as psychiatric adverse events. Multiple trials and observational studies have previously associated bupropion with increasing the risk of medically important adverse events, including seizures, anxiety, depression, and insomnia (Aubin 2012). New evidence may also help us to directly compare the safety and efficacy of antidepressants with other front-line smoking cessation medications, providing a further aid to decision making when helping people to quit tobacco smoking.

OBJECTIVES

To assess the evidence for the efficacy, safety and tolerability of medications with antidepressant properties in assisting long-term tobacco smoking cessation in people who smoke cigarettes.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and cluster-RCTs.

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Types of participants

We included tobacco smokers of any age, with or without a history of mental illness. We did not include pregnant women, as these smokers are covered in a separate Cochrane Review (Coleman 2015).

Types of interventions

We included trials studying pharmacotherapies with antidepressant properties for smoking cessation. We included trials assessing different doses, durations and schedules of antidepressants.

We excluded trials where an additional, uncontrolled non-antidepressant intervention component was used in only one of the trial arms. This is because the confounding effects of this intervention would have made it difficult to determine whether any change in outcome was related to the antidepressant or the confounding intervention component. Additionally, we excluded trials investigating antidepressant use for smoking harm reduction or relapse prevention, as they are covered elsewhere (Lindson-Hawley 2016 and Livingstone-Banks 2019, respectively).

Comparators

The following comparators were eligible for assessing safety, efficacy and tolerability: placebo, no pharmacotherapy, alternative therapeutic control, or different dosages/treatment regimes of the same antidepressant.

Types of outcome measures

Primary outcomes

- Efficacy, measured as smoking cessation

For this outcome we only included studies that set out to report smoking cessation rates at least six months after baseline, in line with the standard methods of Cochrane Tobacco Addiction. Where cessation was assessed at multiple intervals, we report only the longest follow-up data. Additionally, where multiple definitions of abstinence are assessed, we report the strictest of these definitions (e.g. continuous/prolonged abstinence over point prevalence abstinence). We also report biochemical validation of abstinence over self-reported abstinence (but it was not necessary for abstinence to have been biochemically validated for a study to be included).

Secondary outcomes

- Safety, measured as:
  - number of people experiencing adverse events (AEs) of any severity (e.g. abnormal test findings, clinically significant symptoms and signs, changes in physical examination findings, hypersensitivity, and progression or worsening of underlying disease)
  - number of people experiencing psychiatric AEs (e.g. adverse events relating to mental health)
  - number of people experiencing serious adverse events (SAEs), i.e. events that result in death, are life-threatening (immediate risk of death), require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, and/or result in congenital anomaly or birth defect (e.g. seizures, overdoses, suicide attempts, death by suicide, all-cause mortality).

We also recorded the following SAEs specifically, as these have previously been associated with the use of antidepressants for smoking cessation.

- Number of people experiencing seizures
- Number of people experiencing overdoses
- Number of people experiencing suicide attempts
- Number of people experiencing death by suicide
- Number of people experiencing all-cause mortality

- Tolerability, measured as the number of participants who dropped out of the trial due to adverse events

For all safety and tolerability outcomes, we considered studies with follow-up of any length.

Search methods for identification of studies

Electronic searches

We identified studies from the Cochrane Tobacco Addiction Specialized Register. At the time of the updated search in May 2019, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL; 2019, Issue 4); MEDLINE (via OVID) to update April 2019; Embase (via OVID) to April 2019; PsycINFO (via OVID) to update April 2019; US National Library of Medicine to April 2019. See the Cochrane Tobacco Addiction website for full search strategies and a list of other resources searched to populate the Register. We searched the Register for reports of studies evaluating bupropion, nortriptyline or any other pharmacotherapy classified as having an antidepressant effect. Search terms included relevant individual drug names or antidepressant* or antidepressive*. See Appendix 1 for the Register search strategy.

Searching other resources

We searched ClinicalTrials.gov (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform (ICTRP) through the Cochrane Tobacco Addiction Specialized Register.

Data collection and analysis

Selection of studies

Two review authors (of JHB, JLB, NL, SH) independently screened titles and abstracts resulting from our searches for relevance, and obtained full-text records of reports of eligible or possibly eligible studies. Two review authors (of JHB, JLB, NL, SH) then independently screened each full-text record for eligibility. Any disagreements were resolved through discussion with a third review author. For conference abstracts or trial registry entries where the record contained insufficient evidence for us to determine the eligibility of the study, we attempted to contact study investigators to obtain any additional data needed to make a final decision. We recorded all screening decisions made and presented the flow of studies and references through the reviewing process using a PRISMA flow diagram (Moher 2009).

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Data extraction and management

Two review authors (of BH, JHB, JLB, NL, SH) independently extracted the following study data and compared the findings. Any discrepancies were resolved by mutual consent.

- Type of antidepressant
- Country and setting
- Recruitment method
- Definition of smoker used
- Participant demographics (i.e. average age, gender, average cigarettes per day)
- Intervention and control description (including dose, schedule, and behavioural support common to all arms)
- Efficacy outcome(s) used in meta-analysis, including length of follow-up, definition of abstinence, and biochemical validation of smoking cessation
- Any analysis investigating the interaction between efficacy and participants' depression status
- Safety and tolerability outcomes, including AEs, psychiatric AEs, SAEs, types of SAEs, withdrawals due to treatment
- Sources of funding and declarations of interest

Assessment of risk of bias in included studies

We assessed included studies for risks of selection bias (method of random sequence generation and allocation concealment), bias due to an absence of blinding (taking into account both performance and detection bias in a single domain), attrition bias (levels and reporting of loss to follow-up), and any other threats to study validity, using the Cochrane 'Risk of bias' tool (Higgins 2011). For each new study in this update, two review authors (of JHB, JLB, NL, SH) independently assessed each study for each domain, in accordance with 'Risk of bias' guidance developed by Cochrane Tobacco Addiction to assess smoking cessation studies. Where there was any disagreement on the assessment, it was resolved through discussion with a third review author.

We considered studies at high risk of performance and detection bias where there was no blinding of participants or personnel or where there was evidence of unblinding; at unclear risk if insufficient information was available with which to judge; and at low risk if the study reported blinding of participants and personnel in detail and there was no evidence of unblinding. We considered studies to be at low risk of attrition bias where over half of the participants were followed up at the longest follow-up and where numbers followed up were similar across arms (difference < 20%).

Measures of treatment effect

Smoking cessation

We calculated cessation rates for all studies that reported cessation at least six months following baseline. For each study, we used the strictest available criteria to define cessation as described above.

Where data were available, we expressed cessation as a risk ratio (RR) for each study. We calculated this as follows: (quitters in treatment group/total randomized to treatment group)/(quitters in control group/total randomized to control group), alongside 95% confidence intervals (CIs). A RR > 1 indicates increased likelihood of quitting in the intervention group than in the control condition.

Adverse events (AEs) and serious adverse events (SAEs)

We calculated AE rates for all studies that reported adequate data, regardless of study length. Where numerical data were available, we expressed safety and tolerability data as RRs (95% CI). We calculated this as follows: (number of participants reporting (S)AEs in treatment group/total randomized to treatment group)/(number of participants reporting (S)AEs in control group/total randomized to control group). A RR > 1 indicates an increased likelihood of experiencing an AE or SAE in the intervention group than in the control condition.

In addition to overall AEs and overall SAEs, we calculated RRs (95% CI) for the following safety and tolerability outcomes, where data were available.

- Psychiatric AEs
- Seizures
- Overdoses
- Suicide attempts
- Death by suicide
- All-cause mortality
- Dropout due to adverse events
- Insomnia
- Anxiety

Unit of analysis issues

We only judged one cluster-RCT to be eligible for inclusion (Siddiqi 2013). This study was not pooled in any meta-analysis due to substantial heterogeneity of programme effects across clusters.

Dealing with missing data

As far as possible, we used an intention-to-treat (ITT) analysis with people who dropped out or were lost to follow-up treated as continuing smokers. Where participants appeared to have been randomized, but were not included in the data presented by the authors (and we were unable to obtain these), we noted this in the study description (see Characteristics of included studies). We extracted numbers lost to follow-up from study reports and used these to assess the risk of attrition bias.

Assessment of heterogeneity

Before pooling studies, we considered both methodological and clinical variance between studies. Where pooling was deemed appropriate we investigated statistical heterogeneity using the I^2 statistic (Higgins 2003). This describes the percentage variability in effect estimates that is due to heterogeneity rather than sampling error (chance).

Assessment of reporting biases

Where a comparison included a sufficient number of studies (≥ 10), we generated funnel plots to analyse and report on potential publication bias as advised by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

We therefore generated funnel plots for the following comparisons.

- Bupropion versus placebo/control - smoking cessation
- Bupropion versus placebo/control - AEs
- Bupropion versus placebo/control - SAEs

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- Bupropion versus placebo/control - seizures
- Bupropion versus placebo/control - suicide attempts
- Bupropion versus placebo/control - death by suicide
- Bupropion versus placebo/control - all-cause mortality
- Bupropion versus placebo/control - dropout due to drug
- Bupropion versus placebo/control - anxiety
- Bupropion versus placebo/control - insomnia
- Bupropion and nicotine replacement therapy (NRT) versus NRT alone - smoking cessation
- Bupropion versus NRT - smoking cessation

Data synthesis

For each type of medication and comparison where more than one eligible trial was identified, we performed separate meta-analyses of cessation and safety outcomes using Mantel-Haenszel fixed-effect methods. We pooled RRs and 95% CIs from individual study estimates to estimate pooled RRs (95% CIs). Where studies contributed more than one intervention arm to a pooled analysis, we split the control arm to avoid double-counting.

We also carried out post hoc, exploratory analyses to inform our approach to safety and tolerance for the next update of this review. We combined the following comparisons when evaluating AEs, psychiatric AEs, SAEs, and dropouts due to adverse effects.

- Bupropion compared to placebo/control
- Bupropion plus NRT compared to NRT alone
- Bupropion plus varenicline compared to varenicline alone

The rationale for this was that these studies all tested the additional effect of bupropion, and there was no evidence of an interaction for safety and tolerability outcomes (whereas there may be for effectiveness). We subgrouped studies by their comparison type, though acknowledge that these subgroups may currently be underpowered to detect differences between groups.

Subgroup analysis and investigation of heterogeneity

For comparisons where we had sufficient data, we separated participant data into the following subgroups to determine whether antidepressants had differential effects on the relevant population or intervention groups.

- Split by mental health diagnoses: mental health diagnoses versus no mental health diagnoses
- Split by level of behavioural support: multisession group support versus multisession individual counselling versus low intensity support versus not specified. To be identified as low intensity, support had to be regarded as part of the provision of routine care, i.e. time spent with smoker (including assessment for the trial) less than 30 minutes at the initial consultation, with no more than two further assessment and reinforcement visits.

Where reported, we also extracted data from analyses evaluating a potential interaction between current depression or past history of depression and quit rates. We relied upon the definition of depression used by study authors, which included both formal diagnoses and scores on validated depression scales. This interaction is investigated in more detail in van der Meer 2013.

Sensitivity analysis

We carried out the following sensitivity analyses.

- We excluded studies from meta-analyses that were judged to be at high risk of bias for any of the assessed bias domains. We judged whether this exclusion notably altered the pooled RRs (95% CI).
- We excluded studies from meta-analyses with industry support. We did this in two stages: 1) we excluded studies that were funded by the pharmaceutical industry; 2) we excluded studies that were funded by the pharmaceutical industry or where the study medication was provided by the pharmaceutical industry. We judged whether this exclusion notably altered the pooled RRs (95% CI).

Summary of findings and assessment of the certainty of the evidence

We created 'Summary of findings' tables using standard Cochrane methodology (Higgins 2019), for the following comparisons, which we judged to be most clinically relevant.

- Bupropion compared to placebo/control
- Bupropion plus NRT compared to NRT alone
- Bupropion plus varenicline compared to varenicline alone

We judged these comparisons to be of most relevance because bupropion is currently the only antidepressant used as a front-line therapy for smoking cessation worldwide.

Following standard Cochrane methodology (Higgins 2019), we used GRADEpro GDT software and the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for smoking cessation, SAEs, and dropout due to adverse events of the drug, and to draw conclusions about the certainty of the evidence within the text of the review (Schünemann 2013). We chose these outcomes as they are important factors to consider regarding pharmaceutical efficacy, safety and tolerability, and are therefore useful to both clinicians and patients when deciding whether to provide or use a smoking cessation pharmacotherapy.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies

Results of the search

The most recent literature search for this update generated 397 records. After duplicates were removed, 362 records remained for title and abstract screening. We ruled out 213 records at this stage, leaving 149 records for full-text screening. At this stage we identified 33 new, included studies (reported across 85 records in total) and three ongoing studies. See Figure 1 for full details of record/study flow information for the most recent updated search.

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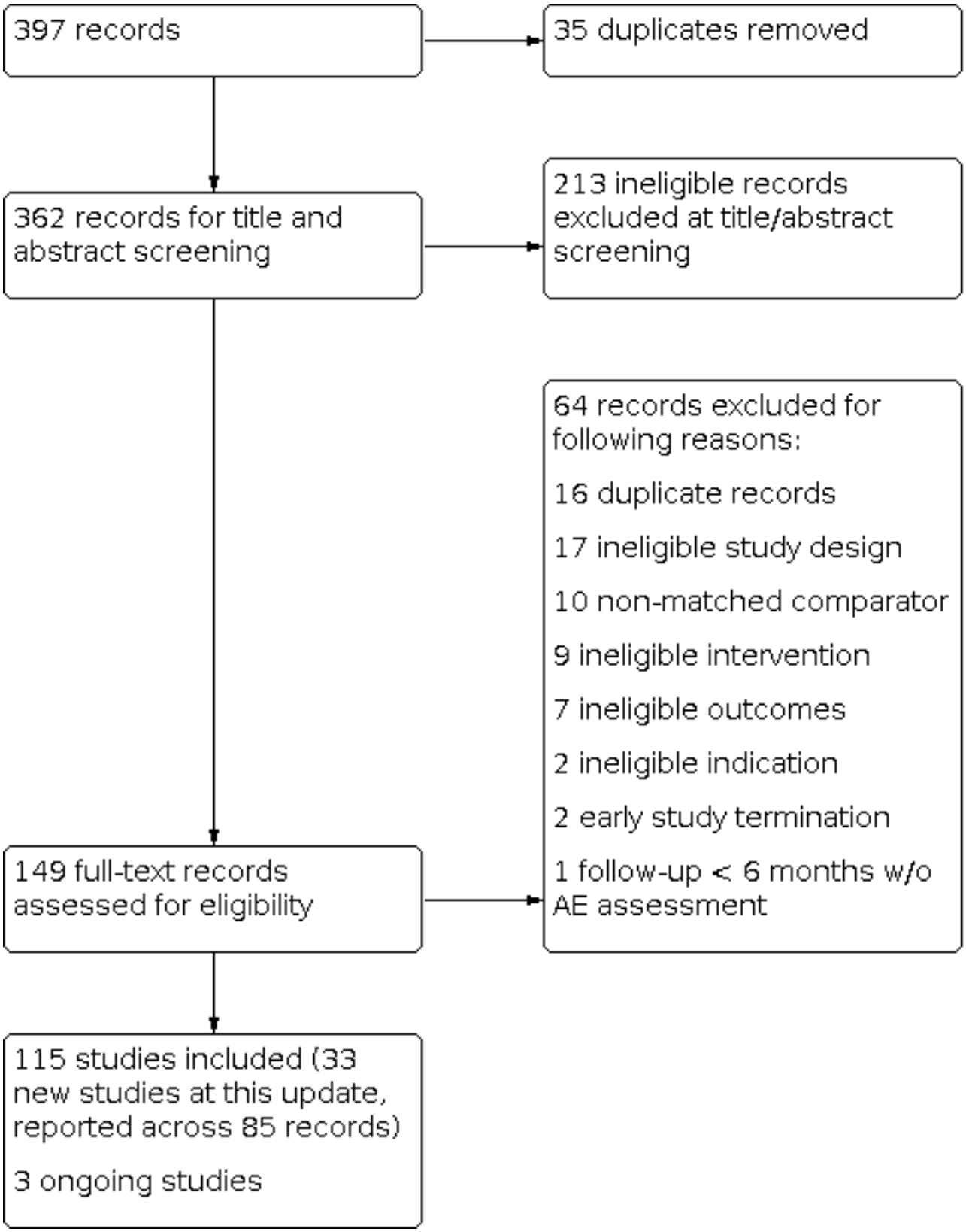
Figure 1. Flow diagram for 2019 search update only



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Included studies

We identified 33 additional eligible trials at this update, yielding a total of 115 included trials. The new trials studied:

- bupropion: Anthenelli 2016; Benli 2017; Cinciripini 2018; CTRI/2013/07/003830; Ebbert 2014; Elsasser 2002; Fatemi 2013; Gilbert 2019; Gray 2011; Gray 2012; Johns 2017; Karam-Hage 2011; Moreno-Coutino 2015; NCT00132821; NCT00308763; NCT00495352; NCT00593099; NCT01406223; Perkins 2013; Rose 2014; Rose 2017; Sheng 2013; Singh 2010; Tidey 2011; Urdapilleta-Herrera 2013; Weiner 2012; White 2005; Zincir 2013
- EVT302: Berlin 2012
- fluoxetine: Minami 2014; NCT00578669
- lazabemide: Berlin 2002
- St John's wort: Barnes 2006

Further details of these newly included, as well as previously included studies, including dosing schedules, are recorded in the Characteristics of included studies tables.

Bupropion

Overall, we included 87 studies of bupropion. Outcomes for four of these studies are based only on conference abstracts or pharmaceutical company data (Ferry 1992; Ferry 1994; Selby 2003; SMK20001).

The majority of trials were conducted in North America, but we also included studies from Australia (Myles 2004); Brazil (Haggström 2006); China (Sheng 2013); Europe (Aubin 2004; Dalsgarð 2004; Fossati 2007; Górecka 2003; Rovina 2009; Stapleton 2013; Wagena 2005; Wittchen 2011; Zellweger 2005); India (CTRI/2013/07/003830; Johns 2017; Singh 2010); Israel (Planer 2011); New Zealand (Holt 2005); Pakistan (Siddiqi 2013); Taiwan (NCT00495352); and Turkey (Benli 2017; Uyar 2007; Zincir 2013). Three studies were carried out across multiple continents (Anthenelli 2016; Tonnesen 2003; Tonstad 2003).

A number of trials specifically recruited cohorts of participants with health conditions, including:

- alcoholism (Grant 2007; Hays 2009; Karam-Hage 2011)
- bipolar disorder (NCT00593099)
- cancer (Schnoll 2010)
- cardiovascular disease (Eisenberg 2013; Planer 2011; Rigotti 2006; Tonstad 2003)
- chronic obstructive pulmonary disease (Górecka 2003; Tashkin 2001; Wagena 2005)
- mild depression (Moreno-Coutino 2015)
- psychiatric conditions (Anthenelli 2016)
- schizophrenia (Evins 2001; Evins 2005; Evins 2007; Fatemi 2013; George 2002; George 2008; NCT00495352; Weiner 2012)
- post-traumatic stress disorder (Hertzberg 2001)
- tuberculosis or suspected tuberculosis (Siddiqi 2013; CTRI/2013/07/003830)

Three of the studies in people with cardiovascular disease, and one other, enrolled hospital inpatients (Eisenberg 2013; Planer 2011; Rigotti 2006; Simon 2009).

Trials also studied specific populations of:

- adolescents (Gray 2011; Gray 2012; Killen 2004; Muramoto 2007)
- African-Americans (Ahluwalia 2002; Cox 2012)
- healthcare workers (Zellweger 2005)
- hospital staff (Dalsgarð 2004)
- low-income and minority (NCT00308763)
- Maori (Holt 2005)
- males (Rose 2017)
- smokers awaiting surgery (Myles 2004)
- smokers who had previously failed to quit smoking using bupropion (Gonzales 2001; Selby 2003)
- smokers who had just failed to quit using nicotine replacement therapy (NRT) (Hurt 2003; Rose 2013; Rose 2014).

More than half the bupropion studies followed participants for at least 12 months from the start of treatment or the target quit day. Twenty-nine studies followed up participants for six months. The duration of follow-up was below six months for 12 of the included studies, was of unknown duration for six studies, and one study measured number of days abstinent rather than numbers abstinent at a particular time point (Perkins 2013). However, these studies did measure safety outcomes; therefore they contributed data to our meta-analyses of adverse events data, but not smoking cessation data.

In those studies which met or exceeded the six-month follow-up threshold, the majority reported an outcome of sustained (prolonged) abstinence. However, in 25 (33%) studies, only point prevalence rates were given, or the definition of abstinence was unclear.

Forty-six trials evaluated bupropion for smoking cessation as a single pharmacotherapy versus placebo/non-pharmacotherapeutic control, and three studies compared different doses of bupropion (Hurt 1997; Muramoto 2007; Swan 2003). Both Muramoto 2007 and Swan 2003 compared a 150 mg dose per day with a 300 mg dose per day, whereas Hurt 1997 looked at 100 mg per day versus 150 mg per day versus 300 mg per day. We pooled studies in which bupropion was used in combination with another pharmacotherapy or versus another pharmacotherapy in separate comparisons, as listed below.

- Bupropion as an adjunct to NRT versus NRT alone (16 trials)
- Bupropion as an adjunct to varenicline versus varenicline alone (6 trials)
- Bupropion versus NRT (10 trials)
- Bupropion versus varenicline (10 trials)
- Bupropion versus nortriptyline (3 trials)
- Bupropion versus gabapentin (1 trial)

Nortriptyline

We included 10 studies of the tricyclic antidepressant, nortriptyline in this review. Hall and colleagues conducted three trials (Hall 1998; Hall 2002; Hall 2004), and Prochazka and colleagues two (Prochazka 1998; Prochazka 2004), with all these trials conducted in the USA. One study was conducted in Australia (Richmond 2013), two in Brazil (Da Costa 2002; Haggström 2006), one in the Netherlands (Wagena 2005), and one in the UK (Aveyard 2008).

Richmond 2013 was the only study to be conducted in a specialist population, recruiting male prisoners who had been incarcerated

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for at least one month and had at least six months remaining of their sentences.

All studies were placebo controlled. They used nortriptyline doses of 75 mg/day to 100 mg/day or titrated doses to serum levels recommended for depression during the week prior to the quit date.

Treatment duration ranged from 12 to 14 weeks. Nearly all studies used a definition of cessation based on a sustained period of abstinence. Aveyard 2008, Hall 1998, Hall 2002, Hall 2004, and Richmond 2013 reported outcomes at ≥ 12 months of follow-up and the other six studies had a maximum follow-up of six months.

The three studies by Hall and colleagues used factorial designs to test nortriptyline versus placebo crossed with different intensities of behavioural support (Hall 1998; Hall 2002; Hall 2004). Conversely, the remaining studies provided a set amount of behavioural support to all participants, ranging from brief behavioural counselling to repeated group and individual sessions.

Six studies tested nortriptyline as a monotherapy, and four studies tested nortriptyline as an adjunct to NRT.

Selective serotonin reuptake inhibitors (SSRIs)

Fluoxetine

Seven studies of fluoxetine have been included in this review, with two of these studies identified for inclusion in the current update (Minami 2014; NCT00578669).

The majority of these trials took place in the USA (Brown 2014; Minami 2014; NCT00578669; Niaura 2002; Saules 2004; Spring 2007), and one in Iceland (Blondal 1999). Participants were recruited from clinics (Blondal 1999; Brown 2014; Niaura 2002; Saules 2004; Spring 2007), the community (Minami 2014), or through an unknown recruitment method (NCT00578669).

Brown 2014 was the only study to be conducted in a specialist population, recruiting smokers with elevated depressive symptoms.

Six of these studies conducted follow-up to at least six months for cessation outcomes. Minami 2014 had a follow-up duration of fewer than six months, so we only evaluated adverse events data for this study.

Four studies used varying doses of fluoxetine as a single pharmacotherapy: Niaura 2002 compared a 30 mg daily dose, a 60 mg daily dose, or placebo for 10 weeks; Spring 2007 used 60 mg or placebo for 12 weeks; NCT00578669 compared 20 mg daily for eight weeks preceding and following the target quit date to placebo. Minami 2014 also compared fluoxetine as a monotherapy (20 mg daily for 8 weeks prior to and following the target quit date) to placebo only.

The remaining three trials investigated fluoxetine as an adjunct to NRT, and used similar doses of fluoxetine: Blondal 1999 used 20 mg/day or placebo for three months as an adjunct to nicotine inhaler; Saules 2004 used 20 mg/day or 40 mg/day or placebo for 10 weeks as an adjunct to nicotine patch; and Brown 2014 compared 10 weeks of 20 mg daily fluoxetine, 16 weeks of 20 mg daily fluoxetine, or no additional treatment in participants using nicotine patch for eight weeks.

Paroxetine

One trial assessed paroxetine (20 mg, 40 mg or placebo) for nine weeks as an adjunct to nicotine patch (Killen 2000). It was conducted in the USA, with participants recruited from the community. It measured smoking cessation (defined as 7-day point prevalence) at six months follow-up.

Sertraline

One trial with six-month follow-up assessed sertraline (200 mg/day) for 11 weeks versus placebo in conjunction with six individual counselling sessions. All participants had a past history of major depression (Covey 2002).

Monoamine oxidase inhibitors

Moclobemide

Moclobemide was tested for smoking cessation in one placebo-controlled trial, carried out in France (Berlin 1995). Participants were recruited using advertisements in community healthcare settings. Treatment with 400 mg/day began one week before quit day and continued for two months, reducing to 200 mg/day for a further month. No behavioural counselling was provided. Final follow-up for smoking cessation (defined as prolonged abstinence) was at 12 months.

Selegiline

Five long-term trials testing selegiline are included in this review, carried out in the USA (George 2003; Kahn 2012; Killen 2010; Weinberger 2010), and Israel (Biberman 2003). All studies recruited participants from the community.

Almost all studies delivered selegiline as a monotherapy compared to placebo, excluding Biberman 2003, which used a combination therapy of selegiline and nicotine patch compared to placebo.

Three studies used 10 mg/day of oral treatment (Biberman 2003; George 2003; Weinberger 2010), and two used 6 mg/day of patch treatment (Kahn 2012; Killen 2010). The nicotine patches also used in Biberman 2003 delivered 21 mg/day of nicotine for eight weeks. Three studies had treatment durations of nine weeks (George 2003; Kahn 2012; Weinberger 2010), one had a treatment duration of eight weeks (Killen 2010), and one continued therapy for 26 weeks (Biberman 2003). Three of the studies completed follow-up at six months (George 2003; Kahn 2012; Killen 2010), and two continued follow-up to 12 months (Biberman 2003; Weinberger 2010).

Lazabemide

Berlin 2002 is the only study of lazabemide included in this review. Due to its nature as a dose-finding, exploratory study, its follow-up period for smoking cessation was only eight weeks. Therefore, we only consider its safety data within this review.

The study was conducted in both France and Belgium; however, the method of participant recruitment is not reported. Participants were given either 50 mg lazabemide, 100 mg lazabemide or placebo. It was halted early due to liver toxicity observed in trials of the medication for other indications.

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EVT302

Berlin 2012 is the only study of EVT302 included in this review. Its follow-up for smoking cessation is only eight weeks, therefore we only consider its safety data within this review.

The study was conducted in Germany, with participants recruited through media advertisements. It compared EVT302 monotherapy (5 mg/day for 1 week preceding and 7 weeks following the target quit date) with placebo. It additionally compared EVT302 combination therapy with nicotine patch (21 mg/day for 7 weeks post-target quit date) versus placebo EVT302 and nicotine patch.

Venlafaxine

Cinciripini 2005 is the only study of venflaxine included in this review. It recruited from the community and compared venlafaxine at a dose of up to 225 mg/day with placebo. All participants also received nicotine patches and nine brief individual counselling sessions; follow-up was for 12 months.

Hypericum (St John's wort)

Three studies of hypericum are included (Barnes 2006; Parsons 2009; Sood 2010), with Barnes 2006 newly included at this update. These studies took place in the USA (Sood 2010) and the UK (Barnes 2006; Parsons 2009). Participants were recruited from the community (Barnes 2006; Sood 2010) and stop-smoking clinics (Parsons 2009).

All three studies reported prolonged abstinence at six months. Barnes 2006 compared 300 mg/day to 600 mg/day, starting one week prior to the target quit date and continuing for 12 weeks thereafter; Parsons 2009 compared 14 weeks of 900 mg/day St John's wort to placebo, starting two weeks prior to target quit date and continuing for 12 weeks thereafter; Sood 2010 compared 900 mg/day, 1800 mg/day, and placebo for 12 weeks.

S-Adenosyl-L-Methionine (SAMe)

Sood 2012 is the only study of SAMe included in this review. It compared 1600 mg/day or 800 mg/day SAMe to placebo for eight weeks, with smoking cessation follow-up at six months.

Excluded studies

For studies that were potentially relevant, but that we excluded, we have provided our reasons for exclusion in Characteristics of excluded studies. Reasons that records were excluded at full-text stage for this update specifically, are also summarized in Figure 1.

As part of this update to the review, we have excluded studies investigating the use of antidepressants for smoking relapse prevention and harm reduction, as these studies are included in other reviews (Lindson-Hawley 2016; Livingstone-Banks 2019). Therefore, we have now excluded seven studies of relapse prevention (Covey 2007; Croghan 2007; Hall 2011; Hays 2001; Hays 2009; Hurt 2003; Killen 2006), and one of harm reduction (Hatsukami 2004), which were included in the previous update (Hughes 2014).

We identified the following three ongoing studies as part of our search which are likely to be relevant for inclusion when complete.

- NCT03326128: compares two high doses of bupropion (300 mg/day to 450 mg/day, starting 4 weeks prior to and following target quit date).
- NCT03342027: a factorial trial comparing bupropion to placebo, as well as an eight-session tailored behavioural intervention.
- Zawertailo 2018: compares bupropion (150 mg/day for the first 3 days, then twice daily for the remainder of the 12 weeks, starting 7 days prior to target quit day) and varenicline (0.5 mg once daily for first 3 days, then 0.5 mg twice daily for next 4 days, then 1 mg twice daily for the remainder of the 12 weeks, starting 7 days prior to target quit day).

Further details of these ongoing studies are summarized in the Characteristics of ongoing studies table.

Risk of bias in included studies

Overall, we judged 12 studies to be at low risk of bias (low risk of bias across all domains), 28 at high risk of bias (high risk of bias in at least 1 domain), and the remaining 75 at unclear risk of bias. Reasons for the judgements made below are detailed in the Characteristics of included studies table, and a summary illustration of the 'Risk of bias' profile across studies is shown in Figure 2.

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

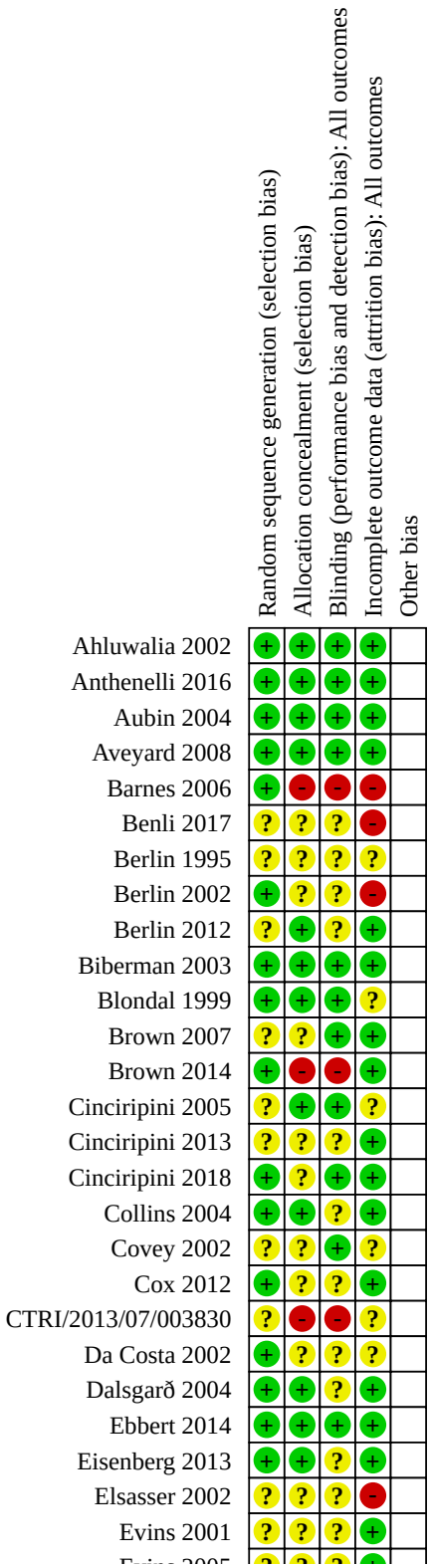

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Figure 2. (Continued)

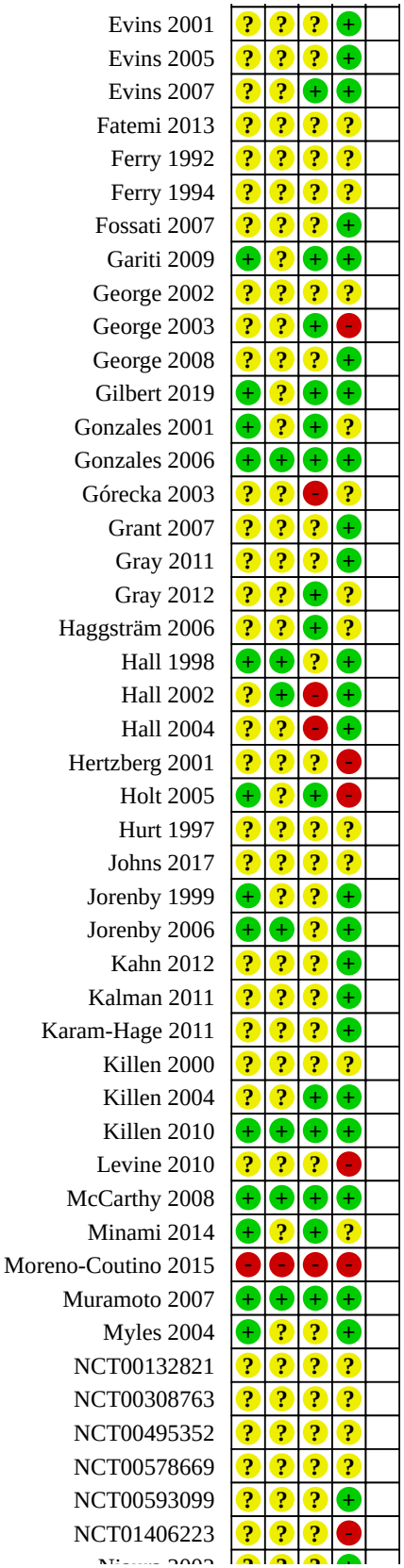

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Figure 2. (Continued)

NCT01406223	?	?	?	-	
Niaura 2002	?	?	?	+	
Nides 2006	+	+	?	+	
Parsons 2009	+	+	+	+	
Perkins 2013	?	?	+	?	
Piper 2007	?	?	?	+	
Piper 2009	?	+	?	+	
Planer 2011	?	?	+	+	
Prochazka 1998	?	?	-	-	
Prochazka 2004	+	+	-	+	
Richmond 2013	?	?	?	+	
Rigotti 2006	+	+	+	+	
Rose 2013	?	?	?	-	
Rose 2014	?	?	?	+	
Rose 2017	?	?	?	+	
Rovina 2009	?	?	-	?	
Saules 2004	?	?	?	?	
Schmitz 2007	+	+	?	+	
Schnoll 2010	?	?	?	+	
Selby 2003	?	?	?	?	
Sheng 2013	+	?	+	+	
Siddiqi 2013	+	+	-	+	-
Simon 2004	+	?	?	+	
Simon 2009	+	?	+	+	
Singh 2010	?	?	-	?	
Smith 2009	?	?	-	+	
SMK20001	?	?	?	+	
Sood 2010	+	?	?	?	
Sood 2012	?	?	?	+	
Spring 2007	+	?	?	+	
Stapleton 2013	+	+	-	+	
Swan 2003	+	+	-	+	
Tashkin 2001	+	+	?	+	
Tidey 2011	+	?	?	+	
Tonnesen 2003	+	+	?	+	
Tonstad 2003	?	?	?	?	
Urdapilleta-Herrera 2013	?	?	?	?	
Uyar 2007	?	?	-	?	
Wagena 2005	+	+	?	+	
Weinberger 2010	?	?	+	?	
Weiner 2012	?	?	?	+	?
White 2005	?	?	-	+	
Wittchen 2011	?	-	-	+	
Zellweger 2005	?	?	?	?	
Zincir 2013	?	?	-	?	-

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Allocation

We assessed selection bias through investigating methods of random sequence generation and allocation concealment for each study. We rated 46 studies at low risk for random sequence generation, 68 at unclear risk and one at high risk (Moreno-Coutino 2015). We judged 31 studies to be at low risk for allocation concealment, 79 at unclear risk and five at high risk. When assessing both random sequence generation and allocation concealment, we assessed studies to be at unclear risk where there was insufficient methodological information available to be sure whether adequate measures had been taken to avoid selection bias.

Blinding

We assessed any risk of bias linked to blinding as one domain. However, we took into account both performance and detection bias when making this judgement. We judged 32 studies to be at low risk of bias for this domain, 64 at unclear risk and 19 at high risk. Where studies stated that they were "double-blind" only, with no explicit clarification of who was blinded, we judged this to be unclear risk.

Incomplete outcome data

We judged studies to be at a low risk of attrition bias where the numbers of participants lost to follow-up were clearly reported and the overall number lost to follow-up was not more than 50%, and the difference in loss to follow-up between groups was no greater than 20%. This is in accordance with 'Risk of bias' guidance produced by Cochrane Tobacco Addiction for assessing smoking cessation studies. We judged 69 of the studies to be at low risk of bias, 34 at unclear risk and 12 at high risk.

Other potential sources of bias

We found three studies with other sources of potential bias beyond those domains detailed previously. Siddiqi 2013 demonstrated substantial heterogeneity of programme effects across the different clusters of their cluster-RCT. Twenty per cent of participants in the control arm smoked only hookah (no cigarettes) compared with 4% in the intervention arm. We judged that this put the study at high risk of bias. Weiner 2012 details that there was insufficient study drug available to meet demand. It is unclear how this was dealt with and whether it is accounted for in the dropouts reported. We judged this to be an unclear risk of bias. Finally, Zincir 2013 details that there were no adverse events recorded during their study. This seems highly unlikely according to the common definition of adverse events, and there is no detail given of how adverse events were measured in the study. We have therefore judged this to put the study at high risk of bias.

Effects of interventions

See: **Summary of findings 1** Bupropion compared to placebo/no pharmacotherapy control for smoking cessation; **Summary of findings 2** Bupropion plus NRT compared to NRT alone for smoking cessation; **Summary of findings 3** Bupropion plus varenicline compared to varenicline alone for smoking cessation

Bupropion versus placebo/no pharmacotherapy control

Smoking cessation

There was evidence to suggest that bupropion was effective when compared to placebo or a non-pharmacotherapeutic control to assist smoking cessation. Our meta-analysis included 46 trials in which bupropion was the sole pharmacotherapy, with 17,866 participants: pooled risk ratio (RR) 1.64, 95% confidence interval (CI) 1.52 to 1.77; I^2 = 15%; high-certainty evidence; Analysis 1.1; Summary of findings 1). The results were not sensitive to the exclusion of studies judged to be at high or unclear risk of bias overall. We excluded one cluster-RCT of bupropion versus no pharmacotherapy from our meta-analysis due to substantial heterogeneity of programme effects across clusters. This trial detected no evidence of a difference between bupropion and no pharmacotherapy (both groups received behavioural support) for smoking cessation at any follow-up point (adjusted RR at 6-month follow-up: 1.1, 95% CI 0.5 to 2.3; 1299 participants) (Siddiqi 2013). Sensitivity analyses excluding studies with industry support did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1).

We found no evidence suggesting that the effect of bupropion on smoking cessation depended upon the level of behavioural support offered to people stopping smoking. Three trials directly compared bupropion and placebo in factorial designs varying the behavioural support. There was no evidence from any of the three trials that the efficacy of bupropion differed between the lower and higher levels of behavioural support (Hall 2002; McCarthy 2008), or by the type of counselling approach used (Schmitz 2007). We also carried out a between-study subgroup analysis of the possible interaction with behavioural support. We did this by classifying studies into low and high intensities of behavioural support (further split into delivery to a group or to individuals), using the criteria set in the Cochrane Review of NRT versus control (Hartmann-Boyce 2018). Low-intensity support consisted of less than 30 minutes at the initial consultation, with no more than two further assessment and reinforcement visits. Only one small trial met this criteria (Myles 2004). We found no evidence of a difference between subgroups (I^2 = 0%; Analysis 1.2).

One trial directly compared bupropion and placebo in a cohort of participants with mental health disorders to a cohort without (Anthenelli 2016). There was no evidence indicating that the effect of bupropion depended upon whether people had or did not have a psychiatric disorder. We also carried out a between studies subgroup analysis to assess the potential interaction between cessation rates and mental health disorders. We did this by pooling studies (or subgroups of studies) into groups depending upon whether the participants were recruited specifically because they had a mental health disorder or they represented the general population (including some studies that excluded people with current mental health disorders). Some of these groups included people with serious mental health disorders, such as people with schizophrenia (Evins 2001; Evins 2005; George 2002), or other disorders including post-traumatic stress disorder (PTSD; Hertzberg 2001), and a mix of mental health disorders (Anthenelli 2016). We found no evidence of a differential effect of bupropion on cessation between subgroups (Analysis 1.3; I^2 = 15%).

Depression

Four studies comparing bupropion to placebo/control analysed whether there was any interaction between depression and smoking quit rates (Anthenelli 2016 (analysis reported in West 2018); Aubin 2004; Cinciripini 2018; Kalman 2011). We did not find any evidence of this (Table 2).

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Safety

There was evidence to suggest that taking bupropion increased the incidence of adverse events (AEs) relative to placebo or non-pharmacotherapeutic control (RR 1.14, 95% CI 1.11 to 1.18; 19 studies, 10,893 participants; Analysis 1.4). However, a moderate degree of heterogeneity was detected between studies (I^2 = 63%). Meta-analysis of 21 studies did not provide clear evidence that the use of bupropion increased the likelihood of serious adverse events (SAEs) (RR 1.16, 95% CI 0.90 to 1.48; I^2 = 0%; 21 studies, 10,625 participants; moderate-certainty evidence; Analysis 1.5; Summary of findings 1), however the CIs encompassed both no difference as well as a clinically significant increase.

There was also evidence to suggest bupropion increased the likelihood of developing psychiatric AEs. We meta-analysed six studies (RR 1.25, 95% CI 1.15 to 1.36; 6 studies, 4439 participants; Analysis 1.6). This effect is largely driven by Anthenelli 2016 (with an overall weighting of 96.9%), however as we judged this study to be at low risk of bias, and the effects are consistent with those detected by the other studies included in the analysis (I^2 = 15%), this is not deemed to be problematic.

There was insufficient evidence to determine whether bupropion use was associated with the likelihood of seizures (RR 2.93, 95% CI 0.64 to 13.37; I^2 = 0%; 13 studies, 7344 participants; Analysis 1.7), risk of overdose (RR 2.15, 95% CI 0.23 to 19.86; I^2 = 0%; 5 studies, 5585 participants; Analysis 1.8), suicide attempts (RR 1.62, 95% CI 0.29 to 8.92; I^2 = 0%; 10 studies, 6484 participants; Analysis 1.9), risk of death by suicide (RR 0.34, 95% CI 0.01 to 8.26; I^2 = n/a; 14 studies, 8822 participants; Analysis 1.10), or all-cause mortality risk (RR 0.89, 95% CI 0.42 to 1.87; I^2 = 0%; 21 studies, 11,403 participants; Analysis 1.11). In all cases the number of events reported were very low, which resulted in substantial imprecision and CIs encompassing both clinically significant benefit and harm.

However, there was evidence that those randomized to receive bupropion were more likely to report symptoms of anxiety (RR 1.42, 95% CI 1.21 to 1.67; I^2 = 40%; 11 studies, 7406 participants; Analysis 1.12) and insomnia (RR 1.78, 95% CI 1.62 to 1.96; I^2 = 12%; 22 studies, 11,077 participants; Analysis 1.13) at follow-up.

Tolerability

There was evidence that the risk of dropout due to AEs of the drug was higher in groups receiving bupropion relative to placebo or no pharmaceutical treatment (RR 1.37, 95% CI 1.21 to 1.56; I^2 = 19%; 25 studies, 12,340 participants; high certainty evidence; Analysis 1.14; Summary of findings 1). Our point estimate suggests that participants taking bupropion had a 21% to 56% increased risk of dropping out relative to control.

We carried out sensitivity analyses (not shown) for all of the above safety and tolerability analyses, removing studies at overall high risk of bias, where this was relevant. In no cases did this change the interpretation of the effect. Additional sensitivity analyses, excluding studies with industry support, did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1).

Bupropion plus nicotine replacement therapy (NRT) versus NRT alone

Smoking cessation

There was moderate statistical heterogeneity in the results of 12 studies comparing bupropion plus nicotine replacement therapy (NRT) to NRT alone for smoking cessation (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 52%; 12 studies, 3487 participants; low certainty evidence; Analysis 2.1; Summary of findings 2). The analysis thus found no clear evidence of a benefit of using bupropion plus NRT over using NRT alone. Nine of the 12 studies used nicotine patch, but two studies provided participants with nicotine lozenge (Piper 2009; Smith 2009), and one offered a choice of NRT (Stapleton 2013). However, splitting the analysis into these subgroups did not explain the heterogeneity detected (I^2 = 0% for subgroup differences), nor did the exclusion of studies that did not use a bupropion placebo in the control arm (Smith 2009; Stapleton 2013). Removing the three studies deemed to be at an overall high risk of bias did not change the interpretation of the pooled effect estimate (Rose 2013; Smith 2009; Stapleton 2013). Sensitivity analyses excluding studies with industry support did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1). Although the direction of the effect estimate changed when studies funded by the pharmaceutical industry, or where the medication was supplied by the pharmaceutical industry, were excluded; 95% CIs still encompassed evidence of benefit as well as harm.

Depression

None of the relevant included studies investigated depression as a moderator of smoking quit rates.

Safety

There was evidence to indicate an increased risk of AEs when using combination bupropion and NRT relative to taking NRT alone (RR 1.21, 95% CI 1.02 to 1.43; I^2 = 0%; 2 studies, 313 participants; Analysis 2.2); however the number of events was low (n = 192), and when one study at high risk of bias was removed the outcome become more imprecise and the CI spanned one (RR 1.24, 95% CI 0.98 to 1.56). There was insufficient evidence for the other safety outcomes we analysed for this comparison (SAEs, seizures, suicide attempts, death by suicide, all-cause mortality). Very few studies had relevant data, and those that did recorded few events. In the case of the SAEs outcome, the removal of one study deemed to be at high risk of bias changed the effect estimate from RR = 1.52 (95% CI 0.26 to 8.89; I^2 = 0%; 3 studies, 607 participants; very low certainty evidence; Analysis 2.3; Summary of findings 2) to RR = 1.00 (95% CI 0.06 to 15.83; I^2 = n/a; 2 studies, 538 participants). Although this did not change the clinical interpretation of the result it does demonstrate that the effect estimate was highly dependent on this potentially biased study.

There was some evidence that bupropion plus NRT led to increased reporting of insomnia in comparison to NRT alone (RR 1.55, 95% CI 1.24 to 1.93; I^2 = 0%; 2 studies, 556 participants; Analysis 2.8); however there was no clear evidence of an increase in anxiety in the bupropion plus NRT groups (RR 1.58, 95% CI 0.97 to 2.56; I^2 = 47%; 3 studies, 1218 participants; Analysis 2.9). In both cases the results were based on a small number of studies and event rates were low (< 300).

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Tolerability

Only two studies measured dropout due to AEs of the drug, providing insufficient information to draw conclusions and an imprecise pooled effect estimate (RR 1.67, 95% CI 0.95 to 2.92; I^2 = 0%; 2 studies, 538 participants; low certainty evidence; Analysis 2.10; Summary of findings 2).

Removing studies judged to be at high risk of bias from safety and tolerability analyses did not affect the interpretation of these effects, and sensitivity analyses, excluding studies with industry support, did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1).

Bupropion plus varenicline versus varenicline alone

Smoking cessation

Our analysis did not find evidence that combination bupropion and varenicline resulted in higher smoking cessation rates than varenicline alone (RR 1.21, 95% CI 0.95 to 1.55; I^2 = 15%; 3 studies, 1057 participants; moderate certainty evidence; Analysis 3.1; Summary of findings 3). Confidence intervals encompassed the possibility of no clinically significant difference in quit rates as well as a clinically significant benefit of bupropion combined with varenicline. We did not carry out a sensitivity analysis to account for risk of bias as we did not judge any of the studies in the analysis to be at high risk. A sensitivity analysis excluding studies with industry support did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1).

Depression

None of the relevant included studies investigated a potential link between depression and quit rates.

Safety

There was evidence to indicate an increased risk of AEs, as well as psychiatric AEs, when taking combination bupropion and varenicline compared to varenicline alone (AEs: RR 1.09, 95% CI 1.02 to 1.17; I^2 = 78%; 4 studies, 1043 participants; Analysis 3.2) (psychiatric AEs: RR 1.15, 95% CI 1.03 to 1.30; I^2 = 75%; 2 studies, 835 participants; Analysis 3.4). However, in both cases we observed substantial heterogeneity, meaning these pooled estimates should be treated with caution.

We did not find evidence to suggest an increased likelihood of SAEs (low certainty evidence; Summary of findings 3), overdoses, seizures, suicide attempts, death by suicide, or all-cause mortality in the combination bupropion and varenicline trial arms in comparison to varenicline alone. However, there were few studies and events for these outcomes. In all cases (apart from those outcomes with no events; Analysis 3.5; Analysis 3.8) CIs encompassed one (Analysis 3.3; Analysis 3.6; Analysis 3.7; Analysis 3.9).

There was some evidence that randomization to combination bupropion and varenicline resulted in greater reporting of anxiety (RR 1.55, 95% CI 1.01 to 2.38; I^2 = 0%; 2 studies, 499 participants; Analysis 3.10) and insomnia (RR 1.45, 95% CI 1.14 to 1.84; I^2 = 0%; 2 studies, 499 participants; Analysis 3.11) than varenicline alone at follow-up. However, these results should be treated with caution as there were a low number of events in both analyses (< 200).

Tolerability

We did not find evidence to suggest an increased likelihood of dropout due to drug in the combination bupropion and varenicline trial arms in comparison to varenicline alone. However, results were imprecise and CIs encompassed one (low certainty evidence; Analysis 3.12; Summary of findings 3).

Where it was relevant to carry out sensitivity analyses removing studies judged to be at high risk of bias for the above safety and tolerability analyses, we found no evidence of a change in the clinical interpretation of results. Further sensitivity analyses excluding studies with industry support did not indicate that our findings were sensitive to the inclusion of these studies (see Table 1).

Exploratary safety and tolerability analyses combining comparisons

We carried out exploratory post hoc analyses combining the AEs (Analysis 4.1), psychiatric AEs (Analysis 4.2), SAEs (Analysis 4.3), and dropout due to adverse events (Analysis 4.4) outcomes across the above three comparisons (i.e. bupropion versus control; bupropion plus NRT versus NRT; bupropion plus varenicline versus varenicline). We subgrouped by the original comparison to test for any potential interactions. Significant subgroup differences were not detected for any of the outcomes; however these results should be treated with caution as some of the subgroups were underpowered. Overall pooled effects indicated that AEs (RR 1.14, 95% CI 1.11 to 1.17; I^2 = 70%; subgroup differences I^2 = 3%; 25 studies, 12,249 participants; Analysis 4.1), psychiatric AEs (RR 1.24, 95% CI 1.15 to 1.33; I^2 = 45%; subgroup differences I^2 = 23%; 8 studies, 5274 participants; Analysis 4.2) and dropouts due to AEs of the drug (RR 1.35, 95% CI 1.20 to 1.52; I^2 = 12%; subgroup differences I^2 = 44%; 30 studies, 14,108 participants; Analysis 4.4) were all increased by bupropion. However, there was substantial overall heterogeneity for the adverse event outcome, and some moderate heterogeneity between subgroups for the dropout due to AEs outcome - although the latter did not reach statistical significance (P = 0.17). There was still no clear evidence of an increased risk of SAEs when using bupropion. However, despite combining more studies there was still some imprecision in this result, meaning that 95% CIs still incorporated a potential increase in SAEs when using bupropion, as well as no increase (RR 1.17, 95% CI 0.93 to 1.47; I^2 = 0%; subgroup differences I^2 = 0%; 28 studies, 12,500 participants; Analysis 4.3).

Bupropion versus front-line smoking cessation monotherapies

Smoking cessation

We found evidence to suggest bupropion was less effective than varenicline for smoking cessation (RR 0.71, 95% CI 0.64 to 0.79; I^2 = 0%; 6 studies, 6286 participants; Analysis 5.1), whereas there was no clear evidence that bupropion resulted in better cessation rates than NRT (RR 0.99, 95% CI 0.91 to 1.09; I^2 = 18%; 10 studies, 8230 participants; Analysis 6.1). This was based upon our meta-analyses of 10 relevant studies, in which we pooled studies investigating all forms of NRT (patch, lozenge, or a choice). When comparing the results of our analyses across separate subgroups of NRT (including combination patch and lozenge) we found that there was no strong evidence of significant subgroup differences (I^2 = 47.8%; P = 0.12). In neither case did removing studies deemed to be at an overall high risk of bias change the interpretation of the effect estimates.

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Depression

One post hoc analysis found that bupropion was more effective than NRT in those with a history of depression (Stapleton 2013). See Table 2.

Safety

There was evidence that randomization to bupropion resulted in minimal difference in reporting of AEs when compared to both varenicline and NRT (Analysis 5.2; Analysis 6.2). The same was true of SAEs, however there were much fewer events in these analyses, meaning they were underpowered and we can have less certainty in their results (Analysis 5.3; Analysis 6.3). When focusing on psychiatric AEs only there was no evidence of a difference when comparing bupropion to varenicline (Analysis 5.4); and heterogeneity was so high when comparing bupropion to NRT that it was deemed inappropriate to present a pooled estimate (I^2 = 92%; Analysis 6.4). There was insufficient evidence to indicate whether bupropion increased the risk of many of the other safety outcomes assessed (seizures, overdoses, suicide attempts, death by suicide and all-cause mortality) when compared to varenicline and NRT due to a paucity of relevant data, meaning that when estimates could be calculated these were extremely imprecise with CIs encompassing both potential benefit and harm of the intervention.

We also found evidence that participants in the bupropion groups experienced more insomnia and anxiety than people in the varenicline groups (insomnia: RR 1.40, 95% CI 1.22 to 1.60; I^2 = 9%; 3 studies, 5208 participants; Analysis 5.10; anxiety: RR 1.28, 95% CI 1.07 to 1.53; I^2 = 0%; 2 studies, 4705 participants; Analysis 5.11) and NRT groups (insomnia: RR 1.31, 95% CI 1.10 to 1.55; I^2 = 47%; 2 studies, 4128 participants; Analysis 6.10; anxiety: RR 1.31, 95% CI 1.06 to 1.62; I^2 = 67%; 2 studies, 4855 participants; Analysis 6.11) at follow-up. However, we detected moderate heterogeneity for both the insomnia and anxiety outcomes for the comparison to NRT, and when we carried out a sensitivity analysis, removing the study judged to be at high risk of bias, for the anxiety outcome (Analysis 6.11) the 95% CIs shifted to incorporate no between-group difference in anxiety (RR 1.23, 95% CI 0.99 to 1.53; I^2 = 13%; 1 study, 4028 participants).

Tolerability

Compared to both varenicline (RR 1.12, 95% CI 0.96 to 1.31; I^2 = 23%; 6 studies, 6103 participants; Analysis 5.12) and NRT (RR 1.14, 95% CI 0.95 to 1.38; I^2 = 33%; 4 studies, 4825 participants; Analysis 6.12) there was no clear evidence that bupropion led to an increase in trial dropouts due to AEs; however in both cases the CIs encompassed fewer dropouts in the comparator as well as no difference.

We carried out sensitivity analyses for all of the safety and tolerability analyses, removing studies judged to be at high risk of bias, where appropriate. None of these analyses resulted in a difference in the clinical interpretation of effects.

Bupropion versus other pharmacotherapies

Smoking cessation

There was no clear evidence that bupropion was more effective than nortriptyline in aiding smoking cessation (RR 1.30, 95% CI 0.93 to 1.82; I^2 = 0%; 3 studies, 417 participants; Analysis 7.1), although event rates were low (101 participants), and the result imprecise. This result was similar when one study judged to be at high risk of bias (Hall 2002), was removed from the analysis.

Depression

Only two trials examined the interaction between depression and quit rates for bupropion and nortriptyline (Hall 2002; Wagena 2005). Both of the within-study analyses found that participants classified as depressed were more likely to quit using bupropion than nortriptyline (Table 2).

Safety

There was insufficient evidence to determine whether bupropion increased the risk of any of the safety outcomes included in this review when compared to nortriptyline (Analysis 7.2; Analysis 7.3), or gabapentin (Analysis 8.1). Where data were available, it was sparse and resulted in imprecise pooled estimates encompassing one. In one instance (bupropion versus nortriptyline; insomnia outcome) heterogeneity was so high that it was not appropriate to present a pooled estimate (I^2 = 90%; Analysis 7.3).

Tolerability

There was also insufficient evidence to determine whether bupropion increased the risk of trial dropouts due to adverse events when compared to both nortriptyline (Analysis 7.4) and gabapentin (Analysis 8.2), with imprecise estimates in both cases.

Where possible, for the above safety and tolerability outcomes, we carried out sensitivity analyses removing studies judged to be at high risk of bias; however in the rare cases where this was appropriate there was no appreciable change in the interpretation of the effect estimates.

Bupropion at different doses

Smoking cessation

There was no clear evidence to indicate a differential effect between a 150 mg or 300 mg dose of bupropion on the likelihood of smoking cessation. Whilst the pooled estimate was 1.08 in favour of a 300 mg dose, the 95% CI encompassed a potential benefit of either dose (RR 1.08, 95% CI 0.93 to 1.26; I^2 = 49%; 3 studies, 2042 participants; Analysis 9.1).

Depression

None of the relevant included studies investigated a potential link between depression and quit rates.

Safety

We were unable to draw conclusions about any of the safety outcomes for this comparison. Analyses that could be carried out (SAEs Analysis 9.2; overdoses Analysis 9.3; suicide attempts Analysis 9.4; death by suicide Analysis 9.5; all-cause mortality Analysis 9.6; insomnia Analysis 9.7; anxiety Analysis 9.8), suffered from substantial imprecision due to a low number of events (ranging from 0 to 99), and in all cases 95% CIs encompassed one.

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Tolerability

Our analysis of dropouts due to adverse event data also suffered from imprecision (Analysis 9.9), and we were unable to draw conclusions.

A sensitivity analysis removing studies judged to be at high risk of bias was only appropriate for the cessation outcome; removing the one study deemed to be at high risk of bias did not alter the clinical interpretation of the result.

Other antidepressant monotherapies versus control

Smoking cessation

Pooling six trials comparing nortriptyline to placebo showed evidence of benefit of nortriptyline over placebo (RR 2.03, 95% CI 1.48 to 2.78; I^2 = 16%; 6 studies, 975 participants; Analysis 10.1) for smoking cessation. Removing two studies judged to be at high risk of bias did not influence the result (Hall 2002; Prochazka 1998).

We did not find clear evidence to indicate that selective serotonin reuptake inhibitors (SSRIs) increased the likelihood of smoking cessation relative to control (RR 0.93, 95% CI 0.71 to 1.22; I^2 = 0%; 4 studies, 1594 participants; Analysis 11.1); however there was a low number of events across studies (193 participants) and this should be taken into account. We subgrouped our meta-analysis by the type of SSRI used in the trial (2 fluoxetine: Niaura 2002; Spring 2007; 1 paroxetine: Killen 2000; 1 sertraline: Covey 2002), and found no evidence of a subgroup difference (I^2 = 0%).

We also found no clear evidence that monoamine oxidase inhibitors (MAOIs) increased the likelihood of smoking cessation relative to control (RR 1.29, 95% CI 0.93 to 1.79; I^2 = 0%; 6 studies, 827 participants; Analysis 12.1); however, again event rates were low, resulting in imprecision (193 participants). There was no effect of removing the one study deemed to be at high risk of bias (George 2003). Our meta-analysis included one trial of moclobemide (Berlin 1995) and five of selegiline (Biberman 2003; George 2003; Kahn 2012; Killen 2010; Weinberger 2010), and we subgrouped these accordingly. We did not identify any evidence of a subgroup difference (I^2 = 0%).

One trial of venlafaxine (Cinciripini 2005) showed no evidence of increased smoking cessation compared to placebo (RR 1.22, 95% CI 0.64 to 2.32; I^2 = n/a; 1 study, 147 participants; Analysis 13.1). However, the effect estimate was imprecise and CIs encompassed both potential benefit and harm.

Two small trials comparing St John's wort to placebo (Parsons 2009; Sood 2010), provided no clear evidence to suggest it was a better smoking cessation aid than placebo when pooled (RR 0.81, 95% CI 0.26 to 2.53; I^2 = 29%; 2 studies, 261 participants; Analysis 14.1); however there was substantial imprecision.

The one trial assessing S-Adenosyl-L-Methionine (SAMe) compared to placebo provided no evidence of benefit for smoking cessation (RR 0.70; CI 0.24 to 2.07; I^2 = n/a; 1 study; 120 participants; Analysis 15.1); however, the number of included participants and the number of events were small.

Depression

One within-study comparison found that a past history of depression did not appear to moderate the efficacy of nortriptyline, but subgroup numbers were small (Hall 1998). However, another within-study analysis found that the most effective factor for ensuring the efficacy of nortriptyline was a negative history of depression (Da Costa 2002).

Of the three studies conducting post hoc analyses of fluoxetine (Saules 2004; Spring 2007) and paroxetine (Killen 2000) to assess the interaction between depression and antidepressant quit rates, none provided evidence to support this interaction (George 2003; Kahn 2012).

The two studies conducting post hoc analyses of selegiline to assess the interaction between depression and antidepressant quit rates also did not provide evidence to support this interaction (George 2003; Kahn 2012).

Safety

One trial investigated the likelihood of SAEs when randomized to receive nortriptyline in comparison to placebo (Haggsträm 2006). No SAEs were reported in either trial arm (Analysis 10.2). The insomnia and anxiety outcomes provided insufficient evidence of any effect for this comparison (Analysis 10.3; Analysis 10.4).

There was insufficient evidence to indicate whether SSRIs increased the risk of AEs relative to placebo. Only one small trial of fluoxetine investigated this (NCT00578669; Analysis 11.2).

For the comparison of MAOIs relative to placebo, there was no evidence of increased risk of experiencing either AEs (Analysis 12.2), psychiatric AEs (Analysis 12.3), or SAEs (Analysis 12.4); however the latter two analyses suffered from substantial imprecision and should be treated with caution. Substantial imprecision and heterogeneity also meant that we were unable to draw conclusions regarding insomnia and anxiety (Analysis 12.5; Analysis 12.6).

The one study assessing safety outcomes for St John's wort versus placebo (Parsons 2009), did not provide sufficient evidence to assess whether it increased the likelihood of SAEs or all-cause mortality specifically (Analysis 14.2; Analysis 14.3), and a study of SAMe versus placebo (Sood 2012), did not provide sufficient evidence on AEs or insomnia (Analysis 15.2; Analysis 15.3).

Tolerability

Our meta-analysis including four studies comparing nortriptyline to placebo found evidence that dropout due to treatment was approximately twice as likely when randomized to nortriptyline (RR 1.99, 95% CI 1.18 to 3.36; I^2 = 23%; 4 studies, 537 participants; Analysis 10.5). This result should be treated with caution due to imprecision; however the removal of two studies judged to be at high risk of bias did not change the interpretation of the result (Hall 2004; Prochazka 1998).

There was also evidence to suggest SSRIs may increase the likelihood of dropout due to drug (RR 2.59, 95% CI 1.70 to 3.94; I^2 = 0%; 3 studies, 1270 participants; Analysis 11.3). When the four included studies were subgrouped into two of fluoxetine (Niaura 2002; Spring 2007), and one of sertraline (Covey 2002), there was no evidence of a subgroup difference (I^2 = 0%).

There was some evidence that there may be an increased risk of drug discontinuation in the MAOI groups, and this persisted when

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we removed one study judged to be at high risk of bias. However, there was substantial imprecision in this analysis (Analysis 12.7).

One study each assessed dropout due to drug for St John's wort versus placebo (Parsons 2009; Analysis 14.4), venflaxine versus placebo (Cinciripini 2005; Analysis 13.2), and SAMe versus placebo (Sood 2012; Analysis 15.4). These studies did not provide sufficient evidence to draw clear conclusions.

Other antidepressant combination therapies versus control

Smoking cessation

Pooling four trials using nortriptyline as an adjunct to nicotine patch therapy (Aveyard 2008; Hall 2004; Prochazka 2004; Richmond 2013), did not provide evidence of a benefit of combination nortriptyline and NRT for smoking cessation relative to NRT alone (RR 1.21, 95% CI 0.94 to 1.55; I^2 = 26%; 4 studies, 1644 participants; Analysis 16.1); however there was imprecision around the effect estimate, with the CIs encompassing both no difference and a clinically significant benefit. The interpretation of the result remained the same when we removed studies judged to be at an overall high risk of bias.

Three trials evaluated fluoxetine as an adjunct to NRT (Blondal 1999; Brown 2014; Saules 2004), but also did not provide evidence of an increased likelihood of smoking cessation relative to NRT alone when pooled (RR 0.70, 95% CI 0.48 to 1.03; I^2 = 0%; 3 studies, 466 participants; Analysis 17.1). Again, interpretation did not change when we removed studies judged to be at risk of bias, and there was evidence of imprecision. However, in this instance CIs encompassed the possibility of no difference and a clinically significant harm.

Depression

One study comparing nortriptyline plus NRT to NRT alone found no evidence supporting depression as a moderator of abstinence in either the combination nortriptyline and NRT or the placebo arms of the trial (Aveyard 2008).

Safety

One trial investigated the effect of combination nortriptyline and NRT on the likelihood of insomnia when compared to NRT alone (Prochazka 2004). However the study only reported a very small number of events across trial arms, resulting in substantial imprecision, and making it impossible to draw any conclusions (Analysis 16.2).

There was also insufficient evidence from one study investigating the effect of selegiline plus NRT versus NRT alone on SAEs (Biberman 2003; Analysis 18.1). Similarly Berlin 2012 alone provides insufficient data to assess the effects of EVT302 plus NRT versus NRT alone on AEs (Analysis 19.1) and SAEs (Analysis 19.2).

Tolerability

One trial investigated the effect of combination nortriptyline and NRT on the likelihood of trial discontinuation (Prochazka 2004); however events were low, making it impossible to draw conclusions (Analysis 16.3). There was insufficient information available from the one study comparing dropout due to AEs between selegiline plus NRT versus NRT alone (Biberman 2003; Analysis 18.2), and the one study comparing EVT302 plus NRT versus NRT alone (Berlin 2012; Analysis 19.3) to draw conclusions.

Other antidepressants at different doses

Smoking cessation

We are unable to evaluate the efficacy of 300 mg versus 600 mg St John's wort, as the one trial comparing these differences (Barnes 2006) had too small a sample size (28 participants), with no individuals abstinent from smoking at 12 months follow-up. One study compared the efficacy of 30 mg versus 60 mg of fluoxetine, and found the same quit rates in both groups (RR 1.00, 95% CI 0.63 to 1.59; I^2 = n/a; 656 participants; Analysis 20.1); however this result should be treated with caution due to imprecision.

Depression

These studies did not investigate depression as a moderator of smoking quit rates.

Safety

Berlin 2002 only followed up participants to eight weeks and therefore we did not use efficacy data from this study; however they reported safety data. The study compared 100 mg with 200 mg daily doses of lazabemide. No SAEs were recorded during the trial (Analysis 21.1). There was insufficient evidence to conclude whether participants randomized to the higher dose were more likely to suffer from symptoms of insomnia (Analysis 21.2) or anxiety (Analysis 21.3).

Due to the very small sample size of Barnes 2006, there was insufficient evidence to assess the likelihood of AEs in participants receiving a 300 mg daily dose of St. John's wort versus a 600 mg dose (28 participants; Analysis 22.2). Similarly, there was insufficient evidence investigating the effect of a 800 mg daily dose of SAMe versus a 1600 mg daily dose on the risk of AEs (Sood 2012; Analysis 23.1).

Tolerabiliy

Niaura 2002 found some evidence that a 60 mg daily dose of fluoxetine compared to a 30 mg dose daily increased the likelihood of trial discontinuation due to drug treatment (RR 0.64, 95% CI 0.46 to 0.87; I^2 = n/a; 1 study, 656 participants; Analysis 20.2).

However, there was insufficient evidence to conclude whether participants randomized to the higher 200 mg dose of lazabemide were more likely to drop out of the trial due to the medication than participants randomized to the lower 100 mg dose (Berlin 2002; Analysis 21.4), or whether participants randomized to a 1600 mg dose of SAMe were more likely to drop out than those randomized to a 800 mg dose (Sood 2012; Analysis 23.2).

DISCUSSION

Summary of main results

This review summarizes and evaluates the evidence investigating the efficacy, safety and tolerability of different types of antidepressant for smoking cessation. This review includes 115 studies in total. Forty-six trials of 17,866 participants provide a large, high-certainty evidence base confirming the benefit of bupropion used as a single pharmacotherapy for smoking cessation (Summary of findings 1). The pooled estimate suggests

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that bupropion increased long-term quitting success by 52% to 77% when compared with placebo. Treatment effects appeared to be comparable across the range of populations, settings and types of behavioural support studied, including those with and without a past history of depression. There is evidence to suggest that bupropion increases the risk of adverse events (AEs), including psychiatric AEs, and the likelihood that users will discontinue treatment; however evidence does not currently suggest that bupropion increases the risk of serious adverse events (SAEs).

Our review finds no evidence of an additional benefit of adding bupropion to nicotine replacement therapy (NRT) (low-certainty evidence; Summary of findings 2) or varenicline treatment (moderate-certainty evidence; Summary of findings 3) when compared to NRT or varenicline alone, respectively. There was insufficient evidence to draw conclusions on safety outcomes when using bupropion as an adjunct to NRT or varenicline. This is due to a lack of studies assessing these outcomes, and few events recorded for those studies that did (very low-certainty and low-certainty evidence, respectively).

The evidence does not suggest a difference in the efficacy of bupropion plus NRT, or nortriptyline, for smoking cessation. However, participants taking bupropion may be between 21% and 36% less likely to quit than those treated with varenicline, based on evidence from 6286 participants. The evidence relating to the safety of treatment is inconclusive when comparing bupropion to NRT, varenicline and nortriptyline due to a paucity of studies, overall participants, and events.

We found evidence that nortriptyline is also an effective agent to aid smoking cessation when compared with placebo, based on a meta-analysis of six studies, including 975 participants. However, there is no clear evidence that other antidepressants, including selective serotonin reuptake inhibitors (SSRIs), monoamine oxidase inhibitors (MAOIs), venflaxine, St John's wort, and S-Adenosyl-L-Methionine (SAMe), are effective as cessation aids. Therefore, despite SSRIs being commonly used to treat depression there does not seem to be any justification for continuing to pursue their use for smoking cessation, where other more clearly effective options exist.

Few studies examined whether current or previous depression moderated the effectiveness of antidepressants to aid smoking cessation. Those comparing bupropion to placebo found no evidence of an interaction between depression and use of bupropion. Studies contributing to other comparisons found varied but uncertain results.

Overall completeness and applicability of evidence

The searches conducted for this study were broad and identified any studies where a drug was described as being an 'antidepressant' or 'antidepressive'. In cases where we were unsure of whether a medication was classed as an antidepressant, we conducted a brief literature search to clarify whether they had been used in other research as antidepressants, so as to ensure we included all relevant medications. We also searched trial registers to identify any ongoing or completed but unpublished, registered studies assessing the efficacy and safety of antidepressants for smoking cessation.

Studies included in this review recruited adult smokers who were typically motivated to quit. Of the study populations included in our review, the lowest mean cigarettes smoked per day was 10, and the highest was 44, meaning that most studies included participants with significant tobacco addiction. These results may not apply to populations with few symptoms of tobacco addiction. In addition, the minority of studies specifically recruited participants with mental health disorders. Of these five studies, one was weighted particularly heavily in the meta-analysis (Anthenelli 2016). Anthenelli 2016 recruited a subset of participants with mental health disorders, who were described as 'clinically stable', suggesting that they may not be entirely representative of the wider population diagnosed with a mental health disorder. Further studies are needed among those with depression to provide greater confidence in our findings, which suggest that bupropion is as effective for smoking cessation in people with a mental health diagnosis as those without.

Certainty of the evidence

Of the 115 studies included in this review, we judged 12 to be at low risk of bias for all domains, and 28 to be at high risk in one or more domains. We judged the remaining 75 studies to be at an unclear risk due to a lack of reporting of key information. In these cases it is impossible to know whether these studies were at any risk of bias or whether the information was simply not reported. To investigate the potential impact of studies that we judged to be at high risk of bias on results, we carried out sensitivity analyses, removing studies judged to be at high risk from analyses and observing the effects on results (where this was possible). In most cases this had no effect on the clinical interpretation of the analyses.

We assessed the certainty of the evidence by creating 'Summary of findings' tables and carrying out GRADE ratings (Schünemann 2013) for three of the comparisons (bupropion versus placebo/no pharmacotherapy control (Summary of findings 1); bupropion plus NRT versus NRT alone (Summary of findings 2); bupropion plus varenicline versus varenicline alone (Summary of findings 3). The efficacy of bupropion versus placebo/pharmacotherapy control for smoking cessation generated high-certainty evidence. We judged combination bupropion and varenicline to be of moderate certainty, whilst we judged the combination bupropion and NRT to be of low-certainty evidence. We judged the safety outcomes for bupropion versus placebo/pharmacotherapy control of SAEs and dropout due to drug to have moderate- and high-certainty evidence, respectively. However, for the bupropion combination therapy with NRT or varenicline comparisons, we judged the evidence for these safety outcomes to be of very low- and low-certainty, respectively. The main reason for downgrading the evidence was imprecision (low overall numbers of participants and events), as well as risk of bias in one case (judgements of high risk that may affect the result), and inconsistency (moderate heterogeneity in analysis detected) in another case.

Potential biases in the review process

We consider the review process used to be robust, and do not believe we have introduced any biases. For outcome assessment, we followed the standard methods used for Cochrane Tobacco Addiction cessation reviews. Our search of the Cochrane Tobacco Addiction Specialized Register, allowed us to capture three ongoing studies. However, there may be unpublished data that our searches did not uncover.

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We generated and interpreted funnel plots for all analyses that included 10 or more studies. Four of these were for outcomes summarized in our 'Summary of findings' tables (smoking cessation, SAEs and dropout due to adverse events of the drug) and contributed to our GRADE ratings for the following comparisons: bupropion versus placebo/pharmacotherapy control (Figure 3, Figure 4, Figure 5, respectively), and smoking cessation for bupropion plus NRT versus NRT alone (Figure 6). None of these plots appeared to demonstrate evidence of publication bias. However, only 12 studies contributed to the funnel plot for bupropion plus NRT versus NRT alone (a relatively small number), so this should be interpreted with caution. We also tested whether the inclusion of studies funded by the pharmaceutical industry, or where a pharmaceutical company had supplied the medication for the study, was impacting on the pooled results of our analyses. In no case did there appear to be any clear evidence of this (Table 1).

Figure 3. Funnel plot of comparison: 1 Bupropion versus placebo/control, outcome: 1.1 Smoking cessation.

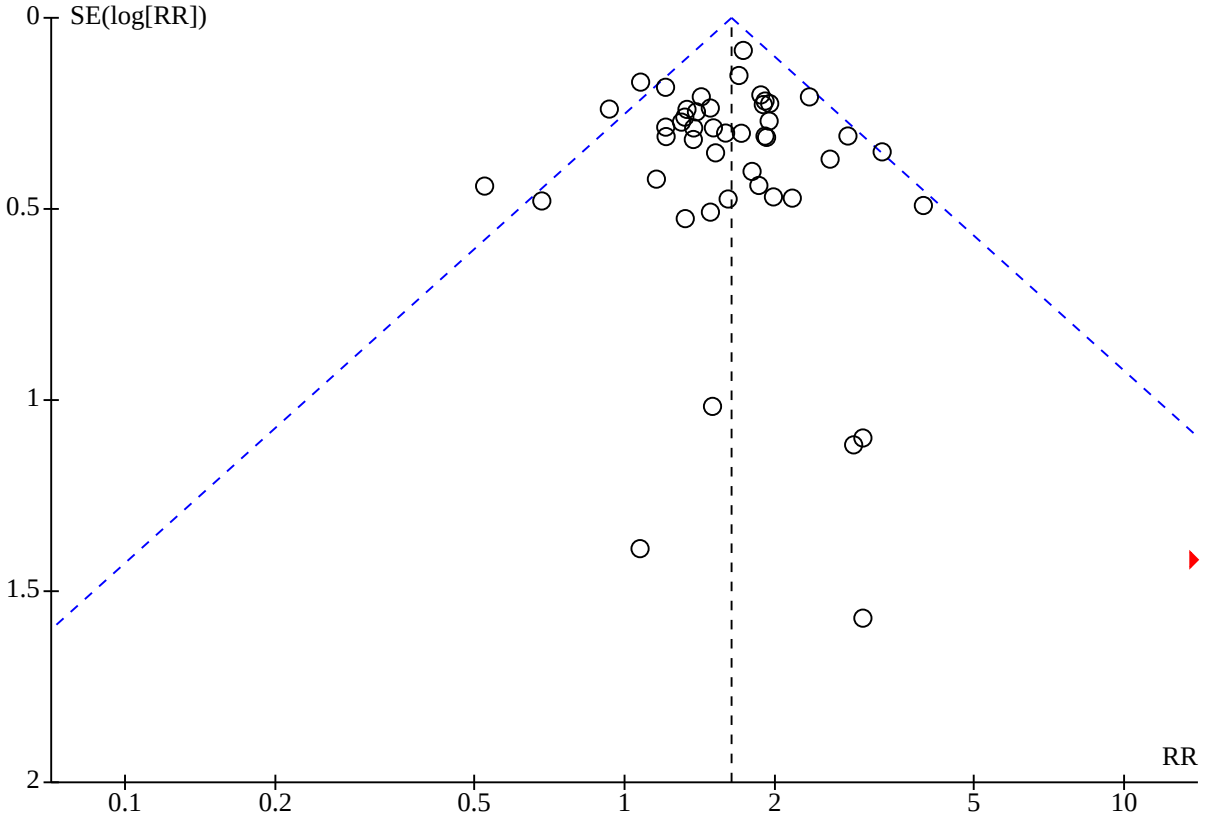

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Figure 4. Funnel plot of comparison: 1 Bupropion versus placebo/control, outcome: 1.5 Serious adverse events.

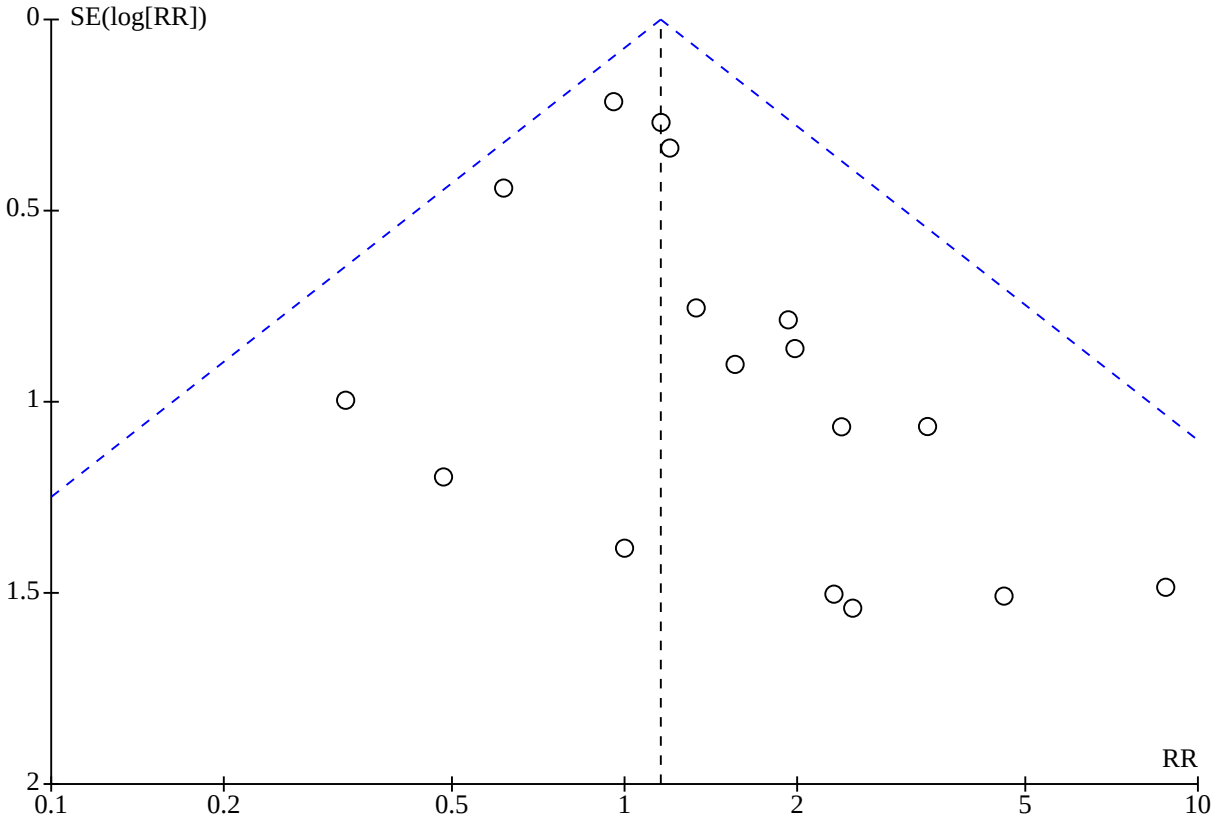

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Figure 5. Funnel plot of comparison: 1 Bupropion versus placebo/control, outcome: 1.14 Dropouts due to drug.

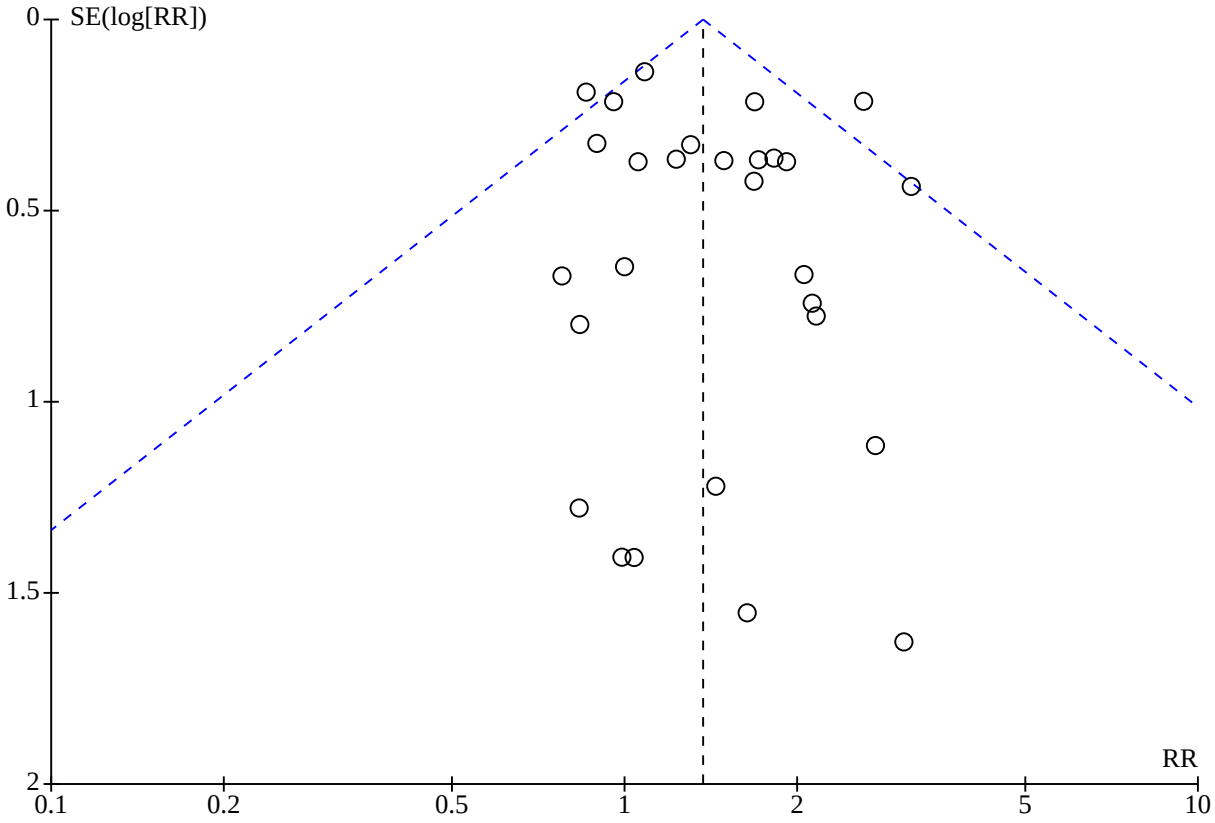

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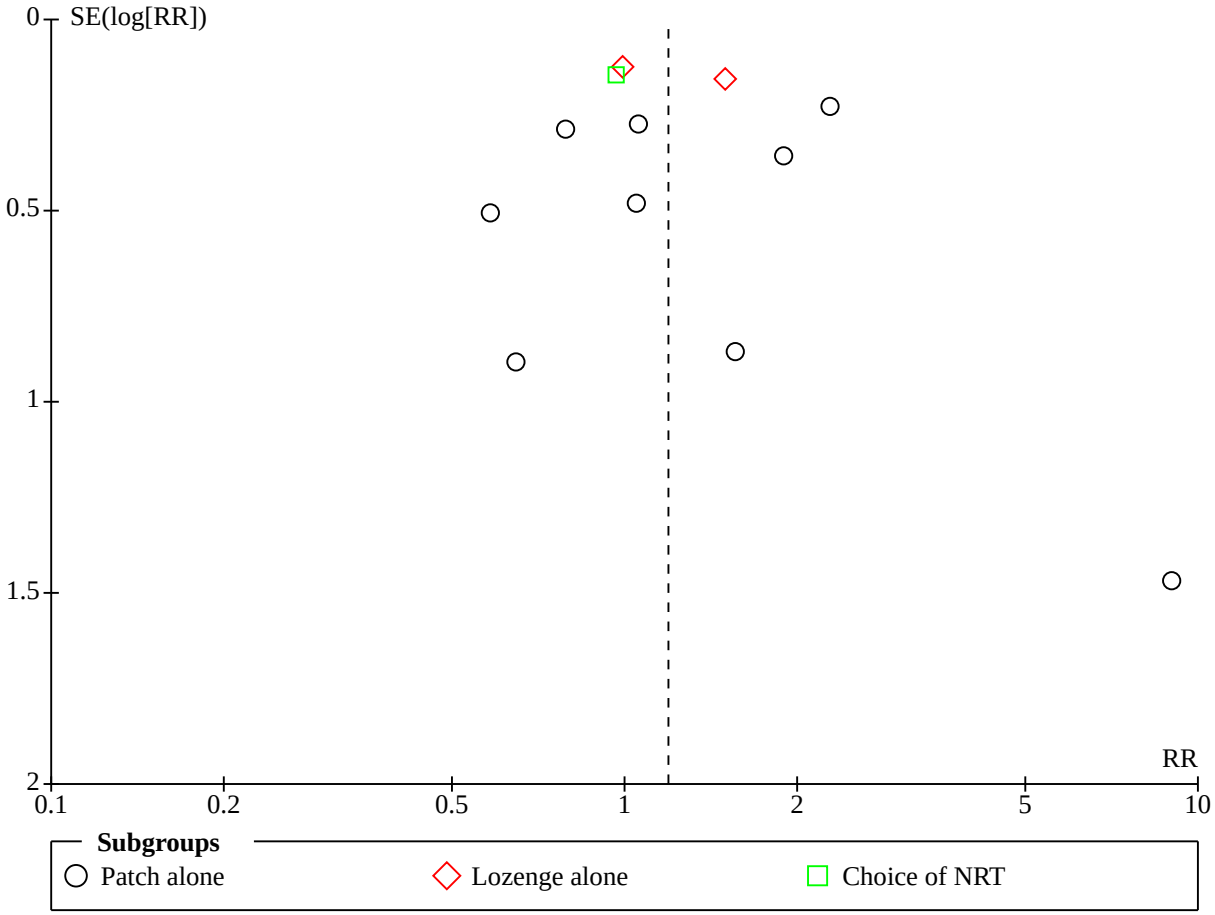
Figure 6. Funnel plot of comparison: 2 Bupropion and NRT versus NRT alone, outcome: 2.1 Smoking cessation.



We considered participants lost to follow-up as smokers, which is current best practice in this field (West 2005). The Cochrane Tobacco Addiction policy is to present effect estimates as risk ratios (RRs), as these are easier to interpret than odds ratios (ORs), but this means that where there are no events measured in both comparison groups RRs cannot be calculated, and therefore do not contribute to the meta-analysis. We considered alternative statistical approaches to deal with this, but concluded that other approaches would be more difficult to interpret and that overall conclusions would not change as a result.

Agreements and disagreements with other studies or reviews

The findings of this review are in agreement with the conclusions of other reviews and guidelines in a variety of populations (Cahill 2013; Hughes 2005; McRobbie 2005; Mills 2006, Tsoi 2010). USA smoking cessation guidelines continue to recommend bupropion as a first-line therapy (Fiore 2008), and recommend nortriptyline as a second-line therapy due to possible AEs. Open uncontrolled trials and observational studies of bupropion have shown real-life quit rates comparable to those found in the clinical trials included in this review (Paluck 2006; Wilkes 2005). In addition, our findings regarding the beneficial effect of bupropion for smoking cessation, specifically in smokers with mental illness, are consistent with a subset from a separate Cochrane Review evaluating smoking cessation treatments exclusively in populations with current or past depression (van der Meer 2013).

However, our findings on the effectiveness of bupropion as an adjunct to NRT differ from the results of the United States Public Health Service (USPHS) clinical practice guideline (Fiore 2008). Whereas we did not detect a significant difference in efficacy when bupropion and NRT were used together compared to NRT alone, the USA guideline reported an OR of 1.30 (95% confidence interval (CI) 1.0 to 1.80) favouring combination therapy (Fiore 2008, Table 6.28). The difference in meta-analytic outcomes may be because our analysis included several studies of hard-to-treat populations not included in the USPHS analysis. Also, it could be because our analysis was a collation of 12 direct, within-study randomized comparisons, whereas the USPHS carried out an indirect across-study comparison of the results from the combination arms of three trials and the patch-alone arms of 32 studies.

Cahill 2013 used both direct and indirect statistical comparisons to compare the efficacy of bupropion to NRT and varenicline, using network meta-analysis. The effect estimates generated resulted in similar conclusions to the ones drawn here, i.e. bupropion and single-form NRT resulted in similar quit rates and varenicline resulted in higher quit rates than bupropion. However, indirect comparisons made by Cahill 2013 also suggested that combination

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NRT was more effective than bupropion, whereas our subgroup analysis did not provide clear evidence of this.

Similar to our findings, other studies and systematic reviews looking at the SAE profile of bupropion remain inconclusive (Cahill 2013; Grandi 2011; Wightman 2010). Whilst our review did not find that bupropion significantly increased the incidence of seizures (RR 1.64, 95% CI 0.08 to 33.95), with substantial imprecision detected, the point estimate does indicate a rate of approximately 1.5 events per 1000 people taking bupropion, compared to a rate of 1 per 1000 cases presented elsewhere (Cahill 2013).

In contrast to the findings of the very large-scale EAGLES trial, we have concluded that bupropion significantly increases psychiatric AEs (Anthenelli 2016). Whilst Anthenelli 2016 contributes over 95% of psychiatric AE data to our meta-analysis, it concluded that bupropion does not significantly increase the incidence of psychiatric AEs. This discrepancy may be the result of including psychiatric AEs of any severity in our relevant meta-analysis, whereas Anthenelli 2016 used a composite measure of only moderate and severe intensity psychiatric events for their primary analysis. It is not possible for us to corroborate whether we would find the same if we were only to include moderate and severe psychiatric events, as study reporting does not allow us to discriminate between these events according to severity.

Taking into account the combined evidence from this review and Cahill 2013, suggesting that varenicline is more efficacious than bupropion, and evidence from Cahill 2016, suggesting that psychiatric AEs are not increased by varenicline; varenicline may be a more suitable option for people who wish to take a prescription medication to quit smoking, especially those with mental health disorders.

AUTHORS' CONCLUSIONS

Implications for practice

- Bupropion and nortriptyline are effective pharmacological aids for smoking cessation. There is no good evidence that one is superior to the other. Bupropion increases the rate of long-term quitting by approximately 52% to 77%, and this effect appears to be stable regardless of the amount of behavioural support provided, and whether participants have current or a history of mental health disorders.
- Bupropion may cause an increase in adverse events (AEs), and specifically psychiatric AEs, leading to discontinuation of drug use in some users (approximately 9%). However, estimates of serious adverse events (SAEs, i.e. events that result in hospitalization, disability or death) include the possibility of no difference as well as a potential 1% increase when compared to placebo.
- There is no evidence of higher quit rates when combining bupropion with either nicotine replacement therapy (NRT) or varenicline relative to each drug taken alone.
- Bupropion appears to be as effective as NRT for smoking cessation; however varenicline may result in somewhere between 27% to 56% higher quit rates than bupropion.
- There is a paucity of data investigating the efficacy and safety of antidepressants other than bupropion for smoking cessation, but there is sufficient data to show that, in the light of the effectiveness of other medications, selective serotonin reuptake inhibitors (SSRIs) offer no worthwhile increase in smoking cessation rates.
- The evidence is insufficient to draw conclusions about whether existing depression modifies the efficacy of antidepressants for smoking cessation.

Implications for research

- There is high-certainty evidence that bupropion increases quit rates at six months or longer in adults motivated to quit. We consider that further research is highly unlikely to change our confidence in the efficacy of bupropion in this population. However, further studies could increase our confidence in the likelihood of SAEs and any future studies comparing bupropion to placebo should ensure these are recorded and reported in detail.
- More studies assessing the efficacy and safety of different doses of bupropion, as well as doses higher than 300 mg would clarify the most effective bupropion dosing strategy.
- More high-certainty studies are needed to assess the efficacy of bupropion when combined with varenicline treatment or NRT treatment.
- More high-certainty studies are needed to assess whether bupropion is particularly efficacious for supporting smoking cessation in people with depression.
- New studies of any antidepressant used as a treatment for smoking cessation should ensure that they measure and report on the number of participants experiencing SAEs and AEs, as well as reporting on the number of dropouts due to treatment. These numbers should be reported separately by study arm, as well as overall. Specifically, studies of bupropion should report on numbers of psychiatric AEs and provide more detail on the severity of these events.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Ahluwalia 2002

Study characteristics	
Methods	Study design: RCT Country: USA Setting: community-based healthcare centre Recruitment method: community volunteers
Participants	600 African American smokers randomized; 70% female, average age 44; average cigarettes per day 17; 27% had possible clinical depression CES-D > 16
Interventions	• Bupropion, 300 mg/day for 7 weeks • Placebo Common components: 8 sessions of in-person or telephone counselling and self-help guide
Outcomes	• Smoking cessation: prolonged absinence at 26 weeks. Validated by CO ≤ 10 ppm, discrepancies resolved with cotinine ≤ 20 mg • Adverse events: measured for 26 weeks
Funding Source	National Cancer Institute. GlaxoSmithKline provided study medication.

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Ahluwalia 2002 *(Continued)*

Author conflicts of interest	Dr Ahluwalia has served as a consultant for GlaxoSmith2Kline and Pharmacia Consumer. GlaxonSmithKline provided study medication but played no role in the design, conduct of the study, or interpretation and analysis of the data.
Notes	Continuous abstinence rates shown in Figure 3 of paper. Figures obtained from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization codes were generated in blocks of 50 and sent to the pharmaceutical company..."
Allocation concealment (selection bias)	Low risk	Quote: " ... [the pharmaceutical company]... packaged the treatment and then shipped the blinded drug to the investigator." Shows blinded drugs were provided to investigator
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Blinding was successful. At the end of treatment, 58% (150/259) of participants correctly guessed that they received bupropion SR [sustained release], and 41% (104/253) correctly guessed they received placebo."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Approximately 32% lost to follow-up in each group; included as smokers

Anthenelli 2016

Study characteristics

Methods	Study design: RCT Countries: USA, Australia, Canada, Denmark, Finland, Germany, New Zealand, South Africa, Spain, Bulgaria, Russian Federation, Slovakia, Argentina, Brazil, Chile, and Mexico Setting: clinical trial centres, academic centres, and outpatient clinics treating patients with and without psychiatric disorders Recruitment method: from the investigators' own clinics; through newspaper, radio, and television advertising; fliers and posters
Participants	8144 participants; 56% female; average age 46.5; average cigarettes per day 21, mean FTND 5.8 Specialist population: participants were made up of two cohorts (a psychiatric cohort (N = 4074) and a non-psychiatric cohort (N = 3984)). Participants were included in the psychiatric cohort if they met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria for mood disorders including major depressive disorder or bipolar disorder; anxiety disorders including panic disorder, with or without agoraphobia, post-traumatic stress disorder, obsessive-compulsive disorder, social phobia, and generalized anxiety disorder; psychotic disorders including schizophrenia and schizoaffective disorders; or borderline personality disorder. Participants in the non-psychiatric cohort had no confirmed history of DSM-IV-TR Axis I or II disorders.
Interventions	• Bupropion sustained release and placebo varenicline and placebo nicotine patch. 150 mg twice a day for 12 weeks • Varenicline and placebo bupropion sustained release and placebo nicotine patch. 1 mg twice a day for 12 weeks • Transdermal nicotine patch and placebo varenicline and placebo bupropion sustained release. 21 mg per day with taper for 12 weeks

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Anthenelli 2016 *(Continued)*

	• Placebo bupropion sustained release and placebo varenicline and placebo nicotine patch. For 12 weeks. Common components: smoking cessation counselling consisting of 10 minute sessions at each of the 15 clinic visits, totalling 2 hours and 30 minutes
Outcomes	• Smoking cessation: continuous abstinence from week 9 to week 24 post-quit date (validated by CO ≤ 10 ppm) • Adverse events: measured within 12-week treatment period, or for 30 days thereafter
Funding Source	Pfizer and GlaxoSmithKline
Author conflicts of interest	RMA reports receiving grants from Pfizer and Alkermes, and providing consulting and advisory board services to Pfizer, Arena Pharmaceuticals, and Cerecor. RMA's writing of this manuscript was supported, in part, by National Institute on Alcohol Abuse and Alcoholism grant numbers U01 AA013641 and R01 AA019720; National Institute on Drug Abuse/Veterans Affairs Co-operative Studies numbers 1031 and 1032; and Veterans Affairs Merit Award number NEUA-003-08S. NLB reports providing consulting and advisory board services to Pfizer and GlaxoSmithKline, and having been a paid expert witness in litigation against tobacco companies. RW reports receiving grants from Pfizer, Johnson & Johnson, and GlaxoSmithKline, and receiving personal fees for advisory board services from Pfizer and GlaxoSmithKline. RW's salary is funded by Cancer Research UK. AEE reports receiving grants from Pfizer and Forum Pharmaceuticals, and receiving personal fees for advisory board services from Pfizer and Reckitt Benckiser. AEE's writing of the manuscript was supported by a National Institute on Drug Abuse Career Award in Patient-Oriented Research, number K24 DA030443. LSA, TM, DL, and CR are employees and stockholders of Pfizer. JA is an employee of GlaxoSmithKline and stockholder of that company. AK is a PAREXEL employee working on behalf of GlaxoSmithKline.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomisation administrator, independent from the clinical study team, prepared the computer-generated randomisation schedule used to assign participants to treatment using a block size of 8 (1:1:1:1 ratio) for each of the 20 diagnosis by region combinations."
Allocation concealment (selection bias)	Low risk	Quote: "Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system. Study product kit codes did not allow deciphering of randomised treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignments."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “The triple dummy design feature required participants to take study medications as masked tablets dispensed in separate varenicline and bupropion pill bottles each with matching placebo along with either applying active or placebo patches on a daily basis.” Quote: “Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system. Study product kit codes did not allow deciphering of randomised treatment or block size. As such, participants, investigators, and research personnel were masked to treatment assignments.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	439/2037 (21.6%) of the varenicline group, 448/2034 (22.0%) of the bupropion group, 481/2038 (23.6%) of the patch group and 483/2035 (23.7%) of the placebo group were lost to follow-up. Therefore, loss to follow-up was less than 50% and similar across study arms.

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Aubin 2004

Study characteristics	
Methods	Study design: RCT Country: France Setting: 74 cessation outpatient clinics Recruitment: volunteers
Participants	504 participants randomized: 56% female, average age 41, average cigarettes per day: not stated
Interventions	• Bupropion 300 mg for 7 weeks • Placebo Common components: motivational support at clinic visits at baseline, w3, w7, w12 and 3 phone calls TQD, 2 to 3 days later, w5, w18
Outcomes	Abstinence at w26 (continuous from w4) Validation: CO < 10 ppm
Funding Source	GlaxoSmithKline
Author conflicts of interest	The lead author (H J Aubin) is a paid consultant of GSK
Notes	First included as Lebargy 2003 based on abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "The computerized randomization schedule, prepared by the sponsor, was inaccessible to the investigator who was provided with a specific set of sequential treatment numbers."
Allocation concealment (selection bias)	Low risk	Quote: "The computerized randomization schedule, prepared by the sponsor, was inaccessible to the investigator who was provided with a specific set of sequential treatment numbers."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind" "Blinding was assured by matching the placebo to the bupropion tablets..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	26% of the placebo and 27% of the bupropion groups lost; included as smokers

Aveyard 2008

Study characteristics	
Methods	Study design: RCT Country: UK Setting: National Health Service stop smoking clinics Recruitment: people attending clinics

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Aveyard 2008 *(Continued)*

Participants	901 smokers, ≥ 10/day; 46% female, average age 43, average cigarettes per day 21
Interventions	• Nortriptyline. 75 mg/day, for 8w including tapering (max dose for 6w) • Placebo capsules All participants received free NRT and had behavioural support, the majority attending group sessions run by cessation specialists
Outcomes	• Smoking cessation: prolonged abstinence at 12 months from day 15 post-quit (validated by CO at 4w, saliva cotinine (collected by post) at 6 months and 12 months)
Funding Source	Cancer Research UK and National Institute for Health Research. Medication provided by King Pharmaceuticals
Author conflicts of interest	PA has done consultancy work for the pharmaceutical and biotechnology industry that has led to payments to him and his institution. This includes work for companies providing smoking cessation treatment, including NRT. MM has received consultancy income from the European Network for Smoking Prevention and has provided scientific consultancy services through the University of Oxford ISIS Innovation to the National Audit Office and G-Nostics.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "An independent statistician generated the randomisation schedule in Stata. We used block randomisation, with randomly ordered block sizes of two, four, and six, stratified by stop smoking adviser."
Allocation concealment (selection bias)	Low risk	Study nurses recruited participants, and the study administrator (who had not met the participants) allocated participants in sequence against the list for each adviser. Only the administrator and the pharmacist knew the allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Advisers, participants, and study staff...were blind to allocation... tablets were encapsulated, and identical powder filled capsules provided the placebos."
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% intervention, 17% control lost at 12 months, included as smokers. Authors note that majority of losses were already smoking.

Barnes 2006

Study characteristics

Methods	Study design: RCT Country: UK Setting: private consulting room in a community pharmacy Recruitment method: advertisements were placed in newspapers regional to the pharmacy; information leaflets were placed in the pharmacy, along with a window display on smoking cessation which mentioned the study; local radio interviews were given
Participants	28 participants randomized; 17% female; average age 42.8; average cigarettes per day 15.5; FTND: 26 ppts < 8 and 2 ppts ≥ 8

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Barnes 2006 *(Continued)*

Interventions	• St John's Wort, 300 mg per day • St John's Wort, 300 mg twice per day Common components: one hour of general smoking cessation advice and motivational support
Outcomes	• Smoking cessation: 12 months continuous abstinence following quit date (validated by CO)
Funding Source	Lichtwer Pharma (UK) Ltd
Author conflicts of interest	Lead author received funding by fellowship from Lichtwer Pharma UK Ltd
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A computer-generated randomisation list of random treatment assignments ('A' or 'B', corresponding to lower and higher dosages of SJW, respectively) in blocks of 4 without stratification was prepared in advance."
Allocation concealment (selection bias)	High risk	Quote: “Participants enrolled into the study were assigned to the next consecutive treatment.” As the pharmacist was unblinded, they would therefore have been aware of the allocation of the participants.
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: “This was a prospective, open, uncontrolled, pharmacy-based, pilot study.”
Incomplete outcome data (attrition bias) All outcomes	High risk	11/15 in once daily arm + 10/13 in twice daily arm were lost to follow-up. Therefore, loss to follow-up is greater than 50% in each trial arm.

Benli 2017

Study characteristics

Methods	Study design: RCT Country: Turkey Setting: a smoking cessation clinic Recruitment method: participants applied to the smoking cessation clinic directly by calling the Turkish Ministry of Health's 'stop smoking' helpline and making an appointment.
Participants	An unspecified number of participants were randomised. 405 participants were analysed. 17.5% female; average age 35.2; average age 35.2; average cigarettes per day 23; mean FTND 6.3
Interventions	• Bupropion. Provided for 3 months • Varenicline. Provided for 3 months Common components: behavioural therapy support with a biopsychosocial approach
Outcomes	• Smoking cessation: 7-day PPA at 12 months. Validated by a CO level ≤ 5 ppm
Funding Source	No funding

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Benli 2017 *(Continued)*

Author conflicts of interest	The authors declare that they have no competing interests
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distribution rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution." Comment: no further detail is provided.
Allocation concealment (selection bias)	Unclear risk	Quote: "Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distribution rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution." Comment: no further detail is provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Patients who were to receive the medication were randomly determined by the medication support center in order to provide a constant distribution rate of varenicline and bupropion and so that physicians would not be aware of the medication distribution" Comment: some attempt appears to have been made to blind physicians to group assignment, however no further detail is given, so it is unclear whether participants and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only those followed up at 12 months are included in analysis

Berlin 1995

Study characteristics

Methods	Study design: RCT Country: France Setting: clinic Recruitment: by adverts in general practices or from occupational medicine departments
Participants	88 smokers randomized; no current major depression or anxiety disorders; 57% had history of MDD
Interventions	• Moclobemide, 400 mg/day for 1w pre- and 2 months post-TQD, 200 mg for 3rd month • Placebo No behavioural intervention or counselling
Outcomes	• Smoking cessation: prolonged abstinence at 1 year (validated at all visits up to 6 months by plasma cotinine ≤ 20 ng/mL. 1-year abstinence based on telephone self-report by 6 month quitters) • Adverse events: measured until 91 days post-quit
Funding Source	Roche
Author conflicts of interest	None specified

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Berlin 1995 *(Continued)*

Notes	There were no serious adverse reactions. Insomnia was more common in drug (36%) than placebo (7%) groups. There were 4 dropouts for adverse effects/relapse in drug and 2 in placebo

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Double-blind, but blinding at allocation not explicit
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but further detail not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Relapses and subjects lost from follow-up were considered treatment failures." Number lost to follow-up not reported

Berlin 2002

Study characteristics

Methods	Study design: RCT Countries: France and Belgium Setting: General practices and anti-smoking clinics
Participants	330 participants randomized; 43.9% female; average age 39.9; average cigarettes per day 24.7; mean FTND 6.2
Interventions	• Lazabemide, 50 mg twice daily for 8 weeks • Lazabemide, 100 mg twice daily for 8 weeks • Placebo, twice daily for 8 weeks Common components: brief cognitive behavioral intervention at each visit, totalling 2 hours
Outcomes	• Smoking cessation: follow-up is 8 weeks, too short to be included in this review • Adverse events: measured over a period of 8 weeks
Funding Source	F Hoffmann-La Roche
Author conflicts of interest	None detailed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “subjects were assigned a treatment number according to the computer-generated randomization table”

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Berlin 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Eligible subjects were assigned a treatment number according to the computer-generated randomization table." Comment: no further information is provided, therefore who was blinded and how is unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter proof-of-concept study" Comment: no further information is provided
Incomplete outcome data (attrition bias) All outcomes	High risk	60% in placebo (68/114); 62% 100 mg/day lazabemide (67/108); and 54% 200 mg/day lazabemide (58/108) were lost to follow-up. Therefore, loss to follow-up is above 50% in all groups.

Berlin 2012

Study characteristics	
Methods	Study design: RCT Country: Germany Setting: investigation centres Recruitment method: media advertisements
Participants	412 participants randomized; 37.4% female; average age 35; average cigarettes per day 19; mean FTND 5.4
Interventions	• EVT302, 1 x 5 mg tablet per day for 8 weeks (1 week pre-quit and 7 weeks post-quit) • Placebo EVT302, 1 x 5 mg per day for 8 weeks (1 week pre-quit and 7 weeks post-quit) • Placebo EVT302 and nicotine patch. Placebo EVT302 dosing was 1 x 5 mg per day for 8 weeks (1 week pre-quit and 7 weeks post-quit). Nicotine patch (21 mg/24 hours) was given for 7 weeks post-quit. Common components: educational booklet on smoking cessation and a 10-minute counselling session at each visit, totalling 1 hour and 50 minutes
Outcomes	• Smoking cessation: follow-up is 12 weeks, too short to be included in this review • Adverse events: recorded over 8 weeks
Funding Source	Evotec NeuroSciences GmbH
Author conflicts of interest	Ivan Berlin has received consultancy payments and travel funding from Pfizer Ltd and Sanofi Aventis in the last 5 years. He received a consultancy payment from Evotec Ltd for preparing the current study's research protocol. Ian M Hunneyball, Doris Greiling, Stephen Jones and Hermann Fuder were employees of Evotec. Hans-Detlev Stahl is an employee of ClinPharm International GmbH Prufzentrum Leipzig.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomisation was performed by an independent statistician. A block size of 20 was used with each block containing medication assignments in a 7:7:3:3 ratio for EVT302 5 mg/day or placebo and EVT302 5 mg/day or placebo on top of NP [nicotine pill]. No stratification was used. Medication numbers

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Berlin 2012 *(Continued)*

		were generated for a total of 25 blocks. The randomisation list was uploaded into the [interactive voice recognition system (IVRS)] allowing the centralised use of randomisation." No detail of how sequences were generated
Allocation concealment (selection bias)	Low risk	Quote: "A central randomisation with an interactive voice recognition system (IVRS) was used which indicated the treatment to deliver upon the investigators' call."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study stated as being double-blinded, although no further information is given beyond this. Nicotine pill is unblinded, however
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are all below 50% - EVT302: 16 (10%); placebo: 14 (11%); EVT302 + nicotine pill: 5 (8%); placebo + nicotine pill: 2 (3%)

Biberman 2003

Study characteristics	
Methods	Study design: RCT Country: Israel Setting: 3 community-based clinics Recruitment: mailing to members of public health service provider
Participants	109 smokers randomised; 38% females, average age 42, average cigarettes per day 27 to 30
Interventions	• Selegiline, 10 mg/day for 26 weeks, nicotine patch 21 mg for 8 weeks including tapering • Placebo and nicotine patch Common components: behavioural support from trained family physician; weekly then fortnightly visits for 12 weeks
Outcomes	• Abstinence at 52 weeks, continuous with validation at each visit • Validation: negative for urine nicotine, cotinine, 3-hydroxycotinine (Niccheck)
Funding Source	None specified
Author conflicts of interest	None specified
Notes	No serious AEs, no significant differences in AEs, 2 selegiline discontinuations

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Four hundred dice-throwing generated a randomized sequence code; 199 containers prepacked with selegiline and 201 containers prepacked with placebo were numbered accordingly." Comment: judged adequate
Allocation concealment (selection bias)	Low risk	Quote: "The code was sealed, kept secretly and was revealed for the first time when the last participant finished the 12 months of follow-up. The first participant who joined the trial after the initial visit run-in phase received the first bottle from the container set number 001, the second

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Biberman 2003 *(Continued)*

		participant from set number 002 and so on. The trial coordinator arranged participant's allocation." Comment: judged adequate
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind" (see above) "No discontinuation difference for selegiline or placebo was observed among the groups, which implies masking success."
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 lost to follow-up, included as smokers in meta-analysis

Blondal 1999

Study characteristics	
Methods	Study design: RCT Country: Iceland Setting: cessation clinic Recruitment: community volunteers
Participants	100 smokers randomized; 62% female; average age 41; average cigarettes per day 28
Interventions	• Nicotine inhaler and fluoxetine. Nicotine inhaler given for 3 months, with option of continuing for 3 months more. Fluoxetine dosing was 10 mg/day initiated 16 days before TQD, increased to 20 mg/day on day 6 • Nicotine inhaler and placebo Common components: 5 x 1 hr group behaviour therapy. Advised to use 6 to 12 inhalers/day for up to 6 months
Outcomes	• Smoking cessation: abstinence at 1 year (sustained from quit day). Validated by CO < 10 ppm at all assessments (6 weeks, 3 months, 6 months, 12 months) • Adverse events: measured for 16 days
Funding Source	Oddur Olafsson Fund, Pharmacia and Upjohn Consumer Health Care. Delta Pharmaceutical Company provided fluoxetine and placebo and fluoxetine analyses. Helsingborg, Sweden provided a grant, nicotine inhalers and nicotine analyses.
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization; part of the randomization procedure was performed by the manufacturer at another location where the code was also kept until it was broken in May 1997.
Allocation concealment (selection bias)	Low risk	Randomization codes applied to pill boxes which were then allocated sequentially. "This part of the randomization procedure was performed by the manufacturer at another location where the code was also kept."

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Blondal 1999 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind." "...pill boxes, with either fluoxetine or an identical appearing placebo containing the same ingredients except fluoxetine, were labelled with numbers ranging from 100 to 210."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Low numbers lost to follow-up but reported results exclude 5 withdrawals; 3 from fluoxetine group due to adverse effects - nervousness and anxiety, 1 from fluoxetine due to pregnancy, 1 from placebo who had purchased fluoxetine

Brown 2007

Study characteristics	
Methods	Study design: 2x2 factorial RCT Country: USA Setting: 2 clinical sites (Butler Hospital, Miriam Hospital) Recruitment: community volunteers
Participants	524 participants randomised; 48% female; average age 44; average cigarettes per day 25
Interventions	• Bupropion 300 mg/day for 12 weeks • Placebo 2 x 2 factorial design. Alternative psychosocial treatments were standard cessation therapy or plus CBT for depression. Both had 12 x 90 min groups twice weekly/weekly/monthly for 12 weeks. TQD 5th session. Collapsed in this analysis
Outcomes	• Smoking cessation: abstinence at 12 months (sustained at 4 visits). Validated by CO ≤ 10 ppm, saliva cotinine ≤ 15 ng/mL • Adverse events: measured for 12 weeks
Funding Source	National Institutes of Health
Author conflicts of interest	None specified
Notes	First included as Brown 2006, part unpublished data. Some genotyping studies combine these participants with those reported in Collins 2004

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomly assigned to one of two treatment sites, where they were to receive one of two manualized group treatments ... Participants were then randomly assigned to receive one of two medication conditions, bupropion or placebo, using the urn randomization technique."
Allocation concealment (selection bias)	Unclear risk	Quote: "Whereas we were able to balance the drug and placebo conditions on an individual basis, behavioral treatments were randomized by group and thus were more susceptible to fluctuations in recruitment and to the availability at both sites of pairings of a senior and a junior therapist trained in CBTD". Knowledge of behavioural assignment was probably not concealed but seems unlikely to have led to individual selection bias.

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Brown 2007 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind." Psychological condition unlikely to be blinded but unlikely to affect comparisons included in this review. "All participants and study staff were blind to medication condition."
Incomplete outcome data (attrition bias) All outcomes	Low risk	81% provided complete outcome data at all follow-ups, not related to treatment condition. All participants included in ITT analyses

Brown 2014

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: via newspaper, radio, and television advertisements
Participants	216 smokers with elevated depressive symptoms (CES-D score ≥ 6) randomized; 38.4% female, average age 45.9; average cigarettes per day 21; mean FTND 5.6
Interventions	• Fluoxetine and nicotine patch, 10 weeks of 20 mg (beginning 2 weeks prior to TQD) • Fluoxetine and nicotine patch, 16 weeks of 20 mg fluoxetine (beginning 8 weeks prior to TQD) • Nicotine patch Common components: nicotine patch for 8 weeks starting on TQD (21 mg/day for 4 weeks, 14 mg/day for 2 weeks, 7 mg/day for last 2 weeks), 5 sessions of brief behavioural smoking cessation treatment (in person and phone over 4 weeks, 20 to 30 mins each), totalling 140 minutes
Outcomes	• Smoking cessation: continuous abstinence at 12 months. Validated by salivary cotinine < 10 ng/mL • Adverse events: measured for 52 weeks
Funding Source	American Cancer Society
Author conflicts of interest	LHP reports receiving grant/research support from Medtronic, Neuronetics, HRSA, and NeoSync; serving on an advisory panel for Abbott; and serving as a consultant for Wiley, Springer, Qatar National Research Fund, and Abbott
Notes	New for 2013 Significantly higher abstinence in 16 week arm than in 10-week arm, results presented separately in meta-analysis with control divided. N abstinent not reported, extrapolated from percentages provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “randomly assigned to one of the three treatment conditions using urn randomization”
Allocation concealment (selection bias)	High risk	Quote: "Open-label"

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Brown 2014 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "Open-label"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 90% followed up at 12 months. Similar rates across arms

Cinciripini 2005

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	135 smokers randomized; 50% female, average age 46, average cigarettes per day 27
Interventions	• Venlafaxine, titrated to max. of 225 mg/day from 3 weels before quit day for 21 weeks, including 2 weeks tapering • Placebo Common components: 6 weeks, 22 mg nicotine patch, and 9 x 15-min behavioural counselling
Outcomes	• Smoking cessation: ppa at 12 months. Validated by CO ≤ 10 ppm and/or saliva cotinine < 15 ng/uL • Adverse events: measured for unspecified period
Funding Source	National Institutes for Health and National Institute for Drug Abuse. Medication provided free of charge by Wyeth Ayerst Laboratories.
Author conflicts of interest	None specified
Notes	First included as Cinciripini 1999 based on abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described. Stratification by depression history
Allocation concealment (selection bias)	Low risk	Randomization by pharmacy, all study personnel with direct patient contact blind
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind... Blinding of the study staff to the medication was maintained using prenumbered pill containers, assigned to each participant at randomization by the pharmacy. All study personnel with direct patient contact were blind to group assignment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Majority of participants followed up (65 intervention; 63 control), participants lost to follow-up counted as smokers

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Cinciripini 2013

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	294 participants randomized; 39% female; average age 44; average cigarettes per day 20; mean FTND 4.5
Interventions	• Bupropion, 12 weeks, started 12 to 19 days before TQD (150 mg/d days 1 to 3, 300 mg/d thereafter) • Varenicline, 12 weeks on same schedule (0.5 mg/day days 1 to 3, 1.0 mg/day, days 4 to 7, 2.0 mg/day thereafter) • Placebo, same schedule as above Common components: 10 individual counselling sessions (6 in person, 4 via phone, 240 mins total)
Outcomes	• Smoking cessation: continuous abstinence after 2-week grace period at 6 months (validated by CO < 10 ppm or salivary cotinine < 15 ng/mL) • Adverse events: measured for 12 weeks
Funding Source	National Institute on Drug Abuse, National Cancer Institute
Author conflicts of interest	Dr Cinciripini served on the scientific advisory board of Pfizer, conducted educational talks sponsored by Pfizer on smoking cessation (2006-2008), and has received grant support from Pfizer.
Notes	New for 2013. In less than 1% of the total cases, participants who did not attend a follow-up were coded as abstinent because they were abstinent at the following data point. All other losses to follow-up counted as smokers. Author provided further detail on AE measurements via email.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “Adaptive randomization,” no further detail provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “Blinded” but no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	73% followed up at 6 months, similar rates across arms, all lost to follow-up known to be smokers

Cinciripini 2018

Study characteristics

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Cinciripini 2018 *(Continued)*

Methods	Study design: RCT Country: USA Setting: hospital-based out-patient clinic specializing in cancer prevention Recruitment method: paid and unpaid media advertising
Participants	385 participants randomised; 41.5% female; average age 49.0; average cigarettes per day 19.7; mean FTND 2.1
Interventions	• Bupropion and varenicline, 150 mg of bupropion per day for days 1–3, then 150 mg twice daily thereafter. 0.5 mg of varenicline per day for days 1–3, then 0.5 mg twice daily for days 4–7, then 1 mg twice daily thereafter • Varenicline, dose and schedule given as in bupropion and varenicline intervention. Matching placebo for bupropion • Matching placebo. Common components: in-person and phone counselling, totalling 215 minutes
Outcomes	• Smoking cessation: prolonged abstinence at 12 months, with relapse defined as smoking on 7 or more consecutive days or smoking at least one cigarette over 2 consecutive weeks within that same time interval (validated by CO < 4 ppm) • Adverse events: measured for 12 months
Funding Source	The project was supported by the United States National Institutes of Health (NIH) grant R01DA024709 (Principle Investigator PMC) and by The University of Texas MD Anderson's Cancer Center Support Grant CA016672, funded by the National Cancer Institute (NCI). Pfizer (New York, NY) provided the active and matching placebo varenicline capsules
Author conflicts of interest	PMC served on the scientific advisory board of Pfizer Pharmaceuticals, conducted educational talks sponsored by Pfizer on smoking cessation (2006–08) and has received grant support and medication support from Pfizer. MKH participated in two multisite Pfizer-funded trials and received varenicline from Pfizer to conduct four NIH-funded trials.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "an algorithm developed and managed by study data managers, whose role was limited to data quality and integrity management".
Allocation concealment (selection bias)	Unclear risk	No details as to how randomly-generated sequence was transferred and implemented to staff delivering medication to participants.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participants, medical and research staff who interacted with participants and the study investigators were blinded to group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 20/56 placebo; 48/166 varenicline; 38/163 combination. Dropout rates are below 50% in each arm

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Collins 2004

Study characteristics	
Methods	Study design: RCT Country: USA Setting: 2 clinical research sites Recruitment: community volunteers
Participants	555 participants randomized; excluding history of psychiatric disorder including MDD; 57% female, average age 46, average cigarettes per day 21
Interventions	• Bupropion. 300 mg/day for 10 weeks beginning 2 weeks before TQD • Placebo Common components: 7 sessions group behavioural counselling
Outcomes	• Smoking cessation: prolonged abstinence at 6 months (from week 2, 7 consecutive days of smoking defined as relapse). Validated by saliva cotinine ≤ 15 ng/mL. • Adverse events: measured for unspecified period
Funding Source	National Cancer Institute, National Institute on Drug Abuse, National Center for Research Resources. Treatment provided free of charge by GlaxoSmithKline.
Author conflicts of interest	None specified
Notes	Replaces Lerman 2002 which reported subset of data. Denominators supplied by 1st author, excludes 114 who withdrew before intervention. Some study details from Lerman 2006. Some genotyping studies combine these participants with those reported in Brown 2007.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was determined by a computer-generated randomization scheme operated by a senior data manager; stratification was carried out by study site" (Lerman 2006)
Allocation concealment (selection bias)	Low risk	Centrally generated and allocation concealed from counsellors and assessors
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo used but blinding procedure not described in detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% lost to follow-up at 6-month follow-up; included as smokers

Covey 2002

Study characteristics	
Methods	Study design: RCT

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Covey 2002 *(Continued)*

	Country: USA Setting: clinic Recruitment: volunteers
Participants	134 smokers with a history of past MDD were randomized; 65% female; average age 44.5
Interventions	• Sertraline, starting dose 50 mg/day, 200 mg/day by week 4 quit day. 9 day taper. Total duration 10 weeks + 9 day taper, including 1-week placebo washout prior to randomization • Placebo Common components: 9 x 45 min individual counselling sessions at clinic visits
Outcomes	• Smoking cessation: 7-day ppa 6 months after end of treatment. Validated by serum cotinine < 25 ng/mL • Adverse events: measured for 35 weeks
Funding Source	Pfizer, Inc and National Institute on Drug Abuse
Author conflicts of interest	"Pfizer, Inc., provided support for conducting the study."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind" "Medications were provided in prepared bottles that were numbered according to the randomization schedule and dispensed at each visit. All study staff at the clinic site were blinded to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "The subjects lost to follow-up after random assignment were considered treatment failures." Total participants lost to follw-up at 6 months not reported

Cox 2012

Study characteristics

Methods	Study design: RCT Country: USA Setting: urban community-based clinic Recruitment: volunteers, via healthcare settings and via community
Participants	540 African American light smokers (≤ 10 cigarettes per day for ≥ 2 years, smoked on ≥25 days in past month); 66% female; average age 47; average cigarettes per day 8; average FTND 3.2
Interventions	• Bupropion, 300 mg for 7 weeks (150 mg 1xd for 3d, then 150 mg 2xd for remainder)

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Cox 2012 *(Continued)*

	• Placebo, same schedule as bupropion Common components: up to 6 one-to-one 15-20 minute individual counselling sessions, self-help guide at start
Outcomes	• Smoking cessation: 7-day ppa at 6 months. Validated by salivary cotinine < 15 ng/mL • Adverse events: measured for 16 weeks
Funding Source	National Cancer Institute, National Institutes of Health, National Institute for Minority Health and Disparities
Author conflicts of interest	Dr JS Ahluwalia serves as a consultant to Pfizer Pharmaceuticals, Inc; Dr NL Benowitz serves as a consultant to Pfizer Pharmaceuticals, Inc, and has been a paid expert witness in litigation against tobacco companies; Dr RF Tyndale holds shares in Nicogen Research, Inc, a company that is focused on novel smoking cessation treatment approaches
Notes	New for 2013 update. SAEs only reported at week 3 (none reported), not included in SAE analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Both participants and investigators were blinded to the pharmacotherapy condition." No further information provided, unclear if counsellors blinded to treatment condition
Incomplete outcome data (attrition bias) All outcomes	Low risk	30% lost to follow-up at 6 months, no difference between groups

CTRI/2013/07/003830

Study characteristics

Methods	Study design: RCT Country: India Setting: 2 primary health centres
Participants	Current smokers currently undergoing treatment for tuberculosis
Interventions	• Bupropion SR. 150 mg given once daily for three days, followed by twice daily for seven weeks No information given as to whether the trial was placebo-controlled All participants given standard counselling, totalling 30 minutes
Outcomes	• Smoking cessation: not specified. Validated by self-report and carbon monoxide monitors
Funding Source	United States Agency for International Developement through World Health Organization

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CTRI/2013/07/003830 *(Continued)*

Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Permuted block randomization, fixed". This however may not be computer generated, and therefore not truly random
Allocation concealment (selection bias)	High risk	Study is open-label, so both participants and researchers are aware of drug allocation.
Blinding (performance bias and detection bias) All outcomes	High risk	Study is open-label, so both participants and researchers are aware of drug allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not specified

Da Costa 2002

Study characteristics

Methods	Study design: RCT Country: Brazil Setting: cessation clinic Recruitment: volunteers to a smokers' support group
Participants	144 smokers randomized; "predominantly female"; age, cigarettes per day not described
Interventions	• Nortriptyline, max. 75 mg/day for 6 weeks including titration period, begun 1 week before start of behaviour therapy • Placebo Common components: 6-weekly group CBT
Outcomes	• Smoking cessation: prolonged abstinence at 6 months after end of treatment (validation method not specified) • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

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Da Costa 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Each patient chose a blind number from a box ...' Comment: probably adequate
Allocation concealment (selection bias)	Unclear risk	Quote: "... with each number corresponding to a “medication kit” that was externally undistinguishable. Patients and professionals participating in this study were blindfolded for this distribution." Comment: potentially adequate but difference in numbers in each group not accounted for
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but insufficient detail provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost in each group not clear

Dalsgarð 2004

Study characteristics	
Methods	Study design: RCT Country: Denmark Setting: 5 hospitals Recruitment: hospital staff
Participants	335 smokers including physicians, nurses, other hospital service and admin staff; 75% female; average age 43; average cigarettes per day 19
Interventions	• Bupropion, 300 mg/day for 7 weeks • Placebo Common components: motivational support around TQD, at weeks 3 and 7, and at 12-week follow-up
Outcomes	• Smoking cessation: prolonged abstinence at 6 months (starting from week 4) Validated by CO < 10 ppm
Funding Source	GlaxoSmithKline
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization was computer generated and blinded
Allocation concealment (selection bias)	Low risk	Allocation was double-blinded and bupropion and placebo tablets were identical in form and number.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind"

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Dalsgarð 2004 *(Continued)*

		Comment: clear that participants were blinded but unclear if all staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	32% of the bupropion group and 43% the placebo group discontinued treatment, included in analysis

Ebbert 2014

Study characteristics	
Methods	Study design: RCT Country: USA Setting: Mayo Clinic in Rochester, Minnesota and University of Minnesota
Participants	506 participants randomized; 47% female; average age 42.0; average cigarettes per day 19.6; mean FTND 5.3
Interventions	• Bupropion SR and varenicline. Bupropion SR was taken once daily (150 mg) for days 1 to 3, then twice daily (total of 300 mg/d) for 12 weeks. Varenicline was taken once daily (0.5 mg) for 3 days, then 0.5 mg twice daily (total of 1 mg/d) for days 4 to 7, and finally to the maintenance dose of 1 mg twice daily (total, 2 mg/d) for 11 weeks. • Varenicline and placebo. Varenicline was taken according to the above dosing and schedule with matching placebo in place of bupropion. Common components: brief behavioral counselling at each clinic visit, totalling 110 minutes
Outcomes	• Smoking cessation: prolonged abstinence (no smoking from 2 weeks after the target quit date) at 52 weeks. Validated by CO • Adverse events: measured for 52 weeks
Funding Source	The clinical trial was supported by National Institutes of Health (NIH) grant CA 138417 (primary investigator, Dr Ebbert). Medication (varenicline) was provided by Pfizer
Author conflicts of interest	All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ebbert reports serving as an investigator for clinical trials funded by Pfizer, receipt of consultancy fees from GlaxoSmithKline, research support from Pfizer, and research support from Orexigen and JHP Pharmaceuticals outside of the current study. Dr Hatsukami reports receipt of research support from Nabi Biopharmaceuticals outside of the current study. Dr Hays reports serving as an investigator for clinical trials funded by Pfizer. Dr Hurt reports receipt of consulting fees from Pfizer, an unrestricted grant from Pfizer Medical Education Group, and provision of expert testimony in Florida tobacco litigation cases.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “computer-generated randomization sequence with variable-sized blocks ranging from 2 to 8 stratified by study site”.
Allocation concealment (selection bias)	Low risk	Central pharmacy was used to allocate interventions

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Ebbert 2014 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Study medication was labeled and dispensed according to participant identification, ensuring that treatment assignment remained concealed from the participant, investigators, and all study personnel having participant contact."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 40/249 varenicline + bupropion; 42/257 varenicline + placebo Dropout rate is below 50% in all trial arms

Eisenberg 2013

Study characteristics	
Methods	Study design: RCT Country: Canada Setting: 38 hospitals Recruitment: hospital patients with acute myocardial infarction
Participants	392 smokers of at least 10 cigarettes per day, hospitalized with enzyme positive acute myocardial infarction. 16% female; average age 54; average cigarettes per day 23; average FTND not specified
Interventions	• Bupropion, 300 mg/day for 9 weeks (150 mg for 3 days, then 150 mg 2 x day for remainder) • Placebo, same schedule as bupropion Common components: 7 one-to-one counselling sessions by research nurses at baseline and all follow-ups of < 20 mins (average 5) – mix of phone and in-person
Outcomes	• Smoking cessation: 12 months continuous abstinence (7 days ppa also reported). Validated by CO ≤ 10 ppm • Adverse events: non-SAEs measured for 9 weeks. SAEs measured for 12 months
Funding Source	Canadian Institutes of Health Research and Heart and Stroke Foundation of Quebec
Author conflicts of interest	Drs Eisenberg and Gervais reported that they served as paid consultants for Pfizer Canada Inc.'s Varenicline Advisory Board. Dr Gervais reported that he received funds from Pfizer Canada Inc., for lectures including service on speaker bureaus, development of educational presentations, and travel/accommodations/meeting ex- penses. Dr Eisenberg received funding from Pfizer Canada Inc., to perform the Evaluation of Varenicline (Champix) in Smoking Cessation for Patients Post-Acute Coronary Syndrome [EVITA] Trial; NCT00794573).
Notes	New for 2013 update Patients not allowed to smoke whilst hospitalized. SAEs reported over 12 months, so not included in analysis. No quit extracted from percentages provided; denominators do not include 9 deaths in bupropion and 6 deaths in placebo group, all deemed not to be related to study medication. Adherence to treatment: 72.3% bupropion, 82% placebo took at least 1 pill per day

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

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Eisenberg 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Randomization was done via an internet website using random blocks of 2 and 4 and was stratified by center to ensure that similar numbers of patients were randomized to the 2 arms of the study at each study center"
Allocation concealment (selection bias)	Low risk	Allocation performed centrally, see above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind." "All clinical end points were adjudicated by members of the Endpoints Evaluation Committee who were blinded to treatment assignment." Comment: no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	77% followed up at 12 months, similar across arms

Elsasser 2002

Study characteristics	
Methods	Study design: RCT Country: USA Setting: community-based Recruitment method: recruited from the community
Participants	17 participants randomized; 41.2% female; average age 16.5; average cigarettes per day not specified; mean FTND not specified All participants were between 14-19 years old
Interventions	• Bupropion SR, 150 mg twice daily for an unspecified duration • Matched placebo, same dose and duration as bupropion SR All participants recieved an unkown number and duration of behavioural modification sessions.
Outcomes	• Smoking cessation: prolonged abstinence between weeks 8-12 - too short a follow-up for consideration for this outcome as part of our review • Adverse events: measured for 12 weeks
Funding Source	Funding receieved from GlaxoWellcome
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “randomized, double-blind, placebo-controlled trial” Comment: no further information given

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Elsasser 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: “randomized, double-blind, placebo-controlled trial” Comment: no further information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “randomized, double-blind, placebo-controlled trial” Comment: no further information given
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates are as follows: 2/9 (22.2%) in the placebo; 4/8 (50%) of the bupropion group. Therefore dropout was higher than 20% between the two groups.

Evins 2001

Study characteristics	
Methods	Study design: RCT Country: USA Setting: outpatient clinic Recruitment: volunteers
Participants	18 smokers with stable schizophrenia (excluding 1 dropout prior to medication); 39% female; average age 45.5/42.7; average cigarettes per day 34
Interventions	• Bupropion. 300 mg/day for 3 months. TQD after week 3 • Placebo Common components: 9 x 1 hour weekly group CBT
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated by CO < 9 ppm or serum cotinine < 14 ng/mL • Adverse events: measured for 24 weeks
Funding Source	National Association for Research on Schizophrenia and Affective Disorders. Medication provided by Glaxo Wellcome Inc
Author conflicts of interest	None specified
Notes	2-year follow-up also reported. 3 additional quitters, not used in meta-analysis since additional therapy used

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Subjects were randomly assigned to 12 weeks of double-blind bupropion SR, 150 mg/day, or an identical appearing placebo tablet added to their usual medication regimen." Comment: unclear if all staff members were blinded

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Evins 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Nineteen subjects were enrolled and 18 subjects completed the 6-month smoking cessation trial."

Evins 2005

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: volunteers
Participants	56 smokers with schizophrenia (excluding 6 dropouts prior to medication); 27% female; average age 45, average cigarettes per day 37/26
Interventions	• Bupropion, 300 mg/day for 3 months • Placebo Common components: 12 session group CBT
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by CO < 9 ppm • Adverse events: measured for unspecified period
Funding Source	National Association for Research on Schizophrenia and Affective Disorders. Medication provided by GlaxoSmithKline
Author conflicts of interest	None specified
Notes	There was a significant treatment effect at EOT.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not stated
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" with "identical placebo tablets." No further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only people taking at least one dose of study medication included in analyses in paper. 5 in each group lost to follow-up and included as smokers

Evins 2007

Study characteristics

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Evins 2007 *(Continued)*

Methods	Study design: RCT Country: USA Setting: community mental health centre Recruitment: outpatients
Participants	51 smokers (≥10 cigarettes per day) with schizophrenia; average age 44; average cigarettes per day 28/25
Interventions	• Bupropion, 300 mg/day for 3 months, nicotine patch, 21 mg for 8 weeks including tapering, 2 mg nicotine gum • Placebo and NRT, same schedule as bupropion 1 Common components: 12 session group CBT, TQD week 4
Outcomes	• Smoking cessation: abstinence at 12 months from TQD. Validated by CO ≤ 8 ppm • Adverse events: measured for unspecified period
Funding Source	Massachusetts Department of Mental Health. Medication provided by GlaxoSmithKline
Author conflicts of interest	None specified
Notes	Used in bupropion + NRT versus NRT comparison

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participants and investigators remained blind to the treatment condition (bupropion or placebo) throughout the follow-up period." "Assessment of treatment assignment was at the level of chance for both participants and staff at Weeks 4 and 12 for both treatment assignments."
Incomplete outcome data (attrition bias) All outcomes	Low risk	20% of the bupropion group and 18% of the placebo group were lost to follow-up at week 12; included as smokers. All other participants followed up at 12 months

Fatemi 2013

Study characteristics

Methods	Study design: RCT Country: USA Setting: not specified Recruitment method: not specified

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Fatemi 2013 *(Continued)*

Participants	24 participants randomized; percentage female unspecified; average age not specified; average cigarettes per day not specified, mean FTND not specified All participants had been diagnosed with schizophrenia or schizoaffective disorder.
Interventions	• Varenicline, 1 mg twice daily for 12 weeks • Buproprion SR, 150 mg twice daily for 12 weeks • Matched placebo Common components: 20 minutes of antismoking counselling at each visit, totalling 80 minutes
Outcomes	• Smoking cessation: definition not specified • Adverse events: measured for 12 weeks
Funding Source	Grant support recieved from the National Institute on Drug Abuse (grant # R01DA024674-01A1) to SHF. Pfizer provided free samples of varenicline and placebo and had no role in design or conduct of this study. Watson Laboratories provided free samples of Bupropion SR.
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information provided
Allocation concealment (selection bias)	Unclear risk	No relevant information provided
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate is 41%, but difference between groups not detailed

Ferry 1992

Study characteristics

Methods	Study design: RCT Country: USA Setting: clinic Recruitment: not specified
Participants	42 male smokers
Interventions	• Bupropion, 300 mg/day for 3 months • Placebo

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Ferry 1992 *(Continued)*

	Common components: group smoking cessation and relapse prevention counselling
Outcomes	• Smoking cessation: sustained abstinence at 6m from end of treatment. Validated by saliva cotinine • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified
Notes	Abstract with no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given

Ferry 1994

Study characteristics

Methods	Study design: RCT Country: USA Setting: Veterans Medical Centre Recruitment: not specified
Participants	190 smokers
Interventions	• Bupropion, 100 mg x 3/day for 12 weeks • Placebo Common components: group smoking cessation and relapse prevention counselling; TQD within first 4 weeks
Outcomes	• Smoking cessation: prolonged abstinence at 12 months (from day 29). Validated by saliva cotinine ≤ 15 ng/mL at 6 months and 12 months • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified

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Ferry 1994 *(Continued)*

Notes	Abstract with long-term abstinence data supplied by author

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	72% followed-up intervention, 61% followed-up control. "The most conservative approach to analysis would reclassify all of these individuals as smokers due to protocol violation."

Fossati 2007

Study characteristics

Methods	Study design: RCT Country: Italy Setting: primary care clinics Recruitment: patients of 71 general practitioners
Participants	593 smokers randomised; 40% female; average age 49; average cigarettes per day 22
Interventions	• Bupropion, 300 mg/day for 7 weeks • Placebo Common components: GP visits at enrolment and 4, 7, 26 & 52 weeks, phone calls 1 day pre-TQD, 3 days post-TQD, 10 weeks post-enrolment. Classified as low intensity
Outcomes	• Smoking cessation: abstinence at 12 months (continuous from week 4). Validated by CO ≤ 10 ppm at each visit • Adverse events: measured for 52 weeks
Funding Source	Mario Negri Institute and GlaxoSmithKline
Author conflicts of interest	Dr Apolone has received consulting and lecture fees from GlaxoSmithKline
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified

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Fossati 2007 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Stated to be double-blind, but not explicit that GPs blind to randomization code.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind", further detail not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	15% Bupropion and 17% placebo did not attend 12-month follow-up, included as smokers

Gariti 2009

Study characteristics	
Methods	Study design: 2x2 factorial RCT Country: USA Setting: university Recruitment: self-referral from community
Participants	260 light smokers (6-15 cigarettes per day) motivated to quit; 57% female, average age 54; average cigarettes per day 11; average FTND 4
Interventions	• Bupropion SR and placebo patch. Bupropion for 9 weeks. Patch for 8 weeks. 10 weeks individualized counselling sessions • Bupropion SR and placebo patch. Bupropion for 9 weeks. Patch for 8 weeks. Four 5-10 minutes counselling sessions • Bupropion SR and nicotine patch. Bupropion for 9 weeks. Patch for 8 weeks. 10 weeks individualized counselling sessions • Bupropion SR and nicotine patch. Bupropion for 9 weeks. Patch for 8 weeks. Four 5-10 minutes counselling sessions
Outcomes	• Smoking cessation: 7-day ppa at 12 months. Validated by CO < 10 ppm; urinary cotinine < 200 ng/mL • Adverse events: measured for unspecified period
Funding Source	National Institute on Drug Abuse
Author conflicts of interest	None specified
Notes	New for 2013 update Used in direct comparison of bupropion and NRT only, pooling 1+2 versus 3+4

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized ‘urn randomization’
Allocation concealment (selection bias)	Unclear risk	Not specified

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Gariti 2009 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind, double-dummy" for medication component. "Neither the nurses nor the participants knew which of the two formulations contained the active formulation."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data included as smokers. Similar losses to follow-up across both groups

George 2002

Study characteristics	
Methods	Study design: RCT Country: USA Setting: mental health clinic Recruitment: outpatients
Participants	32 smokers with schizophrenia motivated to quit; 44% female; average age 41/45; average cigarettes per day 24
Interventions	• Bupropion, 300 mg/day for 9 weeks. TQD 3 weeks • Placebo Common components: 10 x 60-minute weekly group therapy
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by expired CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	National institute on Drug Abuse, US Department of Veterans Affairs, National Alliance for Research on Schizophrenia and Depression. Medication provided by GlaxoSmithKline
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Both subjects and research staff were blinded to study medication assignment. Study medications were prepared by research pharmacists at CMHC, using encapsulation of SR bupropion tablets with blue 00 opaque capsules; placebo capsules contained only a dextrose matrix."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Subjects who were lost during the trial or at 6-month follow-up were counted as smokers." Number followed-up at 6 months not reported

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George 2003

Study characteristics	
Methods	Study design: RCT Country: USA Setting: outpatient smoking research clinic Recruitment: community volunteers
Participants	40 smokers; 63% female; average age 49; average cigarettes per day 23
Interventions	• Selegiline. 10 mg/day for 9 weeks (5 mg/day in week 1 and week 9) • Placebo
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified
Notes	"The main side effects of SEL were anorexia, gastrointestinal symptoms, and insomnia. None of the differences in adverse event ratings were significant in the SEL compared with the PLA group, and the drug was well tolerated compared with the placebo group. Reports of anxiety/agitation in both the SEL and PLA groups during the trial were high." Funding: National Institute on Drug Abuse, US Department of Veteran Affairs, National Alliance for Research on Schizophrenia and Depression

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, adequacy of blinding tested in research staff; results suggested blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	High risk	29/40 not assessed at 6 months. Greater loss to follow-up in placebo, exact data not reported

George 2008

Study characteristics	
Methods	Study design: RCT Country: USA Setting: mental health centre

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George 2008 *(Continued)*

	Recruitment: outpatients
Participants	58 smokers with schizophrenia or schizoaffective disorder (excludes 1 receiving no study medication); 40% female; average age 40; average cigarettes per day ~23
Interventions	• Bupropion, 300 mg/day for 9 weeks, begun 7 days pre-TQD • Placebo Common components: nicotine patch (21 mg/24 hrs) for 8 weeks from TQD and group behaviour therapy 10-weekly sessions
Outcomes	• Smoking cessation: ppa at 6 months. Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	National Institute on Drug Abuse, National Alliance for Research on Schizophrenia and Depression
Author conflicts of interest	None specified
Notes	Bupropion as adjunct to NRT

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double blind" but no additional details given
Incomplete outcome data (attrition bias) All outcomes	Low risk	6/29 intervention and 10/29 control did not complete trial, included as smokers

Gilbert 2019

Study characteristics

Methods	Study design: RCT Country: USA Setting: from the community Recruitment method: newspaper ads and community and university postings
Participants	105 participants randomised; 42% female; average age 26.4; average cigarettes per day 17.9, mean FTND 4.2
Interventions	• Bupropion SR and placebo nicotine patch. 150 mg pill once daily for 3 days, then twice daily for 56 days, then once daily for three days. Placebo nicotine patch schedule given below • Nicotine patch and placebo bupropion. Beginning on first day of cessation: 21 mg for 24 days, 14 mg for 14 days, then 7 mg for 7 days. Placebo bupropion schedule as given above

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Gilbert 2019 *(Continued)*

	• Matched placebos, according to the schedules given above Common components: an abbreviated form of the American Lung Association smoking cessation program
Outcomes	• Smoking cessation: prolonged abstinence at 12 months. Validation method not specified • Adverse events: measured for 62 days
Funding Source	Supported by the National Institute on Drug Abuse (NIDA) Grant R01 DA012289 awarded to David G Gilbert
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: randomized by "urn technique without replacement approach via a 28:28:28:16 ratio to one of four groups."
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Researchers and participants in the quit groups were blind to pill and patch type."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates: 0/34 – bupropion; 0/38 – nicotine patch; 0/35 – placebo

Gonzales 2001

Study characteristics

Methods	Study design: RCT Country: USA Setting: 16 clinical trial centres Recruitment: volunteers who had previously failed to quit using bupropion
Participants	450 smokers who had previously used bupropion for at least 2 weeks without adverse effects and failed to quit; 55% female in placebo arm, 48% female in bupropion arm; average age 45; average cigarettes per day not specified
Interventions	• Bupropion, 300 mg/day for 12 weeks, begun 7 days pre-TQD • Placebo Common components: brief individual counselling at visits weeks 1-7, 9, 12, + telephone counselling at 4 months and 5 months
Outcomes	• Smoking cessation: prolonged abstinence 12 months, starting from week 4. Validated by CO ≤ 10 ppm at each visit

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Gonzales 2001 *(Continued)*

	Adverse events: measured for unspecified duration
Funding Source	GlaxoWellcome Inc
Author conflicts of interest	None specified
Notes	6-month data published. 12-month data presented in a poster used since 2003 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants who satisfied the inclusion criteria were randomized to the treatment phase and received either bupropion SR ... or matching placebo. Eligible participants were assigned a protocol-specific treatment number on the basis of a randomization code provided by GlaxoWellcome."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Even though participants and the site staff were blinded to the drug assignments and the site staff did not encourage participants to speculate on their assignments, the lower placebo abstinence rates in the current study may be attributable to the previous experiences of participants with bupropion in their previous cessation attempts." However, little difference in completion between two arms, suggesting blinding may have been successful.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "...all participants who stopped participating in the study during the treatment phase were considered to be smokers." Number of participants followed-up at 12 months unclear

Gonzales 2006

Study characteristics

Methods	Study design: RCT Country: USA Setting: 19 clinical trial centres Recruitment: community volunteers
Participants	673 participants, with prior exposure to bupropion excluded; 46% female; average age 42; average cigarettes per day 21
Interventions	• Bupropion, 300 mg/day for 12 weeks, begun 7 days pre-TQD • Varenicline, 2 mg/day • Placebo Common components: brief (< 10-minute) standardized individual counselling at 12 weekly visits during drug phase and 11 clinic/phone visits during follow-up, problem solving and relapse prevention
Outcomes	• Smoking cessation: sustained abstinence at 1 year (starting from week 4). Validated by CO ≤ 10 ppm at each visit • Adverse events: measured for 13 weeks
Funding Source	Pfizer, Inc

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Gonzales 2006 *(Continued)*

Author conflicts of interest	Dr Gonzales reports having received research contracts from Pfizer, Sanofi-Aventis, GlaxoSmithKline, and Nabi Biopharmaceuticals; consulting fees and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline; and owning 5 shares of Pfizer stock. Dr Rennard reports having had or currently having a number of relationships with companies who provide product and/or services relevant to outpatient management of COPD. These relationships include serving as a consultant for Adams, Almirall, Altana, Array Bio- pharma, AstraZeneca, Aventis, Biolipox, Centocor, Dey, Critical Therapeutics, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Ono Pharma, Otsuka, RJ Reynolds, Roche, Sankyo, Schering-Plough, Scios, and Wyeth; advising regarding clinical trials for Altana, Astra- Zeneca, Aventis, Centocor, GlaxoSmithKline, Novartis, Pfizer, and Philip Morris; and speaking at continuing medical education programs and performing funded research both at basic and clinical levels for Altana, Astra-Zeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis. Dr Nides reports having received research grants, consulting fees, and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline. Dr Oncken reports having received research grants, consulting fees, and honoraria from Pfizer; receiving, at no cost, nicotine replacement and placebo products from GlaxoSmith- Kline for smoking cessation studies; and receiving honoraria from Pri-Med. Drs Azoulay, Watsky, Gong, Williams, and Reeves and Mr Billing report owning Pfizer stock or having stock options in Pfizer.
Notes	Bupropion was an active control for varenicline. Bupropion versus placebo and bupropion versus varenicline comparisons contribute to review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "predefined ... computer-generated randomization sequence", 1:1:1, using block size of 6, stratified by centre
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Participants and investigators were blinded to drug treatment assignments[, and] ... were not encouraged to guess their treatment assignment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up similar across conditions; 44% bupropion, 39.5% varenicline, 46% placebo, all included in analyses

Górecka 2003

Study characteristics

Methods	Study design: RCT Country: Poland Setting: Smokers' clinic Recruitment: smokers with a diagnosis of COPD and failure to stop smoking with advice alone
Participants	70 smokers with COPD 43% female; average age 56; average cigarettes per day 24
Interventions	• Bupropion, 300 mg/day for 7 weeks • Nicotine patch, 15 mg/day for 8 weeks Common components: support at clinic visits at baseline, 2 weeks, EOT

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Górecka 2003 *(Continued)*

Outcomes	• Smoking cessation: sustained abstinence at 1 year. Validated by CO < 10 ppm • Adverse events: period of measurement unspecified
Funding Source	None specified
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Not described but presumably no blinding, as participants will have known assignment based on patch versus pill
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described

Grant 2007

Study characteristics

Methods	Study design: RCT Country: USA Setting: 2 substance use disorder clinics Recruitment: alcoholics in residential or outpatient treatment programmes
Participants	58 alcoholic smokers; 16% female; average age 40; average cigarettes per day 25
Interventions	• Bupropion, 300 mg for 60 days + nicotine patch 21 mg for 8 weeks including tapering • Placebo and nicotine patch Common components: 1-hour cessation group (and 4-weekly assessment visits)
Outcomes	• Smoking cessation: 7 day ppa at 6 months. No biochemical validation, collaterals contacted, inconsistent, adjusted rates not reported • Adverse events: measured for 4 weeks
Funding Source	National Institute on Alcohol Abuse and Alocholism
Author conflicts of interest	None specified
Notes	

Risk of bias

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Grant 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but unclear who was blinded, no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Higher loss in bupropion (40%) than placebo (21%) but still within 20% range of each other. ITT analysis

Gray 2011

Study characteristics	
Methods	Study design: RCT Country: USA Setting: university research clinic or high school health clinic Recruitment method: through local secondary schools, colleges, universities, and community media advertisements
Participants	All participants were between 12 and 21 years 134 participants randomized; 41.8% female; average age 18.5; average cigarettes per day 10.8; mean FTND 4.2
Interventions	• Bupropion and contingency management. 150 mg once daily for three days, then 150 mg twice daily for remainder of 6-week treatment period. Contingency management consisted of monetary compensation for biologically verified abstinence at visits. Abstinence at the first visit was $10, with subsequent consecutive abstinent visits escalating by USD 3 (USD 13, USD 16, USD 19, and so on). If a participant relapsed, he or she was not eligible for contingent compensation at that visit, and the contingent reward for the next abstinent visit was reset to USD 10 (with eligibility to escalate by USD 3 at subsequent abstinent visits). Thus, the maximum amount of compensation throughout the 6-week treatment period was USD 275. • Bupropion and non-contingnecy management. Bupropion given according to schedule above. Non-contingency mangement consisted of fixed compensation (USD 10 per visit) for attending the twice-weekly treatment visits. • Matched placebo and contingency management • Matched placebo and non-contingnecy management All participants received smoking cessation booklets and were eligible for a weekly bonus payment of USD 5 throughout active treatment for completion of study materials, including daily smoking diaries. In addition, all participants received USD 30 for completing the initial assessment visit, USD 20 for completing the initial medication management visit, and USD 20 for completing the final post-treatment follow-up visit.
Outcomes	• Smoking cessation: 12 weeks - too short a follow-up for this outcome to be considered in this review • Adverse events: measured for 6 weeks

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Gray 2011 *(Continued)*

Funding Source	Funding was provided by the National Institute on DrugAbuse, Grants R01 DA17460 (HPU, KMG), K12DA000357 (KMG), K23 DA020482 (MJC), and R25DA020537 (ALL); by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, Grant K12HD055885 (KJH); and by the US Public Health Service, Grant M01 RR01070 (Medical University of South Carolina Clinical and Translational Research Center)
Author conflicts of interest	Dr Gray has received research support from Pfizer, Inc. (medication and placebo supply for research funded by the National Institute on Drug Abuse). Dr Hartwell has received grant support through Global Research Awards for Nicotine Dependence, an independent competitive grants program supported by Pfizer Inc. Dr Hiott is a past speakers' bureau member of Bristol-Myers Squibb and Abbott Labs. Dr Deas has been an advisory board and speakers' bureau member of Eli Lilly and Company. Dr Upadhyaya is a past consultant and/or advisory board member of Eli Lilly and Company and Shire Pharmaceuticals. Dr Upadhyaya is an ex-stockholder of New River Pharmaceutical Company, is a past speakers' bureau member of Shire Pharmaceuticals and Pfizer, Inc., and has received research support from Cephalon, Inc., Eli Lilly and Company, and Pfizer Inc. Dr Upadhyaya recently became an employee of, and is a holder of stock in, EliLilly and Company. The other investigators deny any potential conflicts of interest.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double blinded; encapsulated by the university Investigational Drug Service so that the active and placebo medication appeared identical”. No further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates: 12/37 (32.4%) in bupropion and contingnecy management; 13/36 (36.1%) in bupropion and non-contingnecy management; 14/29 (48.3%) in placebo % contingnecy management; 10/32 (31.3%) in placebo and non-contingnecy management Loss to follow-up was less than 50% and similar across groups.

Gray 2012

Study characteristics

Methods	Study design: RCT Country: USA Setting: community Recruitment method: community media advertisement (e.g. flyers, newspapers, advertisements)
Participants	29 participants randomized; 51.8% female; average age 18.9; average cigarettes per day 15.6; mean FTND 6.7 Adolescent smokers, aged 15–20

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Gray 2012 *(Continued)*

Interventions	• Bupropion XL + placebo. 150 mg once daily for 7 days, then 300 mg daily thereafter. Placebo capsules were used at times when no active medication was scheduled. • Varenicline + placebo. Participants ≥ 55 kg received 0.5 mg daily for 3 days, 0.5 mg twice daily for 4 days, and then 1 mg twice daily thereafter. Those < 55 kg received 0.5 mg daily for 7 days and then 0.5 mg twice daily thereafter All participants recieved quit smoking brochures and brief individual cessation counselling, totalling 90 minutes.
Outcomes	• Smoking cessation: 12 weeks - too short a follow-up for this outcome to be considered in this review • Adverse events: measured for 12 weeks
Funding Source	Medical University of South Carolina Hollings Cancer Center Pilot Research Program and the National Institutes of Health (K12DA000357, K23DA020482, R25DA020537, and UL1RR029882)
Author conflicts of interest	Dr Upadhyaya is an employee and stockholder of Eli Lilly and Company. The other authors do not have potential conflicts to declare.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The university investigational drug service encased medications in identical-appearing capsules and dispensed them in weekly blister packs with specific instructions on day/ time for each dose."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The paper gives study retention figures, but does not specify whether they are lost to followup.

Haggsträm 2006

Study characteristics

Methods	Study design: RCT Country: Brazil Setting: smoking cessation clinic Recruitment: community volunteers
Participants	156 smokers; FTND > 4; 70% female in placebo and nortriptyline arms, 59% in bupropion arm; average age 44; average cigarettes per day not specified
Interventions	• Bupropion, 300 mg/day for 60 days, placebo nortriptyline, TQD during week 2 • Nortripytyline, 75 mg/day for 60 days, placebo bupropion • Double placebo

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Haggström 2006 *(Continued)*

	Common components: 6 x 15-min individual CBT, weekly then bi-weekly
Outcomes	• Smoking cessation: conintuous abstinence at 6 metres (starting from TQD). Validated by CO ≤ 10 ppm at 3 months and 6 months • Adverse events: measured for 26 weeks
Funding Source	None specified
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy. "Both investigators and patients were blind to the treatment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers lost to follow-up not reported, all included as smokers

Hall 1998

Study characteristics

Methods	Study design: 2x2 factorial RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	199 smokers, 33% had history of MDD; 55% female; average age 40; average cigarettes per day 21-25
Interventions	• Nortriptyline, titrated to therapeutic levels - usually 75 mg/day to 100 mg/day, 12 weeks • Placebo 2 x 2 factorial design. Alternative psychological Rxs were 10 sessions of CBT or 5 sessions of health education control. Collapsed in this analysis
Outcomes	• Smoking cessation: prolonged abstinence at 1 year post-EOT. Validated by CO at weeks 12, 24, 39 and 64 • Adverse events: measured for 6 weeks
Funding Source	National Instutute on Drug Abuse and Veterans Administration
Author conflicts of interest	None specified

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Hall 1998 *(Continued)*

Notes	There were no significant main or intervention effects for MDD category, so these are pooled

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomization, after stratification on history of MDD and number of cigarettes smoked
Allocation concealment (selection bias)	Low risk	Allocation generated at enrolment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Medication was placebo controlled and double blind. Placebo and active drug were identical in appearance." However, no detail on who was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	30% did not complete treatment in placebo and 17% in active groups. Analyses with missing = smoking given

Hall 2002

Study characteristics

Methods	Study design: 3 x 2 factorial RCT Country: USA Setting: cessation research centre Recruitment: community volunteers
Participants	220 smokers; 40% to 47% female; average age 37-43; average cigarettes per day 20-23
Interventions	• Bupropion, 300 mg/day, 12 weeks • Nortriptyline, titrated to therapeutic levels, 12 weeks • Placebo 3 x 2 factorial design. Alternative psychological interventions were Medical Management (MM, physician advice, S-H, 10 mins to 20 mins 1st visit, 5 minds at 2, 6, 11 weeks) or Psychosocial Intervention (PI, as MM plus 5 x 90-min group sessions at 4, 5, 7, 11 weeks)
Outcomes	• Smoking cessation: prolonged abstinence at 1 year (47 weeks post-quit date). Validated by CO ≤ 10 ppm, urine cotinine ≤ 60 ng/mL Adverse events: measured for unspecified period
Funding Source	National Institute on Drug Abuse, National Cancer Institute
Author conflicts of interest	None specified
Notes	No significant interaction between pharmacotherapy and behaviour therapy, so behavioural therapy arms collapsed in main analysis. Bupropion and nortriptyline compared to placebo and head-to-head. Levels of support compared for bupropion only, ppa rates used. Not included in behavioural support subgroup.

Risk of bias

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Hall 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were stratified by number of cigarettes smoked, sex and history of depression vs no history, and randomly assigned to 1 of the 6 experimental cells."
Allocation concealment (selection bias)	Low risk	Quote: "We encapsulated both drugs to maintain the patency of the bupropion formulation and to provide a blinded drug. All participants received capsules that were identical in number and appearance" but blinding of allocation not explicit.
Blinding (performance bias and detection bias) All outcomes	High risk	Double-blind but participants informed about adverse effects of each drug and 87% of participants taking active drug guessed that they were (compared to 67% placebo group). Bupropion participants no more likely than nortriptyline participants to correctly identify which drug they had received.
Incomplete outcome data (attrition bias) All outcomes	Low risk	19% lost to follow-up at 52 weeks. No significant difference across conditions. Included as smokers in analyses

Hall 2004

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	160 smokers; 41% female; average age ~38; average cigarettes per day ~19
Interventions	• Nortriptyline, titrated to 50 ng/mL to 150 ng/mL (~75 mg to 100 mg) for 12 weeks, quit date week 5 • Placebo 2 x 2 factorial design. Nortriptyline versus placebo and brief versus extended treatment. Brief treatment: nicotine patch for 8 weeks from quit date, and 5 group counselling sessions, total 7.5 hrs Extended treatment: first 12 weeks as for brief treatment, then same dose continued to week 52 then tapered. Individual counselling every 4 weeks, total 3 hours to 4.5 hours. Phone counselling, total 40 mins to 80 mins
Outcomes	• Smoking cessation: repeated 7 day ppa at 24 weeks, 36 weeks, 52 weeks. Validated by CO ≤ 10 ppm and urine cotinine ≤ 50 ng/mL at each point • Adverse events: measured for 12 weeks
Funding Source	National Institute on Drug Abuse
Author conflicts of interest	None specified
Notes	Factorial design, brief and extended treatment entered in meta-analysis separately. In the active extended treatment arm, participants were still receiving nortriptyline at the time of final follow-up.
Risk of bias	

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Hall 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization stratified on cigarettes per day, prior NRT use, MDD history; method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "participants given active drug were more likely to guess that they had received active drug (63%) than the placebo participants were to believe they were taking active drug (37%)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% lost at week 52, included as smokers

Hertzberg 2001

Study characteristics	
Methods	Study design: RCT Country: USA Setting: Veterans Affairs Medical Centre (VAMC) Recruitment: VAMC outpatient volunteers
Participants	15 male veterans with post-traumatic stress disorder; average age 50; average cigarettes per day 33
Interventions	• Bupropion, 300 mg/day, 12 weeks begun at least 1 week before TQD • Placebo Common components: individual counselling pre-quit, weeks 1, 2, 4, 8, 12
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated at weeks 2, 8 by CO ≤ 10 ppm • Adverse events: measured for 12 weeks
Funding Source	Glaxo Wellcome Inc, National Cancer Institute
Author conflicts of interest	None specified
Notes	2 of the successful quitters were taking bupropion at 6 months, prescribed after end of study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, no further information provided

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Hertzberg 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Uneven attrition between arms; very high percentage lost to follow-up in placebo group. 30% of the participants receiving bupropion SR did not complete the full 12-week trial; 80% of the placebo group failed to complete the trial and were considered to have resumed smoking.

Holt 2005

Study characteristics	
Methods	Study design: RCT Country: New Zealand Setting: cessation clinic Recruitment: Maori community volunteers aged 16-70
Participants	134 smokers; 72% female; average age 42/38
Interventions	• Bupropion, 300 mg/day for 7 weeks • Placebo Common components: counselling at 3 clinic visits during medication and 3 monthly follow-ups, motivational phone call 1 day before and 2 days after TQD
Outcomes	• Smoking cessation: continuous abstinence at 12 months. Validated by CO at each visit • Adverse events: measured for 12 months
Funding Source	GlaxoSmithKline
Author conflicts of interest	P3 Research, the Wellington School of Medicine and Health Sciences, and the Medical Research Institute of New Zealand have all received research grants from GlaxoSmithKline and Novartis. SH and RB have received fees for consulting and reimbursement for attending symposia from GlaxoSmithKline and Novartis.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization using a computer generated code
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Neither the study team nor the participant was aware of which treatment had been allocated until the end of the 12 month study period."
Incomplete outcome data (attrition bias) All outcomes	High risk	High and uneven loss to follow-up, with less than half of placebo group followed up at 12 months. 36% lost in bupropion group and 52% in placebo at 12 months. "Participants who were lost to follow up were categorised as smokers ... often this was confirmed by family members or friends."

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Hurt 1997

Study characteristics	
Methods	Study design: RCT Country: USA Setting: multicentre Recruitment: community volunteers
Participants	615 smokers; 55% female; average age 44; average cigarettes per day 27
Interventions	• Bupropion,100 mg/day for 7 weeks • Bupropion, 150 mg/day • Bupropion, 300 mg/day • Placebo Common components: physician advice, S-H materials, and brief individual counselling by study assistant at each visit
Outcomes	Smoking cessation: prolonged abstinence at 12 months (starting from day 22). Validated by CO ≤ 10 ppm Adverse events: measured for 52 weeks
Funding Source	Glaxo Wellcome
Author conflicts of interest	None specified
Notes	300 mg compared with placebo in main analysis There was no evidence that history of major depression or alcoholism interacted with treatment condition or was associated with poorer outcomes. Prolonged abstinence rates at 12 months as supplied by Glaxo Wellcome: 300 mg 21; 150 mg 23; Placebo 15

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomized, stratified by site, method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but no detail given on who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Subjects who missed a follow-up visit were considered to be smoking.... The rate of completion of the study increased with the dose and was 57 percent, 65 percent, 64 percent, and 71 percent for the placebo, 100-mg, 150-mg, and 300-mg groups, respectively..."

Johns 2017

Study characteristics

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Johns 2017 *(Continued)*

Methods	Study design: RCT Country: India Setting and recruitment method not specified
Participants	300 participants randomized
Interventions	• Bupropion, 150 mg twice daily for 12 weeks • Varenicline, 1 mg twice daily for 12 weeks • Bupropion and varenicline, taken according to schedules above
Outcomes	• Smoking cessation: continuous abstinence at 6 months. Validated by CO • Adverse events: period of measurement not detailed
Funding Source	None specified
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	States trial was randomized, no further detail given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States only that the study was 'double-blind', no further detail given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

Jorenby 1999

Study characteristics

Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: multicentre clinical trial units Recruitment: community volunteers
Participants	893 smokers; 52% female; average age 43; average cigarettes per day 25
Interventions	• Nicotine patch and bupropion SR. Nicotine patch dosing and schedule 24 hr, 21 mg for 6 weeks, tapered for 2 weeks. Bupropion dosing and schedule was 300 mg for 9 weeks from 1 week before quit day • Bupropion and placebo patch • Nicotine patch and placebo tablets

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Jorenby 1999 *(Continued)*

	• Placebo patch and placebo tablets Common components: brief (< 15 min) individual counselling session at each weekly assessment. One telephone call 3 days after quit day
Outcomes	• Smoking cessation: continuous ppa at 12 months. Validated by CO < 10 ppm at each clinic visit • Adverse events: measured for unspecified period
Funding Source	Glaxo Wellcome
Author conflicts of interest	Dr Jorenby has organized medical education presentations sponsored by Glaxo Wellcome and SmithKline Beecham. Dr Leischow has served as a consultant for McNeil Consumer Products, Pharmacia and Upjohn, and Glaxo Wellcome and has organized medical education presentations sponsored by Glaxo Wellcome. Dr Nides has served as a consultant for Glaxo Wellcome, Novartis, and SmithKline Beecham and has organized medical education presentations sponsored by Glaxo Wellcome. Dr Rennard has served as a consultant for Glaxo Wellcome, Novartis, and SmithKline Beecham and has organized medical education presentations sponsored by Glaxo Wellcome. Dr Muramoto has organized medical education presentations sponsored by Glaxo Wellcome. Mr Daughton has served as a consultant for SmithKline Beecham and Hoechst Marion Roussel and has organized medical education presentations sponsored by Glaxo Wellcome and Hoechst Marion Roussel. Dr Fiore has served as a consultant for Novartis, Glaxo Wellcome, SmithKline Beecham, and McNeil Consumer Products and has organized medical education presentations sponsored by Novartis, Elan Pharma, Lederle Laboratories, Glaxo Wellcome, McNeil Consumer Products, and SmithKline Beecham. Dr Baker has served as a consultant for SmithKline Beecham and has organized medical education presentations sponsored by Elan Pharma and Glaxo Wellcome.
Notes	Primary outcome for study was PP abstinence; this analysis uses continuous abstinence since quit day

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The subjects were randomly assigned to one of four treatments with use of an unequal-cell design...[*but*] Randomization was not balanced within sites."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method unclear
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "All subjects who discontinued treatment early or who were lost to follow-up were classified as smokers." Approximately 20% left the study and provided no additional information. 15% stopped taking medication but participated in follow-up assessments.

Jorenby 2006

Study characteristics

Methods	Study design: RCT Country: USA Setting: multicentre clinical trial units

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Jorenby 2006 *(Continued)*

	Recruitment: community volunteers
Participants	683 smokers (in relevant arms), with prior exposure to bupropion excluded; 41% female; average age 42; average cigarettes per day 22
Interventions	• Bupropion 300 mg for 12 weeks + placebo varenicline • Varenicline 2 mg for 12 weeks + placebo bupropion • Placebo bupropion and placebo varenicline Common components: brief (< 10 min) individual counselling at each weekly assessment for 12 weeks and 5 follow-up visits. One telephone call 3 days after quit day
Outcomes	• Smoking cessation: sustained abstinence at 12 momth, from week 9. Validated by CO < 10 ppm at each clinic visit
Funding Source	Pfizer Inc
Author conflicts of interest	Dr Jorenby reported receiving research support from Pfizer, Nabi Biopharmaceutical, Sanofi-Aventis and consulting fees from Nabi Biopharmaceutical. Dr Hays reported receiving a research grant from Pfizer. Dr Rigotti reported receiving research grant funding and consulting fees from GlaxoSmithKline, which markets smoking cessation medications, and Pfizer and Sanofi-Aventis, which are developing smoking cessation medications. Dr Rigotti also reported receiving consulting fees from Merck, which is developing smoking cessation medications.
Notes	Bupropion was an active control for varenicline. Bupropion versus placebo and bupropion versus varenicline comparisons contribute to the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was completed centrally by using a computer-generated list and sites used an electronic system to assign participants to treatment."
Allocation concealment (selection bias)	Low risk	Quote: "Folders [containing medication or placebo] for all participants (regardless of treatment assignment) were identical throughout the treatment phase including a period of dose titration (week 1) and treatment at the target dose (weeks 2-12)."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "in a double-blind manner," no further information provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over the period of treatment and follow-up 14% of those receiving varenicline were lost to follow-up; 14% randomized to bupropion lost to follow-up; 16% of the placebo group were lost to follow-up. "Participants whose smoking status was unknown or whose carbon monoxide level was higher than 10 ppm were classified as smoking during both the treatment phase and follow-up."

Kahn 2012

Study characteristics

Methods	Study design: RCT

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Kahn 2012 *(Continued)*

	Country: USA Setting: clinics Recruitment: community
Participants	246 smokers; 49% female; average age 46; average cigarettes per day 22
Interventions	• Selegiline patch (6 mg/24hr) for 9 weeks, starting 7 days before TQD • Placebo patch, same schedule as selegeline Common components: 9 weekly individual counselling sessions of approximately 10 mins each
Outcomes	• Smoking cessation: prolonged abstinence at 6 months (continuous from week 6 onwards) Validated by CO < 9 ppm • Adverse events: measured for 26 weeks
Funding Source	National Institutes of Health, National Institute on Drug Abuse
Author conflicts of interest	None specified
Notes	New for 2013 update Some additional information on study characteristics provided by author. Mean compliance rates 91.6% and 91.3% for the selegiline and placebo groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Adaptive randomization," method not reported
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	70% placebo and 74% STS followed up at 12 months

Kalman 2011

Study characteristics

Methods	Study design: RCT Country: USA Setting: not specified Recruitment: Veterans Administration Medical Center

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Kalman 2011 *(Continued)*

Participants	143 smokers with 2 to 12 months alcohol abstinence, with history of alcohol abuse or dependence; mean age 49; 17% female; average cigarettes per day 20.8; mean FTND 5.9
Interventions	• Bupropion, 8 weeks (started 1 week before TQD, first 3 days 150 mg/day, rest of period 2 x 150 mg/day) • Placebo, same schedule as above Common components: nicotine patch (7 weeks starting on TQD; 21 mg weeks 1-4, 14 mg weeks 5-6, 7 mg week 7) and 8 weekly counselling sessions starting 1 week before TQD (one-to-one sessions based on CBT and MI)
Outcomes	• Smoking cessation: prolonged abstinence at 24 weeks (no smoking after first 2 weeks after TQD). Validated by salivary cotinine ≤ 15 ng/mL • Adverse events: measured for unspecified period
Funding Source	National Institute of Drug Abuse, National Institute on Alcohol Abuse and Alocholism
Author conflicts of interest	None specified
Notes	New for 2013 update N quit calculated from percentages provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Urn randomization," no further details provided
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but no detail on who was blinded in terms of study staff, including counsellors. "Both medication groups performed at the chance level in judging medication assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 participants who dropped out prior to receiving medication, not included in denominators. Further 18% intervention and 14% control lost at 24 weeks, counted as smoking in analyses.

Karam-Hage 2011

Study characteristics

Methods	Study design: RCT Country: USA Setting: University of Michigan outpatient addictions clinic Recruitment method: patients admitted to the outpatient intensive treatment programme
Participants	Alcohol- and nicotine-dependent patients 11 participants randomized; 55% female; average age 19.7; average cigarettes per day 1 pack; mean FTND 4.8
Interventions	• Bupropion, 150 mg once daily for 7 days, then twice daily for 7 weeks

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Karam-Hage 2011 *(Continued)*

	• Placebo, same scheduling as bupropion Common components: minimal smoking cessation counselling and booklet "You Can Quit Smoking"
Outcomes	• Smoking cessation: 8 weeks - too short a follow-up to be considered for this outcome as part of our review • Adverse events: measured for 8 weeks
Funding Source	University of Michigan's General Clinical Research Center (GCRC) Grant # MO1 RR00042
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 1/5 placebo; 1/6 bupropion

Killen 2000

Study characteristics

Methods	Study design: RCT Country: USA Setting: clinic Recruitment: advertisements
Participants	224 smokers; 46% female; average age 46; average cigarettes per day 26
Interventions	• Nicotine patch and paroxetine. Nicotine patch for 24 hr, 21 mg, 8 weeks. Paroxetine at 20 mg for 9 weeks including tapering) • Nicotine patch and paroxetine. 40 mg paroxetine. Patch as above • Nicotine patch and placebo paroxetine Common components: self-help manual and 15 min behavioural counselling at weeks 1 and 4
Outcomes	• Smoking cessation: 7-day ppa at 10 weeks, 26 weeks, and 6 months. Validated by CO < 9 ppm and saliva cotinine < 20 ng/mL at each visit • Adverse events: measured for 26 weeks
Funding Source	University of California Tobacco-Related Disease Research Program, SmithKline Beecham

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Killen 2000 *(Continued)*

Author conflicts of interest	None specified
Notes	40 mg and 20 mg dose pooled in meta-analysis from 2009. 20/75 quit on 40 mg, 15/75 on 20 mg

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but unclear who exactly was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Those failing to provide confirmation [of smoking status] were reclassified as smokers." Number lost to follow-up not reported

Killen 2004

Study characteristics

Methods	Study design: RCT Country: USA Setting: continuation high schools Recruitment: adolescents at schools
Participants	211 adolescent smokers, at least 1 failed quit attempt; 31% female; average age 17; average cigarettes per day 15
Interventions	• Bupropion and nicotine patch. Bupropion at 150 mg for 9 weeks from 1 week before TQD. Nicotine patch for 8 weeks • Placebo and nicotine patch Common components: weekly 45-min group sessions, skills training
Outcomes	• Smoking abstinence: 7 day ppa at 6 months. Validated by saliva cotinine < 20 ng/mL at 6 months (CO at EOT) • Adverse events: measured for unspecified period
Funding Source	National Cancer Institute. GlaxoSmithKline provided medication
Author conflicts of interest	None specified
Notes	Low compliance with both bupropion and patch therapy

Risk of bias

Bias	Authors' judgement	Support for judgement

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Killen 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Double-blind." Though further details not provided, assessment of blind suggests it was successful (30% placebo and 31% bupropion correctly guessed assignment)
Incomplete outcome data (attrition bias) All outcomes	Low risk	38% bupropion and 35% placebo lost at 6 months, included in analysis

Killen 2010

Study characteristics	
Methods	Study design: RCT Country: USA Setting: community Recruitment: radio, newspapers, community website and notices distributed via local organizations
Participants	243 smokers, 18-65 years old. 30% female; average age 45; average cigarettes per day 19
Interventions	• Selegiline patch. 8 weeks, 6 mg/24 hr, starting on TQD • Placebo. Same schedule as above Common components: 9 sessions of individual counselling to develop cognitive and behavioural skills to resist urges to smoke
Outcomes	• Smoking cessation: 7-day ppa at 12 months. Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	National Institute on Drug Abuse. Medication and matching placebo provided by Somerset Pharmaceuticals, Inc.
Author conflicts of interest	None specified
Notes	New for 2013 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generator
Allocation concealment (selection bias)	Low risk	Participant assigned sequential ID numbers corresponding with drug “pre-packaged and labelled by ID only at an off-site location by an individual who had no association with the participants.”

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Killen 2010 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Treatment assignment was concealed from staff and both research staff and participants were blind to week 52." Assessment of blinding in participants and study staff suggests it was successful
Incomplete outcome data (attrition bias) All outcomes	Low risk	87% followed up at 12 months, same in both arms. Missing counted as smokers

Levine 2010

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: not specified Recruitment: community volunteers
Participants	349 weight-concerned women smokers; average age 42; average cigarettes per day 21; mean FTND 5.2
Interventions	• Bupropion SR. 26 weeks. 150 mg/day for first 2 days and 300 mg/day for remainder of treatment • Placebo, same schedule Counselling conditions • Standard cessation counselling • Standard cessation counselling + material on weight concerns Common components: 12 x 90-minute group counselling sessions delivered over 3 months
Outcomes	• Smoking cessation: prolonged abstinence at 12 months. Validated by CO ≤ 8 ppm and salivary cotinine ≤ 15 ug • Adverse events: measured for 26 weeks
Funding Source	National Institute on Drug Abuse. Medication supplied by GlaxoSmithKline
Author conflicts of interest	Dr Marcus has served as a consultant to GlaxoSmithKline and Sanofi-Aventis. Dr Perkins has served as a consultant for GlaxoSmithKline
Notes	New for 2013 update Counselling arms collapsed in analyses (same intensity, just differed in content). N abstinent calculated from percentages given

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Blocked randomization, method of sequence generation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

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Levine 2010 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	Over half lost to follow-up at 12 months. 48% followed up overall, similar rates between groups

McCarthy 2008

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: cessation clinic Recruitment: community volunteers
Participants	463 smokers; 50% female; average age 36-41; average cigarettes per day 22
Interventions	• Bupropion SR 300 mg for 8 weeks • Placebo Counselling conditions • 8 x 10-min session, 2 prequit, TQD, 5 over 4 weeks • Psychoeducation about medication, support and encouragement. Same number of sessions, 80 mins less contact time
Outcomes	• Smoking cessation: 7 day ppa at 12 months. Validated by CO ≤ 10 ppm. Prolonged self-reported abstinence also assessed • Adverse events: measured for 9 weeks
Funding Source	National Cancer Institute, National Instutute on Drug Abuse. GlaxoSmithKline provided placebo medication
Author conflicts of interest	Douglas E Jorenby has received research support from Nabi Biopharmaceutical and Pfizer, Inc. and consulting fees from Nabi Biopharmaceutical. Saul Shiffman serves as consultant to GlaxoSmithKline Consumer Healthcare on an exclusive basis regarding over-the-counter smoking cessation products and also is a partner in a company that is developing a new nicotine medication. He is a cofounder of invivodata, inc., which provides electronic diary services for clinical research. In 1998 the University of Wisconsin appointed Dr Fiore to a named Chair, made possible by an unrestricted gift to the university from GlaxoWellcome. GlaxoSmithKline provided complimentary active and placebo medication used in this study
Notes	Counselling conditions collapsed in main analysis, entered separately in subgroup analysis by intensity. Psychoeducation arms placed in multisession individual counselling subgroup due to high level of contact received, though not classified as counselling in paper.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table

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McCarthy 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Staff who screened and enrolled participants were unaware of the experimental condition to be assigned
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind (for medication). "Research staff who interacted with participants were blind to participants' medication condition assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	171 (37%) failed to attend quit date visit or lost to follow-up, similar across groups, included in ITT analysis

Minami 2014

Study characteristics	
Methods	Study design: RCT Country: USA Setting: community. Recruitment method: "recruited from local community"
Participants	Patient with elevated depressive symptoms, as indicated by a Center for Epidemiologic Studies Depression Scale (CES-D) score > 6 206 participants randomized; 48% female; average age 43; average cigarettes per day 21; mean FTND 5.5
Interventions	• Fluoxetine. 20 mg each morning, 8 weeks prior to target quit date and 8 weeks following • Placebo. According to the schedule detailed above Common components: 8-week supply of nicotine patches and brief counselling, totalling a maximum of 150 minutes
Outcomes	• Smoking cessation: 8 weeks - too short a follow-up for this outcome to be considered as part of this review • Adverse events: measured for 8 weeks pre-quit, although whether they recorded post-quit is not clearly specified
Funding Source	NIDA
Author conflicts of interest	Dr Price reports receiving grant/research support from Medtronic, Neuronetics, NIH, HRSA, and NeoSync; serving on an advisory panel for Abbott; and serving as a consultant for Wiley, Springer, Qatar National Research Fund, and Abbott.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "urn randomization to balance the groups on gender, depressive symptoms (CES-D ≥16), and nicotine dependence (FTND ≥ 7)."
Allocation concealment (selection bias)	Unclear risk	No relevant information given

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Minami 2014 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “assignment was double-blind, such that neither participants nor study staff (including physicians, research assistants, and counselors) were aware of whether the participant was taking fluoxetine or placebo."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

Moreno-Coutino 2015

Study characteristics	
Methods	Study design: RCT Country: Mexico Setting: smoking cessation clinic Recruitment method: people seeking smoking cessation treatment at clinic
Participants	Heavy smokers with minimal/mild depressive symptomatology. 60 participants randomized; 38% female; average age 45; average cigarettes per day 18.2; mean FTND 4.7
Interventions	• Bupropion. 150 mg once daily for 2 weeks prior to target quit date, then 150 mg twice daily from 1 week prior to target quit date until 4 months of treatment • Nicotine patch. 21 mg starting 2 weeks before target quit date. 4 weeks at 21 mg following target quit date, 14 mg for 2 weeks, then 7 mg for two weeks • Bupropion and nicotine patch. Given according to schedules above Common components: 4 individual in-person CBT sessions (over 4 weeks, 2 pre-quit and 2 post-quit), plus 0.1 mg low nicotine cigarettes
Outcomes	• Smoking cessation: at 12.5 months • Adverse events: period of measurement not specified
Funding Source	Mexican National University Macro-project in Addictions
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Quote: “Those who agreed to continue in the study, entered the raffle (three different color balls in a dark box) to assign a treatment setting, and were evaluated."
Allocation concealment (selection bias)	High risk	Quote: “Those who agreed to continue in the study, entered the raffle (three different color balls in a dark box) to assign a treatment setting, and were evaluated."
Blinding (performance bias and detection bias)	High risk	Quote: “evaluations and treatments were conducted by clinical psychologists who were not blind to the study."

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Moreno-Coutino 2015 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropout rate from each group (> 50%). Significantly more dropouts from NRT only arm

Muramoto 2007

Study characteristics	
Methods	Study design: RCT Country: USA Setting: research clinic Recruitment: adolescent community volunteers
Participants	312 adolescents (14 to 17); 46% females; median age 16; median cigarettes per day 11
Interventions	• Bupropion, 300 mg for 7 weeks • Bupropion, 150 mg for 7 weeks • Placebo Common components: brief (10-20 mins) individual counselling session pre-quit and at each weekly assessment
Outcomes	• Smoking cessation: 7-day ppa at 6 months. Validated by CO < 10 ppm (cotinine at weeks 2 and 6 only) • Adverse events: measured for 26 weeks
Funding Source	National Cancer Institute, The Robert Wood Johnson Foundation, GlaxoSmithKline
Author conflicts of interest	Dr Muramoto has received research contracts from GlaxoSmithKline, Pfizer, and Sanofi-Aventis and is a speaker for Pfizer. Dr Leischow is a speaker and consultant for Pfizer, and at the time this study was conducted he was receiving research support from GlaxoSmithKline.
Notes	300 mg arm contributes to main analysis. 2/105 quit in 150 mg group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Active study medication and identical-appearing placebo were prepackaged into 3 sets of identical-appearing blister cards in accordance with a computer-generated randomization list."
Allocation concealment (selection bias)	Low risk	Quote: "... a research assistant assigned the subject the next treatment number (and associated blister cards) in sequence."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Study subjects and researchers remained blind to treatment group assignment throughout the study." "9.6% in the 300 mg group accurately guessed their treatment assignment. Across all treatment groups, there were no significant differences in the proportion of subjects who accurately guessed their treatment group."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Slightly higher lost to follow-up/declined further participation in placebo group (30%) than active arms (18%). ITT analysis

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Myles 2004

Study characteristics	
Methods	Study design: RCT Country: Australia Setting: preoperative clinic Recruitment: smokers awaiting surgery
Participants	47 smokers expected to undergo surgery within 8-14 weeks; 34% female; average age 45/40; 49% smoked 21-30 cigarettes per day
Interventions	• Bupropion. 300 mg for 7 weeks • Placebo Common components: advice at baseline, 1 phone call 2-4 days after TQD. Low intensity
Outcomes	• Smoking cessation: 28 day ppa at 6 months. Validated by CO ≤ 10 ppm • Adverse events: not clearly specified
Funding Source	Alfred Hospital Research Trust, Glaxo Wellcome
Author conflicts of interest	None specified
Notes	More dropouts in placebo group. Only 20 had surgery

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated from a table of random numbers into one of two groups: active (bupropion) or placebo (identical appearance)
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	17% lost to follow-up in the bupropion group; 9% lost to follow-up in the placebo group. "Patients lost to follow-up were assumed to still be smoking."

NCT00132821

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: sleep clinic Recruitment: not specified

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NCT00132821 *(Continued)*

Participants	59 participants enrolled; smoking at least 20 cigarettes per day. No further patient characteristics given
Interventions	Starting 1 week prior to quit day • Bupropion. 150 mg for 3 days and 300 mg for 60 days • Placebo bupropion Added on quit day • Nicotine patch (21 mg for 6 weeks, 14 mg for 1 week, and 7 mg for 1 week) • Placebo nicotine patch
Outcomes	• Smoking cessation: at 12 months (no definition of abstinence given). Validated by CO • Adverse events: not specified whether adverse events were recorded
Funding Source	National Institute on Drug Abuse
Author conflicts of interest	None specified
Notes	Study detailed in trials registry only and results not reported. Attempt to contact the investigator for further information was unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

NCT00308763

Study characteristics

Methods	Study design: RCT Country: USA Setting: not specified Recruitment: not specified
Participants	594 younger, low-income, and minority smokers enrolled. No further patient characteristics given
Interventions	• Nicotine patch and placebo bupropion SR. If smoking > 20 cigarettes per day will be initially given 21 mg patch; 10-19 cigarettes per day 14 mg patch; 5-9 cigarettes per day 7 mg patch. If initially placed on the 21 mg patch: 21 mg patch for 4 weeks, 14 mg patch for 4 weeks, 7 mg patch for 2 weeks; if initially

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NCT00308763 *(Continued)*

	placed on 14 mg patch: 14 mg patch for 6 weeks, 7 mg patch for 4 weeks; if initially placed on 7 mg patch: 7 mg patch for 10 weeks. Bupropion scheduling as below. • Placebo nicotine patch and bupropion SR. Bupropion titrated to 150 mg, then 150 mg daily for approximately 11 weeks. Placebo patch scheduled as above. • Nicotine patch and bupropion SR. Same scheduling as above.
Outcomes	• Smoking cessation: at 12 months (no definition of abstinence given). Validated by CO and saliva cotinine • Adverse events: not specified whether adverse events were recorded
Funding Source	NIH (R01HL066025)
Author conflicts of interest	None specified
Notes	Study detailed in trials registry only and results not reported. Attempt to contact the investigator for further information was unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

NCT00495352

Study characteristics

Methods	Study design: RCT Country: Taiwan Setting: not specified Recruitment: not specified
Participants	360 motivated psychiatric outpatients with schizophrenia enrolled. No further patient characteristics detailed
Interventions	• High-dose NRT • Low-dose NRT • Bupropion
Outcomes	• Smoking cessation: at 8 weeks, too short a follow-up for consideration in this review • Adverse events: not specified whether adverse events were recorded

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NCT00495352 *(Continued)*

Funding Source	Yu-Li Hospital; Department Of Health, Executive Yuan, ROC (Taiwan); National Health Research Institutes, Taiwan
Author conflicts of interest	None specified
Notes	Study detailed in trials registry only and results not reported. Attempt to contact the investigator for further information was unsuccessful

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No relevant information given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

NCT00578669

Study characteristics

Methods	Study design: RCT Country: USA Setting and recuirment method not specified
Participants	Participants had elevated depression symptoms. 206 participants randomized; 48% female; average age 44; average cigarettes per day 21; mean FTND 5.7
Interventions	• Fluoxetine. 20 mg once daily, 8 weeks prior to target quit date and weeks thereafter • Placebo. Given according to schedule detailed above Common components: nicotine patch as well as "standard smoking cessation treatment"
Outcomes	• Smoking cessation: 7-day ppa at 12 months. Validated by CO and saliva cotinine • Adverse events: measured for a period of one year
Funding Source	None specified
Author conflicts of interest	None specified
Notes	

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NCT00578669 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Placebo controlled, but no further information on blinding provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Clinical trial registry implies 100%, but not explicitly, so we concluded there was not sufficient information given

NCT00593099

Study characteristics	
Methods	Study design: RCT Country: USA Recruitment method: outpatient mental health clinics Setting: not specified
Participants	Participants were clinically stable outpatients with DSM-IV diagnoses of bipolar I disorder. 5 participants randomized; 60% female; average age 57; average cigarettes per day 20; mean FTND 6.4
Interventions	• Bupropion. 75 mg for 3 days following quit date, increased to 150 mg for 4 days, then increased to final dose of up to 150 mg twice daily by day 15. Continued for an additional 8 weeks • Placebo. Same dose and scheduling as bupropion Common components: weekly sessions of manualized group behavioral therapy
Outcomes	• Smoking cessation: not specified • Adverse events: measured for 10 weeks
Funding Source	NIDA; National Alliance for Research in Schizophrenia and Depression
Author conflicts of interest	Dr Weinberger reports receiving grant support from Sepracor, Inc. and the National Alliance for Research on Schizophrenia and Depression (NARSAD). Dr George reports that he received grant support from the National Institute on Drug Abuse (NIDA), NARSAD, The Donaghue Medical Research Foundation, Sanofi-Aventis, Targacept, and Sepracor. Inc. He is on Advisory Boards and a consultant to Pfizer, Inc. Eli Lilly, Janssen, and Evotec. Dr Chengappa reports that he received grant support from Janssen-Ortho, Inc, Stanley Medical Research Institute, NIDA, NARSAD. He is on Advisory Boards for Astra Zeneca and Lilly.
Notes	
Risk of bias	

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NCT00593099 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Paper states that the trial was placebo controlled, but no further information is given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 1/3 in placebo; 1/2 in bupropion. Therefore loss to follow-up was less than 50% and similar between groups.

NCT01406223

Study characteristics	
Methods	Study design: RCT Country: USA Setting and recruitment method not specified
Participants	76 participants randomized; 53% female; average age 38.8
Interventions	• Bupropion and varenicline. Bupropion was given 150 mg once daily for the first week, then twice daily for remainder of the 12-week treatment period. Varenicline was adminstered 0.5 mg once daily starting one week preceding the target quit date, 0.5 mg twice daily for the remaining 4 days of that week, then 1 mg twice daily of the remainder of the 12-week treatment period. • Placebo and varenicline. Given according to the relevant schedules detailed above.
Outcomes	• Smoking cessation: not specified • Adverse events: measured for 13-week treatment period
Funding Source	Not specified
Author conflicts of interest	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias)	Unclear risk	Stated that the study is placebo controlled and there is “double masking”, but no further detail is given

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NCT01406223 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout rates are as follows: 12/18 varenicline; 18/20 varenicline

Niaura 2002

Study characteristics	
Methods	Study design: RCT Country: USA Setting: 16 clinical trial centres Recruitment: community volunteers
Participants	989 non-depressed smokers; 61% female; average age 42; average cigarettes per day 28
Interventions	• Fluoxetine. 30 mg for 10 weeks, starting 2 weeks before TQD • Fluoxetine. 60 mg for 10 weeks, starting 2 weeks before TQD • Placebo Common components: 9 sessions (60-90 mins) individual CBT. Included coping skills, stimulus control techniques and relapse prevention
Outcomes	• Smoking cessation: multiple ppa at 32 weeks from TQD. Validated by saliva cotinine < 20 ng/mL at each visit • Adverse events: measured for 6 months
Funding Source	Eli Lilly and Company
Author conflicts of interest	None specified
Notes	Originally based on abstract and data from authors. From 2002 based on full report. Numbers quit derived from rounded quit rates (10% quit in each group)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but further detail not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data in treatment phase addressed, but unclear whether missing data in follow-up phase addressed. At 12 months, 42% missing data, similar across all arms; missing data counted as smokers in our analyses.

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Nides 2006

Study characteristics	
Methods	Study design: RCT Country: USA Setting: 5 clinical sites Recruitment: volunteers (phase II study)
Participants	638 smokers (255 in relevant arms, including 2 bupropion and 4 placebo who did not start medication); 51% female; average age 41; average cigarettes per day 20
Interventions	• Bupropion, 300 mg for 7 weeks • Varenicline, 2 mg for 7 weeks (other dose regimens not used in review) • Placebo Common components: up to 10 mins counselling at 7 weekly clinic visits, 12 weeks and 24 weeks
Outcomes	• Smoking cessation: continuous abstinence at 12 months (starting from week 4). Validated by CO • Adverse events: measured for 11 weeks
Funding Source	Pfizer
Author conflicts of interest	Dr Nides has received research grants, consulting fees, and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline. Dr Oncken has received research grants, consulting fees, and honoraria from Pfizer; received, at no cost, nicotine replacement and placebo products from GlaxoSmithKline for smoking cessation studies; and received honoraria from Pri-Med. Dr Gonzales reports having received research contracts from Pfizer, Sanofi-Aventis, GlaxoSmithKline and Nabi Biopharmaceuticals; consulting fees and honoraria from Pfizer, Sanofi-Aventis, and GlaxoSmithKline; and owning 5 shares of Pfizer stock. Dr Rennard has had or currently has a number of relationships with companies that provide product and/or services relevant to outpatient management of chronic obstructive pulmonary disease. These relationships include serving as a consultant (Adams, Almirall, Altana, Array Biopharma, AstraZeneca, Aventis, Biolipox, Centocor, Dey, Critical Therapeutics, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Ono Pharma, Otsuka, RJ Reynolds, Roche, Sankyo, Schering-Plough, Scios, and Wyeth); advising regarding clinical trials (Altana, AstraZeneca, Aventis, Centocor, GlaxoSmithKline, Novartis, Pfizer, and Philip Morris); speaking at continuing medical education programmes; and performing funded research at both basic and clinical levels (Altana, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis). He owns no stock in any pharmaceutical companies. Drs Watsky and Reeves and Mr Anziano are employees of Pfizer and own Pfizer stock or have stock options.
Notes	Bupropion was an active control for varenicline. Bupropion versus placebo and bupropion versus 2 mg varenicline comparisons contribute to review. Inclusion of 6 pretreatment dropouts has minimal effect on risk ratio

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...a randomization list was computer generated using a method of randomly permuted blocks and a pseudorandom number generator."
Allocation concealment (selection bias)	Low risk	Quote: "Investigators assigned medication to subjects in numerical order of acceptance into the study."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind", "to preserve treatment blinding," no further information provided

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Nides 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Subjects who dropped out for any reason were considered to be smokers at all subsequent time points." 9.5% of varenicline tartrate 0.3 mg, once daily; 7% of varenicline tartrate 1.0 mg, once daily; 11 % of varenicline tartrate 1.0 mg, twice daily; 6% of bupropion hydrochloride 150 mg, twice daily and 13% of the placebo group were lost to follow-up.

Parsons 2009

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: UK Setting: smoking cessation clinic Recruitment: direct mail from general practitioner (GP), stop smoking service, newspaper advertisements
Participants	143 adult smokers; 62% female; average age 46; average cigarettes per day 21; mean FTND 5.5
Interventions	• St John's wort, 900 mg/day (300 mg x 3/day) for 14 weeks, started 2 weeks prior to TQD • Placebo, same schedule as above Common components: 7 weekly individual behavioural support sessions in clinic
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated by CO ≤ 10 ppm • Adverse events: serious adverse events at anytime within the study, and side effects in the first 4 weeks after quit day (2 weeks prior to quit day to 4 weeks afterward)
Funding Source	Cancer Research UK
Author conflicts of interest	None specified
Notes	New for 2013 Factorial trial - also tested the use of chromium versus placebo for weight loss. Arms collapsed for analysis; no difference detected

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Via computer program
Allocation concealment (selection bias)	Low risk	Independent statistician sent randomization codes to medication packing company, medication allocated in sequence. Researchers blind to allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “Participants, therapists, and outcome assessors were blind to the treatment allocation.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 90% followed up at 6 months, similar between groups

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Perkins 2013

Study characteristics	
Methods	Study design: cross-over trial Country: USA Setting: university research centre Recruitment method: "recruitment notices" were used
Participants	45 participants randomized; 60% female; average age 36; average cigarettes per day 16; mean FTND 4.6
Interventions	• Bupropion, 150 mg once daily for 3 days, then 150 mg twice daily for 2 weeks • Placebo, same schedule as above
Outcomes	• Smoking cessation (strictest definition): measures days abstinent per participant, which is not a relevant outcome to our review • Adverse events: measured over three-week treatment period
Funding Source	Funded by National Institutes of Health
Author conflicts of interest	Dr Perkins has served as a consultant for Embera Neurotherapeutics, which is unrelated to the current study. Dr Lerman has served as a consultant for GlaxoSmithKline, Pfizer and Astra Zeneca. She has received research funding, unrelated to the current study, from Pfizer and Astra Zeneca. Dr Chengappa has research funding from Pfizer that is unrelated to the current study. Dr Sparks, Mr Karelitz and Ms Jao have no potential conflicts of interest or disclosures to report.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "assigned randomly", but no further information provided
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Low risk	Analysis of participants knowledge of drug allocation revealed no significant differences between trial arms: "The respective number (percentage) of subjects identifying the medication as bupropion, modafinil, placebo or do not know were four, two, five and 34 (8.9, 4.4, 11.1 and 75.6%) of 45 during the bupropion condition; seven, three, four and 31 (15.6, 6.7, 8.9 and 68.9%) of 45 during the modafinil condition; and four, three, eight and 30 (9.1, 6.8, 18.2 and 67.9%) of 44 (1 subject with missing data) during the placebo condition. None of these values differed by medication condition, indicating successful blinding."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

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Piper 2007

Study characteristics	
Methods	Study design: RCT Setting: none specified Country: USA Recruitment: volunteers
Participants	608 smokers; 58% female; average age 42; average cigarettes per day 22
Interventions	• Nicotine gum and bupropion. Gum at 4 mg. Bupropion at 300 mg • Placebo gum and bupropion • Double placebo Common components: three 10-min counselling sessions over 3 weeks
Outcomes	• Smoking cessation: ppa at 12 months. Validated by CO or blood cotinine • Adverse events: measured for unspecified period
Funding Source	National Institutes for Health
Author conflicts of interest	In 1998 the University of Wisconsin appointed Dr Fiore to a named chair, made possible by an unrestricted gift to the university from GlaxoWellcome. Dr Baker has received monies to conduct clinical trials from pharmaceutical companies (Nabi, Glaxo, Pfizer, Sanofi)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomization was conducted in double-blind fashion using blocked randomization within each of the 10 [orientation session] cohorts." No further information provided
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	32% of bupropion and 36% of placebo groups lost at 12 months. "Participants who could not be reached at follow-up were considered to be smoking for the purposes of follow-up analyses."

Piper 2009

Study characteristics	
Methods	Study design: RCT Country: USA Setting: community

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Piper 2009 *(Continued)*

	Recruitment: volunteers
Participants	1504 smokers; 58% female; average age 45; average cigarettes per day 21.4
Interventions	• Bupropion SR. 150 mg twice/day, 1 week pre-quit, 8 weeks post-quit • Bupropion and nicotine lozenge. Duration and dosage as below • Nicotine lozenge. 2 mg or 4 mg for 12 weeks (based on dose-for-dependence level as per instructions) • Nicotine patch (24 hr, 21, 14, and 7 mg titrated down over 8 week period post-quit) • Nicotine lozenge and nicotine patch. Duration and dosage as above • Placebo bupropion • Placebo bupropion and placebo lozenge • Placebo lozenge • Placebo patch • Placebo lozenge and placebo patch Common components: 7 one-to-one 10 to 20-min counselling sessions
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by CO < 10 ppm • Adverse events: measured for 10 weeks
Funding Source	Majority of funding from National Institute on Drug Abuse and National Center for Research Resources. Medication provided to participants at no extra cost by GlaxoSmithKline.
Author conflicts of interest	The authors report the following potential conflicts of interest for the last 5 years: Dr Smith has received research support from Elan Corporation. Dr Baker has served as an investigator on research projects sponsored by pharmaceutical companies, including Sanofi-Synthelabo, Pfizer Inc, and Nabi Biopharmaceuticals. Dr Jorenby has received research support from the National Institute on Drug Abuse, the National Cancer Institute, Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals. He has received support for educational activities from the National Institute on Drug Abuse and the Veterans Administration and consulting fees from Nabi Biopharmaceuticals. Dr Fiore has received honoraria from Pfizer. He has served as an investigator on research studies at the University of Wisconsin that were funded by Pfizer, Sanofi-Synthelabo, GlaxoSmithKlein, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin appointed Dr Fiore to a named chair funded by an unrestricted gift to University of Wisconsin from Glaxo Wellcome.
Notes	New for 2013 update Placebo outcomes reported as a whole in published report, author provided data for individual groups. 1 versus 6 in Analyses 1.1, 1.2 and 1.3. 2 versus 3 included in Analysis 1.5. 1 versus 4 in Analysis 1.7.1, 1 versus 3 in Analysis 1.7.2 and 1 versus 5 in Analysis 1.7.3 (intervention arm split in three to avoid triple counting)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not specified. "Randomization was double-blind and used a block randomization scheme with sex and self-reported race as the blocking variables."
Allocation concealment (selection bias)	Low risk	"Staff did not know to which type(s) of medication a participant would be assigned until the moment of randomization, and study staff were blinded to whether the medication was active or placebo."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind" but no further detail provided. "Study staff were blinded to whether the medication was active or placebo"

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Piper 2009 *(Continued)*

		Comment: type of medication (i.e. patch, gum, pill) would have been apparent to both groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	90 dropouts (out of 1504). Analyses conducted using ITT. Individuals with missing data considered to be smoking

Planer 2011

Study characteristics	
Methods	Study design: RCT Country: Israel Setting: hospitals, Jersulem Recruitment: patients hospitalized for acute coronary syndrome in 2 separate campuses in Jerusalem
Participants	151 smokers with diagnosis of acute coronary syndrome, motivated to quit; average age 51.9; 20.1% female; average cigarettes per day 31
Interventions	• Bupropion, 150 mg 1 x day for 3 days, then 2 x day for 2 months • Placebo, same schedule as above Common components: counselling (at least 15 min of motivational support) during hospitalization and continued after discharge (at least 2 visits with physician and nurse at 1 month and 2 months and weekly telephone call by nurse during first and second month, then monthly telephone calls during rest of the year)
Outcomes	• Smoking cessation: self-reported continuous abstinence at 12 months • Adverse events: measured for 12 months
Funding Source	GlaxoSmithKline
Author conflicts of interest	None specified
Notes	New for 2013 update Study stopped early after interim analysis indicated no benefit OR adjusted for age, sex, invasive procedure, risk factors, Fagerstrom score, cigarettes per day: 0.90 (95% confidence interval (CI) 0.39 to 2.09)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized," method not specified
Allocation concealment (selection bias)	Unclear risk	Method not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and staff blind to treatment assignment, "Numbered study bottles were supplied by the study co-ordinator and remained concealed from the patients and medical staff."

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Planer 2011 *(Continued)*

		Comment: no biochemical validation but participants blind to condition so differential misreport unlikely.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 lost to follow-up in each group

Prochazka 1998

Study characteristics	
Methods	Study design: RCT Country: USA Setting: VAMC and Army Medical Centre Recruitment: outpatient clinics and campus advertisements
Participants	214 smokers (excludes 29 early dropouts); 38% female; average age 47
Interventions	• Nortriptyline, maximum 75 mg/day from 10 days pre-quit date to 8 weeks after, tapered for 2 weeks • Placebo capsules Common components: 2 behavioural group sessions prior to drug therapy. During treatment individual support was provided by the study nurse.
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated by CO ≤ 9 ppm at each visit and urine cotinine < 50 ng/mL at 6 months • Adverse events: measured for unspecified period
Funding Source	Department of Veterans Affairs, US Department of Defense
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "An unblinded research pharmacist recommended dosage reductions for those above the therapeutic range and dosage increases for those who were subtherapeutic. To maintain blinding, dose reductions and increases on an equal number of randomly selected placebo-treated subjects were also recommended...our blinding was only partially effective. Because of the high frequency of dry mouth, the nurse and subjects were often able to identify the active drug."
Incomplete outcome data (attrition bias) All outcomes	High risk	75% dropout rate in placebo, 61% in drug group, majority classified as ineffective therapy

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Prochazka 2004

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: outpatient clinic and community volunteers
Participants	158 smokers; 54% female; average cigarettes per day 22
Interventions	• Nortriptyline and nicotine patch, maximum 75 mg/day for 14 weeks, from 2 weeks before TQD tapered for 2 weeks. Nicotine patch 8 weeks from TQD • Placebo capsules and nicotine patch Common components: brief counselling from nurse at weekly visits
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated by CO ≤ 9 ppm at each visit, cotinine < 50 ng/mL at 6 months • Adverse events: measured for unspecified period
Funding Source	Department of Veterans Affairs
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were stratified by history of previous major depression and randomized by means of a computer-generated random number list that was held by the Research Pharmacy Service of the Denver Veterans Affairs Medical Center."
Allocation concealment (selection bias)	Low risk	Quote: "Once a patient was enrolled, the Research Pharmacy Service randomized the subject according to the randomization list." Judged adequate
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "...our blinding was only partially effective. Because of the high frequency of dry mouth, the study nurse was often able to identify the active drug."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Subjects who dropped out were counted as smokers." Number of dropouts not given

Richmond 2013

Study characteristics	
Methods	Study design: RCT Country: Australia Setting: 18 prisons

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Richmond 2013 *(Continued)*

	Recruitment: referral from clinic staff, flyers and posters in prisons
Participants	425 male prisoners aged > 18, incarcerated for ≥ 1 month with ≥ 6 months of current sentence remaining; FTND ≥ 5; average age 34; average cigarettes per day 23; 83% FTND ≥ 6
Interventions	• Nortriptyline, tablet form for 13 weeks (TQD week 3. Week 1: 25 mg/day for 3 days, 50 mg/day for 4 days. Weeks 2 to 12 75 mg/day. Week 13 50 mg/day for 4 days, then 25 mg/day for 3 days) • Placebo, same schedule as above Common components: two x 30-minute counselling sessions with CBT. Self-help materials, access to quitline. 10 weeks NRT patch started on TQD; 21 mg weeks 1-6, 14 mg/day weeks 7-8, 7 mg/day weeks 9-10
Outcomes	• Smoking cessation: continuous abstinence at 12 months. Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	National Health and Medical Research Council, NSW Department of Health, Queensland Department of Health. NRT provided free of charge by GlaxoSmithKline.
Author conflicts of interest	Tony Butler is supported by an ARC future Fellowship
Notes	New for 2013 update N quit extrapolated from percentages provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization algorithm," no further information provided
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Follow-up assessments were conducted… by a prison nurse research assistant who was blind to group allocation." Identical placebo. No further information on blinding provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	80% followed up at 12 months, similar in both groups

Rigotti 2006

Study characteristics

Methods	Study design: RCT Country: USA Setting: hospitals Recruitment: volunteers
Participants	248 smokers hospitalized with cardiovascular disease (excludes 3/3 dropped prior to treatment and 2 placebo deaths during follow-up); 31% female; average age 56; average cigarettes per day 23/21
Interventions	• Bupropion 300 mg for 12 weeks

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Rigotti 2006 *(Continued)*

	• Placebo, same schedule as above Common components: multicomponent CBT cessation and relapse prevention programme, motivational interviewing approach. Begun in hospital, 30-45 mins, 5 x 10 min post-discharge contacts (2 days, 1 week, 3 weeks, 8 weeks, 12 weeks), self-help, chart prompt for physician. Total time 80-95 mins
Outcomes	• Smoking cessation: sustained abstinence at 12 months (at multiple follow-ups) Validated by saliva cotinine at 12 weeks and 52 weeks, CO at 2 weeks and 4 weeks • Adverse events: measured for 52 weeks
Funding Source	National Heart, Lung and Blood Institute, National Institutes of Health General Clinical Research Centers Program, GlaxoSmithKline
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Using a computer program, the study statistician generated a sequence of randomly-permuted blocks of 4 within strata formed by study site and daily cigarette consumption (10 vs 10)."
Allocation concealment (selection bias)	Low risk	Quote: "The study pharmacist used this sequence, concealed from enrolment staff, to assign participants to study arm. Subjects and study personnel, except the statistician and pharmacist, were blind to treatment assignment."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Subjects and study personnel, except the statistician and pharmacist, were blind to treatment assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Subjects were considered smokers if they were lost to follow-up..."; 23% lost to follow-up in the bupropion group and 23% in the placebo group

Rose 2013

Study characteristics

Methods	Study design: RCT Country; USA Setting: clinic Recruitment: community volunteers
Participants	440 smokers who did not respond successfully to cessation treatment with NRT (phase 1 = 335 participants whose smoking did not decrease by > 50% after 1 week NRT (prior to TQD); phase 2 = 105 participants who lapsed within one week after TQD); 50% female; average age 43; average cigarettes per day 22; mean FTND 5.8
Interventions	• Bupropion and nicotine patch. Bupropion for 12 weeks (150 mg/day for 3 days, 300 mg/d for remainder). Nicotine patch (patch dose based on CO, 21 mg/day for CO ≤ 30 ppm, 42 mg/day for CO > 30 ppm) • Placebo and nicotine patch. Dosing as above

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Rose 2013 *(Continued)*

	Common components: cessation programme with nicotine patch (discontinued after 1 week in Phase 1 varenicline arm) and 4 to 6 brief (< 15 mins) counselling sessions
Outcomes	• Smoking cessation: continuous abstinence at 6 months. Validated by CO ≤ 10 ppm • Adverse events: Dr Rose has served as a consultant for Targacept and Philip Morris USA and has a patent purchase agreement with Philip Morris International. Both authors have received research funding from Philip Morris USA
Funding Source	Supported by grant to Duke University from Philip Morris USA. NRT donated by GlaxoSmithKline
Author conflicts of interest	None specified
Notes	New for 2013 update Phase 1 and Phase 2 combined in meta-analysis. Sensitivity analyses including both separately did not detect any significant effect on the pooled result.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	< 50% followed up at 6 months in both phases, similar rates of dropout across all arms. 27 participants censored from reported analyses, mainly for protocol violations, included as smoking here.

Rose 2014

Study characteristics

Methods	Study design: RCT Country: USA Setting: university Recruitment method: newspaper, radio, and television advertisements
Participants	Participants were nicotine patch non-responders (failed to show a reduction of more than 50% in smoking after 1 week of nicotine patch treatment) 222 participants randomized; 54.5% female; average age 44.1; average cigarettes per day 20.7; mean FTND 6.1
Interventions	• Bupropion and varenicline. Bupropion given 150 mg once daily for 3 days, then 150 mg twice daily for remainder of 12-week treatment period. Varenicline given 0.5 mg once daily on days 1–3, 0.5 mg twice daily on days 4–7; and 1 mg twice daily for remainder of 12-week treatment period • Placebo and varenicline. Given according to schedule above

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Rose 2014 *(Continued)*

	Common components: brief support at each study session, totalling 1 hour and 45 minutes
Outcomes	• Smoking cessation (strictest definition): 7-day ppa at 6 months. Validated by CO ≤ 10 ppm • Adverse events: measured for an unspecified period
Funding Source	National Institute on Drug Abuse grant 1P50 DA027840 and a grant from Philip Morris USA. The sponsors had no role in the planning or execution of the study, data analysis, or publication of results. Active bupropion sustained-release and placebo tablets were supplied by Murty Pharmaceuticals, under contract from the National Institute on Drug Abuse.
Author conflicts of interest	The authors have consulting and patent purchase agreements with Philip Morris International for nicotine inhalation technology and consulting agreements with Targacept and Novartis.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “The study was a double-blind, parallel-arm adaptive treatment trial." Placebo tablets were used. No further information provided regarding who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 41/113 (36.3%) for varenicline and bupropion; 38/109 (34.9%) for varenicline and placebo

Rose 2017

Study characteristics

Methods	Study design: RCT Country: USA Setting: research centre (Duke Center for Smoking Cessation) Recruitment method: not specified
Participants	All participants were male 174 participants randomized; 0% female; average age 44.0; average cigarettes per day 20.0; mean FTND 5.5
Interventions	• Bupropion and varenicline. Bupropion scheduling was 150 mg once daily for 3 days, followed by 150 mg twice daily for the remainder of the 12-week treatment period. Varenicline scheduling was 0.5 mg once daily on days 1–3, 0.5 mg twice daily on days 4–7, followed by 1 mg twice daily for the remainder of the 12-week treatment period • Placebo and varenicline. Same schedule as above

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Rose 2017 *(Continued)*

	Common components: precessation patches for 1 week prior to pharmacological treatments above, and brief support was provided at each session, totalling 1 hour and 30 minutes
Outcomes	• Smoking cessation (strictest definition): 11 weeks - too short a follow-up for this outcome to be considered in this review • Adverse events: measured for 12 weeks
Funding Source	Grant 1P50 DA027840 from the National Institute on Drug Abuse and a grant from Philip Morris, USA
Author conflicts of interest	The authors disclose consulting and patent purchase agreements with Philip Morris International relating to reduced risk tobacco products.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind, placebo-controlled, parallel-arm trial”. No further information provided regarding who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: (13.1%) in the bupropion and varenicline arm; 13/90 (14.4%) in the placebo and varenicline arm; 11/84. Therefore dropout was low and similar between groups.

Rovina 2009

Study characteristics

Methods	Study design: RCT Country: Greece Setting: cessation clinic Recruitment: clinic attenders invited to participate
Participants	205 smokers; 40% female; average age 45; average cigarettes per day 37
Interventions	• Bupropion 300 mg/day for 19 weeks + 15 mins physician counselling • Bupropion 300 mg/day for 19 weeks + nonspecific group therapy, 1 hour weekly for 1 month, then every 3 weeks until 19 weeks • Bupropion 300 mg/day for 19 weeks + CBGT, same schedule • CBGT without bupropion
Outcomes	• Smoking cessation: continous abstinence at 12 months after end of treatment. Validated by CO ≤ 10 ppm • Adverse events: measured for 31 weeks

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Rovina 2009 *(Continued)*

Funding Source	None specified
Author conflicts of interest	All the authors of this paper declare that they have no financial or other potential conflicts of interest concerning the subject of this manuscript.
Notes	New for 2013 update 3 versus 4 used analyses, 1 and 2 not included in any analyses (effect of different counselling would confound effect of bupropion) Authors do not report n abstinent, numbers included in meta-analysis extrapolated from applying percentage to overall n randomized

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized, method not stated, 3:1:1:1 ratio
Allocation concealment (selection bias)	Unclear risk	No details reported
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label, participants and staff aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	90% followed up at 12 months, but authors do not specify percentage per group and do not specify how participants lost to follow-up were treated. Authors only provide percentages abstinent, so n abstinent in this review may be inflated.

Saules 2004

Study characteristics

Methods	Study design: RCT Country: USA Setting: cessation clinic Recruitment: volunteers
Participants	150 smokers; 55% female; average age 40
Interventions	• Fluoxetine 40 mg for 14 weeks, nicotine patch for 10 weeks • Fluoxetine 20 mg for 14 weeks, nicotine patch for 10 weeks • Placebo and nicotine patch Common components: TQD end of week 4, CBT 6 sessions starting 2 weeks before TQD, 11 clinic visits
Outcomes	• Smoking cessation: at 12 months (unspecified definition). Validated by CO < 10 ppm • Adverse events: measured for 15 weeks
Funding Source	National Institute on Drug Abuse, State of Michigan. Nicotine patch provided by McNeil Consumer Healthcare

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Saules 2004 *(Continued)*

Author conflicts of interest	None specified
Notes	Authors provided quit numbers by treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind" but no further information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers lost to follow-up not provided by study arm but high: at six months, only 58 of 150 subjects were followed up. Subjects who dropped out of the study or lost to follow-up were considered to be smoking again.

Schmitz 2007

Study characteristics

Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: research clinic Recruitment: community volunteers
Participants	154 women smokers; average age 48; average cigarettes per day 21
Interventions	• Bupropion 300 mg/day for 7 weeks • Placebo Common components: either CBT based on relapse prevention model, or group support therapy, both 7 weekly 60-min meetings, TQD morning of 1st session, 10 days after start of medications
Outcomes	• Smoking cessation: 7 day ppa at 12 months. Validated by CO ≤ 10 ppm, saliva cotinine < 15ng/mL • Adverse events: 7 weeks
Funding Source	National Institute on Drug Abuse. Bupropion provided by GlaxoSmithKline.
Author conflicts of interest	None specified
Notes	Group therapy variants collapsed in main analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Urn procedure, balancing on a range of outcome-related variables

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Schmitz 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "Investigators and research staff were blind to the randomization codes, which were kept by a faculty member independent of the research and treatment team."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," further information not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	14 'enrolment failures' who did not receive any treatment are excluded from analyses. Other non-completers and losses to follow-up included in ITT analysis

Schnoll 2010

Study characteristics	
Methods	Study design: RCT Country: USA Setting: not specified (presumably clinic) Recruitment: patient lists from physicians treating people with cancer
Participants	246 cancer patients smoking ≥ 2 cigarettes per day; 48% female; average age 54.8; average cigarettes per day 17.5; mean FTND 3.2; 32% had tobacco-related tumours
Interventions	• Bupropion 9 weeks, started 2 weeks before TQD (150 mg/d first week, 300 mg/d remaining 8 weeks) • Placebo, same schedule as above Common componenets: 8 weeks nicotine patches and 5 sessions of behavioural counselling (3 in person, 2 over phone)
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by CO ≤ 10 ppm • Adverse events: measured for 9-week treatment period
Funding Source	National Cancer Institute. NRT provided free of charge from GlaxoSmithKline.
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Stratified by depression status. Method of sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Double-blind," no further information provided

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Schnoll 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	65% intervention and 72% control followed up at 6 months

Selby 2003

Study characteristics	
Methods	Study design: RCT Country: Canada Setting: 15 clinical centres Recruitment: community volunteers
Participants	284 smokers previously exposed to bupropion for at least 2weeks, not quit for more than 24 hours in previous month
Interventions	• Bupropion 300 mg for 12 weeks • Placebo Behavioural support not described
Outcomes	• Smoking abstinence, ppa at 12 months. Validated by CO ≤ 10 ppm at treatment visits • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified
Notes	Based on abstract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details given
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details given, unclear how participants lost to follow-up treated in outcome data. 70% intervention group and 50% control group completed study

Sheng 2013

Study characteristics

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Sheng 2013 *(Continued)*

Methods	Study design: RCT Country: China Setting: hospital outpatient centres Recruitment method: newspaper advertisements and by word of mouth
Participants	Participants were mainly male 257 participants randomized; 5.5% female; average age 39.1; average cigarettes per day 22.5; mean FT-ND 5.6
Interventions	• Bupropion 150 mg daily for days 1 to 3, 150 mg twice daily for days 4 to 56, then 150 mg daily for days 57 to 63 and discontinued on day 64 • Placebo, same tablets and schedule as for bupropion above All participants were given the same brief education and counselling was administered to both groups by research staff. Counselling topics included motivation, identification of smoking triggers, coping responses, weight management, and use of the medications. The total duration of conselling was 1 hour and 30 minutes.
Outcomes	• Smoking cessation: 12 weeks - too short a follow-up for this outcome to be considered in this review • Adverse events: not specified
Funding Source	Zhejiang Jinxin Pharmaceutical Co, Ltd
Author conflicts of interest	L-XS, Z-NJ, and G-ZX declare that they have undertaken research and consultancy for, and received honoraria for speaking at meetings for, the manufacturers of smoking cessation medications.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Participants were assigned to one of two study arms using a computer algorithm to generate a random list of treatment assignments."
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: “Participants in the control arm received placebo pills identical in appearance. All study personnel were blinded to treatment assignment. The same brief education and counseling were administered to both groups by a research staff.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 14/127 (11.0%) in the bupropion arm; 18/130 (13.9%) in the placebo. Therefore, dropout rates are low and similar between groups.

Siddiqi 2013

Study characteristics

Methods	Study design: cluster-RCT Country: Pakistan

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Siddiqi 2013 *(Continued)*

	Setting: 33 health centres Recruitment: patients from participating health centres with suspected pulmonary tuberculosis
Participants	1955 adult smokers with suspected tuberculosis (1299 included in arms relevant to this review), smoking ≥ 1 cigarettes per day or smoking hookah on a daily basis; 5% female; average age 41; average cigarettes per day 19 (where one hookah counts as 2 cigarettes)
Interventions	• Bupropion 7 weeks (75 mg/d first week, 150 mg/d thereafter) • No pharmacotherapy Common components: 2 sessions of brief, in-person behavioural support (Note, third arm received usual care only, not included in this review)
Outcomes	Smoking cessation: continuous abstinence at 6 months. Validated by CO ≤ 9 ppm
Funding Source	International Development Research Centre
Author conflicts of interest	Link provided to list of declarations of interest, but link does not give access to active webpage
Notes	New for 2013 Reported narratively only due to substantial heterogeneity of program effects across clusters. 275/659 quit intervention versus 254/640 control, adjusted risk ratio 1.1 (0.5 to 2.3)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Quote: “A researcher who was blinded to center identity” allocated conditions
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No clinics dropped out post-randomization. Over 90% of participants followed up at 6 months
Other bias	High risk	Substantial heterogeneity of programme effects across clusters. 20% of participants in control arm smoked only hookah (no cigarettes) compared to 4% in intervention arm

Simon 2004

Study characteristics

Methods	Study design: RCT Country: USA Setting: VAMC outpatient units Recruitment: outpatients

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Simon 2004 *(Continued)*

Participants	244 smokers, 79% veterans; 5% female; average age 50; average cigarettes per day 24
Interventions	• Bupropion and nicotine patch. Bupropion at 300 mg for 7 weeks. Nicotine patch for 2 months • Placebo bupropion and nicotine patch. Schedules as above Common components: 3 months CBT counselling, self-help materials and telephone follow-up counselling
Outcomes	• Smoking cessation: sustained abstinence at 12 months (sustained at multiple follow ups). Validated by saliva cotinine • Adverse events: measured for 8 weeks
Funding Source	California Tobacco-Related Disease Research Program
Author conflicts of interest	None specified
Notes	Used in bupropion + NRT versus NRT comparison 2 placebo and 3 bupropion deaths excluded from denominators Originally based on abstract, now uses published data and sustained quitting outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "We assigned participants to the 2 study arms by using a computer algorithm to generate a random list of treatment assignments."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "All study personnel engaged in providing interventions to participants were blinded to treatment assignment." "Blinding appeared to be effective in our study; an approximately equal number of participants were able to guess what their treatment had been at the end of the study."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 244 participants enrolled, 3 (1%) were lost to follow-up (all randomized to the placebo arm).... Participants lost to follow-up were considered smokers."

Simon 2009

Study characteristics

Methods	Study design: RCT Country: USA Setting: VAMC hospital Recruitment: hospitalised volunteers
Participants	83 inpatients smoking at least 5 cigarettes per day in previous year, smoking in week before admission, in contemplation or preparation stage of change
Interventions	• Bupropion 300 mg for 7 weeks • Placebo

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Simon 2009 *(Continued)*

	Common components: individual CBT 30-60 min during hospital stay + 5 phone calls at week 1, week 3, week 5, week 8, week 12, recycling encouraged
Outcomes	• Smoking cessation: continuous abstinence at 6 months. Validated at each visit by saliva cotinine < 15 ng/mL • Adverse events: measured for 7 weeks
Funding Source	California Tobacco-Related Disease Research Program
Author conflicts of interest	None specified
Notes	1 death in bupropion, 1 in placebo excluded from analyses

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer algorithm to generate a random list of treatment assignments."
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All study personnel engaged in providing interventions to participants were blinded to treatment assignment." "A significant percentage of participants were able to guess correctly whether they were taking active bupropion or placebo" but as results did not favour intervention group, authors suggest this unblinding did not bias the results.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 withdrawals, 1 lost to follow-up, 1 death in placebo, 2 withdrawals, 1 lost, 1 death in bupropion. All except deaths included in meta-analysis

Singh 2010

Study characteristics

Methods	Study design: RCT Country: India Setting: anti-smoking clinic of Vallabhbhai Patel Chest Institute Recruitment method: not clearly specified
Participants	Participants almost solely men 30 participants randomized; 3.3% female; average age 43.1; average cigarettes per day 18.8; mean FTND 5.6
Interventions	• Bupropion 300 mg daily for seven weeks • Placebo Common components: physician advice based on National Cancer Institute's 5 A's i.e. ASK, ADVICE, ASSESS, ASSIST and ARRANGE. Brief face-to-face personalized anti-smoking advice was given at each of the 11 visits.
Outcomes	• Smoking cessation: 16 weeks - too short a follow-up for this outcome to be considered in this review

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Singh 2010 *(Continued)*

	• Adverse events: measured for six weeks
Funding Source	Quote: "nil"
Author conflicts of interest	None declared
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the baseline, subjects were randomly assigned to two groups" Comment: no further information is given
Allocation concealment (selection bias)	Unclear risk	Quote: "At the baseline, subjects were randomly assigned to two groups" Comment: no further information is given
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "It was a single blind placebo control study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

Smith 2009

Study characteristics

Methods	Study design: RCT Country: USA Setting: 12 primary care clinics Recruitment: volunteers from primary care clinics
Participants	1346 smokers; 56% female; average age 44; average cigarettes per day 20.3
Interventions	• Bupropion. Up-titrated during week pre-quitting, 150 mg twice/day for 8 weeks post-quit • Nicotine lozenge. 4 mg lozenge if first cigarette of day smoked > 30 min after waking, 2 mg otherwise. 1 lozenge every 1-2 hrs post-quit weekk 1-6; 1 lozenge every 2-4 hrs week 7-9; 1 lozenge every 4-8 hours week 10-12 • Nicotine patch. 21 mg post-quit wk 1-4; 14 mg wk 5-6; 7 mg wk 7-8 • Bupropion and nicotine lozenge. Dosing as above • Nicotine patch and nicotine lozenge. Dosing as above Common components: quitline counselling (state provided). All participants received initial session, then could elect to receive up to 4 additional calls + could call for additional support if required.
Outcomes	• Abstinence defintion: 7 day ppa at 6 months. No validation method specified • Adverse events: measured for unspecified period

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Smith 2009 *(Continued)*

Funding Source	Majority of funding from National Institutes of Health, National Institute on Drug Abuse, and National Cancer Institute. Medication provided to participants at no cost by GlaxoSmithKline
Author conflicts of interest	Dr Smith has received research support from Elan Corporation plc. Dr Jorenby has received research support from Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals and has received consulting fees from Nabi Biopharmaceuticals. Dr Fiore has received honoraria from Pfizer Inc and has served as an investigator on research studies at the University of Wisconsin that were funded by Pfizer Inc, Sanofi-Synthelabo, and Nabi Biopharmaceuticals. In 1998, the University of Wisconsin (UW) appointed Dr Fiore to a named Chair funded by an unrestricted gift to UW from Glaxo Wellcome. Dr Baker has served as an investigator on research projects sponsored by pharmaceutical companies including Sanofi-Synthelabo, Pfizer Inc, and Nabi Biopharmaceuticals.
Notes	New for 2013 update No control so does not contribute to primary analysis. 4 versus 2 used in Analysis 1.5. 1 versus 3 used in Analysis 1.7.1, 1 versus 2 used in Analysis 1.7.2, and 1 versus 5 used in Analysis 1.7.3 (n in 1 divided equally between subgroups to avoid triple counting)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Smokers were randomized to the 5 treatment conditions within each clinic with blocking on sex and self-identified race." Insufficient detail with which to judge.
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	158 individuals who did not pick up study medication at first point not included in analyses; 122 withdrawals and 9 deaths considered to be smoking

SMK20001

Study characteristics

Methods	Study design: RCT Country: USA Setting: 6 clinical trial centres Recruitment: volunteers for phase II trial
Participants	286 smokers; 48% female; average age 42; average cigarettes per day not soecified
Interventions	• Bupropion 300 mg for 7 weeks and placebo novel therapy • Double placebo No information about behavioural support
Outcomes	Smoking cessation: continuous abstinence at 12 months. Validated by CO ≤ 10 ppm

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SMK20001 *(Continued)*

Funding Source	GlaxoSmithKline
Author conflicts of interest	None specified
Notes	Identified from GSK trials website. Also included a novel cessation aid

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not specified
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	34% lost in bupropion, 29% placebo, included as smokers

Sood 2010

Study characteristics

Methods	Study design: RCT Country: USA Setting: Community Recruitment: press releases and local advertising
Participants	118 adult smokers; 82% female; average age 38; average cigarettes per day 20; mean FTND 5.0
Interventions	• St John's wort 900 mg/day (300 mg tablet 3 x day for 12 weeks) • St John's wort 1800 mg/day (3 x 300 mg/day tablet first week, 3 x 600 mg/day tablet weeks 2-12) • Matched placebo on same schedule Common components: 12-week behavioural intervention using Mayo Clinic 'Smoke Free and Living It' manual (type and number of sessions not stated)
Outcomes	• Smoking cessation: prolonged abstinence at 24 weeks (2-week grace period following quit date). Validated by CO ≤ 8 ppm • Adverse events: measured for unspecified period
Funding Source	National Cancer Institute
Author conflicts of interest	None specified
Notes	New for 2013 update

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Sood 2010 *(Continued)*

	Groups 1 and 2 combined in meta-analysis; no significant difference between the two (at 24 weeks, 1/39 abstinent intervention 1, 2/40 abstinent intervention 2)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Generated centrally by Mayo Clinic Division of Biostatistics
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Blinded" with matched placebo, no further information provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	43% dropped out within first 12 weeks, unclear how many dropped out by 24 weeks. Not given by arm

Sood 2012

Study characteristics

Methods	Study design: RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	120 smokers; 47% female; average age 40; average cigarettes per day 20; mean FTND 5.2
Interventions	• SAMe 1600 mg/day (via mouth) for 8 weeks • SAMe 800 mg/day. Same schedule as above • Placebo. Same schedule as above Common components: behavioural counselling using "Smoke Free and Living It" manual at every clinic visit (approx. 7)
Outcomes	• Smoking cessation: 7 day ppa at 6 months (prolonged abstinence measured but not reported). Validated by CO ≤ 8 ppm • Adverse events: measured for unspecified period
Funding Source	National Institutes of Health
Author conflicts of interest	None specified
Notes	New for 2013 update SAMe is a dietary supplement used to treat depression No difference between arms 1 and 2, hence combined in meta-analysis

Risk of bias

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Sood 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "Blinded," no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	57% followed up overall, similar rates between groups

Spring 2007

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinic Recruitment: community volunteers
Participants	247 smokers; 54% female; average age 44; average cigarettes per day 23
Interventions	• Fluoxetine 60 mg (titrated up over 2 weeks) for 12 weeks • Placebo Common components: group behavioural counselling, 9 meetings over 12 weeks
Outcomes	• Smoking cessation: prolonged abstinence at 6 months (starting from 2 weeks after quit date). Validated by CO < 10 ppm, urine cotinine < 20 ng/mL • Adverse events: measured for unspecified period
Funding Source	National Institutes of Health, Veterans Affairs. Medication provided by Eli Lilly and Company.
Author conflicts of interest	None specified
Notes	First included as Spring 2004 with unpublished data. Full publication reports sustained abstinence

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study pharmacist stratified participants by depression history and used computer-generated random numbers to assign them to drug or placebo."
Allocation concealment (selection bias)	Unclear risk	Allocated by unblinded pharmacist, method not described
Blinding (performance bias and detection bias)	Unclear risk	Quote: "Research staff and participants were blinded to medication status." "Drug assignment was guessed correctly by 59.8% of placebo and 64.6% of flu-

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Spring 2007 *(Continued)*

All outcomes		oxetine participants. Facilitators guessed correctly for 65.3% of placebo and 55.6% of fluoxetine participants."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals/lost to follow-up 40% for fluoxetine, 48% placebo. Authors report similar results from missing assumed smoking and generalized estimating equation (GEE) analyses. All participants included in meta-analysis

Stapleton 2013

Study characteristics	
Methods	Study design: RCT Country: UK Setting: smoking cessation clinics Recruitment: people attending smoking cessation clinics
Participants	1071 daily smokers; 53% female; average age 41; average cigarettes per day 20
Interventions	• Bupropion 8 weeks, started prior to TQD (exact period not specified), 150 mg/d for first 6 day, then 300 mg for remainder • Bupropion and NRT. Bupropion as above. NRT given as choice of single product, 12 weeks started on TQD, dosage determined on individual basis • NRT. As above Common components: 7 weekly behavioural support sessions as per standard service protocol. Mainly group, 60-90 mins each
Outcomes	• Smoking cessation: prolonged abstinence at 6 months. Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	Department of Health for England. Study medication provided free of charge by Pfizer UK, GSK UK and Novartis UK.
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: “Randomization and packaging was organized by an independent statistician at the host site.”
Allocation concealment (selection bias)	Low risk	Quote: “On enrolment, participants selected their envelope from a large batch and signed it before breaking the seal to reveal their allocation.”
Blinding (performance bias and detection bias) All outcomes	High risk	Open label, no blinding
Incomplete outcome data (attrition bias)	Low risk	61.5% followed up at both 1 month and 6 months, no significant difference between groups. Prolonged abstinence only imputed for 16% of total

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Stapleton 2013 *(Continued)*

All outcomes

Swan 2003

Study characteristics	
Methods	Study design: 2 x 2 factorial RCT Country: USA Setting: HMO Recruitment: volunteers from Group Health Co-op membership
Participants	1524 smokers; 57% female; average age 45; average cigarettes per day 23
Interventions	Factorial design crossing 2 drug doses with 2 intensities of behavioural counselling: • Bupropion 300 mg/day versus 150 mg/day • Free and Clear proactive telephone counselling (4 brief calls), access to quitline and S-H materials vs Zyban Advantage Program (ZAP) tailored S-H materials, single telephone call after TQD, access to Zyban support line
Outcomes	• Smoking cessation: 7 day ppa at 12 months. Validation method not specified • Adverse events: measured for 13 weeks
Funding Source	National Cancer Institute
Author conflicts of interest	None specified
Notes	Based on published data from 2004 No dose/behavioural treatment interaction at 12 months so arms collapsed to compare 300 mg vs 150 mg Effects differed at 3 months and 12 months. Effect of higher dose disappeared and additional support aided recycling

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Open-label randomized trial...The computer code for the procedure calculated probabilities of group assignment that were dynamically modified based on the number of members in each group so that final group sizes were equal. No restrictions such as stratification or blocking were used as part of the randomization process."
Allocation concealment (selection bias)	Low risk	Procedure built into study database
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar percentage lost to follow-up across all groups (approx 15%) Nonresponders treated as smoking

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Tashkin 2001

Study characteristics	
Methods	Study design: RCT Country: USA Setting: multicentre Recruitment: advertisements for volunteers
Participants	404 smokers with mild to moderate COPD (excludes 7 early dropouts who did not take any study medication); 45% female; average age 53-54; average cigarettes per day 28
Interventions	• Bupropion SR 300 mg/day for 12 weeks from 1 week before TQD • Placebo Common components: brief face-to-face counselling at each clinic visit (weeks 1-7, 10, 12), telephone counselling 3 days after TQD
Outcomes	• Smoking cessation: sustained abstinence at 52 weeks (starting from week 4). Validated by CO ≤ 10 ppm at each visit • Adverse events: measured for 12 weeks
Funding Source	Glaxo Wellcome Inc
Author conflicts of interest	None specified
Notes	ITT population defined as those taking at least one dose of study medication

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomised as per code provided by Glaxo Wellcome, using block sizes of four stratified by centre. Within each block of four, two participants were assigned placebo and two bupropion SR. The randomisation codes were kept at the study sites during the trial and we instructed investigators to break the code only for a medical emergency."
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind study, but further detail not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	64% intervention and 73% control followed up at 6 months. "All participants who withdrew from the study were taken to be smokers thereafter."

Tidey 2011

Study characteristics	
Methods	Study design: factorial trial Country: USA

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Tidey 2011 *(Continued)*

	Setting: Providence Veterans Affairs Medical Center and the Brown University Center for Alcohol and Addiction Studies Recruitment method: advertisements posted in the surrounding community and at an outpatient clinic at a local VA medical centre
Participants	Participants diagnosed with schizophrenia or schizoaffective disorder as confirmed by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders 57 participants randomized; 29% female; average age 45.1; average cigarettes per day 27; mean FTND 7.1
Interventions	• Bupropion 150 mg daily for 3 days, then 150 mg twice daily for 3 weeks, starting 1 week prior to TQD • Placebo As this is a factorial trial, all participants were randomized to contingency management or none.
Outcomes	• Smoking cessation: 22 days - too short a follow-up to be considered as part of this review • Adverse events: measured for 22 days
Funding Source	NIH grant R01-DA17566 to the first author and a Senior Research Career Scientist Award from the Department of Veterans Affairs to the second author
Author conflicts of interest	None detailed
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “randomized by coin toss."
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	States "double-blind", but no further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 94% follow-up in all groups, with no between-group differences

Tonnesen 2003

Study characteristics

Methods	Study design: RCT Country: 8 European countries, Australia, New Zealand Setting: 28 clinical trial centres Recruitment: community volunteers
Participants	710 smokers; 51% female; average age 42; median cigarettes per day 20
Interventions	• Bupropion SR 300 mg/day for 7 weeks

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Tonnesen 2003 *(Continued)*

	• Placebo Common components: brief motivational support at weekly clinic visits and telephone support during follow-up. 11 clinic visits and 10 phone calls scheduled
Outcomes	• Smoking cessation: prolonged abstinence at 52 weeks (starting from week 4). Validated by CO ≤ 10 ppm • Adverse events: measured for 52 weeks
Funding Source	GlaxoSmithKline
Author conflicts of interest	S Tonstad has received honoraria from Glaxo-SmithKline for lectures on smoking cessation. R Sweet is a former employee of GlaxoSmithKline. A Hider and J Townsend are currently employees of GlaxoSmithKline. For A Hjalmarsson, PI VanSpiegel, P Tonnesen: no conflict of interest was declared
Notes	First included 2003 as Tonstad 2001 ITT population defined as those taking at least one dose of study medication excludes 3 randomized participants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "GlaxoSmithKline created a randomization schedule in a 3:1 bupropion: placebo ratio. Each centre received a list with treatment numbers and subjects were consecutively assigned a treatment number at the baseline visit."
Allocation concealment (selection bias)	Low risk	Quote: "GlaxoSmithKline supplied bupropion SR 150 mg and placebo-to-match tablets for oral administration as white, film-coated tablets."
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but methods not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	9% of bupropion SR and 12% placebo were lost to follow-up

Tonstad 2003

Study characteristics

Methods	Study design: RCT Country: 10 countries including European countries, Australia, and NZ Setting: 28 clinical trial centres Recruitment: volunteers with CVD
Participants	629 smokers with stable CVD; 23% female; average age 55; average cigarettes per day 25; 49% had history of MI
Interventions	• Bupropion SR 300 mg/day for 7 weeks, begun 1-2 weeks before TQD • Placebo Common components: brief motivational support at weekly clinic visits and telephone support during follow-up. 9 clinic visits and 10 phone calls scheduled

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Tonstad 2003 *(Continued)*

Outcomes	• Smoking cessation: prolonged abstinence at 12 months (starting from week 4). Validated by CO ≤ 10 ppm • Adverse events: measured for 9 weeks
Funding Source	GlaxoSmithKline
Author conflicts of interest	None specified
Notes	First included 2003 as McRobbie 2003. ITT population = 626 defined as those taking at least one dose of study medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind, but no further detail provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number missing follow-up in each group not provided. At 12 months, 38% bupropion and 50% placebo had prematurely discontinued treatment. "Subjects with missing investigator assessments were assumed to be smokers at that visit."

Urdapilleta-Herrera 2013

Study characteristics

Methods	Study design: RCT Country: Mexico Setting: not specified Recruitment: not specified
Participants	94 "chronic smokers" randomised; average age 48; average pack per year 25
Interventions	• Bupropion, no schedule and dose detailed • Placebo, no schedule and dose detailed Common components: CBT
Outcomes	• Smoking cessation: at 1 year (no definition of abstinence given). No validation method detailed. • Adverse events: not detailed whether adverse events were recorded
Funding Source	None specified
Author conflicts of interest	None specified

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Urdapilleta-Herrera 2013 *(Continued)*

Notes	Only limited information available as study is only reported as a conference abstract. Outcome data is insufficient to include in meta-analysis as it is unclear whether percentages reported were calculated using all participants randomized or only those followed up as the denominator. Attempt to contact the authors was unsuccessful. Results are summarized narratively.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No relevant information given
Allocation concealment (selection bias)	Unclear risk	No relevant information given
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: "double-blind" although no information given regarding who was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant information given

Uyar 2007

Study characteristics

Methods	Study design: RCT Country: Turkey Setting: cessation clinic Recruitment: cessation clinic patients
Participants	131 smokers; 19% female; average age 36
Interventions	• Bupropion 300 mg for 7 weeks • Nicotine patch 21 mg for 6 weeks including tapering • Advice and follow-up only Common components: brief counselling on consequences of smoking with follow-up for 24 weeks - more than low intensity
Outcomes	• Smoking cessation: abstinence at 24 weeks (definition not specified). Validated by CO < 10 ppm • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None specified
Notes	First included based on abstract. Contributes to bupropion versus control and bupropion versus nicotine patch

Risk of bias

Bias	Authors' judgement	Support for judgement

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Uyar 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Randomly allocated", method not described, unclear why fewer in control condition
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of any losses to follow-up

Wagena 2005

Study characteristics	
Methods	Study design: RCT Country: Netherlands Setting: university medical centre Recruitment: community volunteers
Participants	255 smokers with or at risk of COPD; 51% female; average age 51; average cigarettes per day 23
Interventions	• Bupropion SR 300 mg/day for 12 weeks • Nortriptyline 75 mg/day for 12 weeks • Placebo bupropion or placebo nortriptyline Common components: individual counselling 10-20 mins at baseline, 1 week and 3 weeks post-TQD (TQD typically day 11). Telephone support TQD, 2 weeks, 4 weeks, 6 weeks, 8 weeks, 11 weeks
Outcomes	• Smoking cessation: prolonged abstinence at 26 weeks (puff-free from week 4). Validated by urine cotinine ≤ 60 ng/mL at 4 weeks, 12 weeks and 26 weeks • Adverse events: none specified
Funding Source	Netherlands Asthma Foundation, Netherlands Organization for Health Research and Development. Lundbeck BV provided nortriptyline free of charge
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated by pharmacist, stratified by COPD severity, block size 33
Allocation concealment (selection bias)	Low risk	Research staff blinded throughout study
Blinding (performance bias and detection bias)	Unclear risk	Double-blind but "at both time points, participants receiving active drug compared with those receiving placebo were more likely to guess that they had re-

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Wagena 2005 *(Continued)*

All outcomes		ceived bupropion SR and nortriptyline treatment (72% vs 43%, P.01; and 62% vs 37%; P=.001; respectively)."
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 (12%) bupropion, 13 (16%) nortriptyline, 12 (13%) lost or withdrawn. All included in ITT analysis

Weinberger 2010

Study characteristics	
Methods	Study design: RCT Country: USA Setting: clinics Recruitment: community volunteers
Participants	101 smokers (excludes 2 taking no medication); 50% femalel; average age 47; average cigarettes per day 22
Interventions	• Selegiline 10 mg/day for 9 weeks (5 mg/day in week 1 and week 9) • Placebo Common components: brief weekly counselling
Outcomes	• Smoking cessation: 7 day ppa at 6 months. Validated by CO and urinary cotinine • Adverse events: measured for 10 weeks
Funding Source	National Institute of Drug Abuse, Veteran's Administration, Women's Health Research at Yale, NIH, University of Toronto
Author conflicts of interest	None specified
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Both participants and research staff were blinded to study medication assignment," Comment: assessments of staff and participants suggest blinding was adequate
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	27.5% selegiline, 42% placebo lost at 6 months. Including all participants is less conservative

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Weiner 2012

Study characteristics	
Methods	Study design: RCT Country: USA Setting: Maryland Psychiatric Research Center Recruitment method: clinically stable outpatients from the Maryland Psychiatric Research Center volunteered to participate
Participants	Participants had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder made through a best estimate diagnostic approach. 46 participants randomised; 19.6% female; average age 49; average cigarettes per day 44.0; mean FTND 5.8
Interventions	• Bupropion 150 mg daily for three days, then 150 mg twice daily from day four onwards, through 12 weeks • Placebo, dose and scheduling the same as bupropion All participants had a 9-week group support programme led by staff trained in the education model of the American Cancer Society Fresh Start Program modified for people with schizophrenia. Each session was structured and incorporated relation exercises with practice "homework". The first group sessions were designed to increase awareness of specific smoking habits and to develop a 'Quit Plan'. A Quit Day Ceremony was held at the fifth group session. Subsequent sessions focused on reworking the Quit Plan. Later groups focused on strategies for participants minimizing weight gain, managing high risk situations, and imagining themselves as non-smokers.
Outcomes	• Smoking cessation: 14 weeks - too short a follow-up for this outcome to be considered as part of this review • Adverse events: measured for 14 weeks
Funding Source	Veterans Affairs Capitol Network (VISN 5) Mental Illness Research, Education, and Clinical Center. National Institute of Mental Health Grant (MH068580-01), Advance Center for Intervention Services Research
Author conflicts of interest	Ms Ball has served as a consultant to ePharmaSolutions and Pfizer; Dr Gold has served as a consultant to Merck, AstraZeneca, Solvay, Pfizer, and GlaxoSmithKline. Dr Evins has served as a consultant to Pfizer, Boehringer, and Schering Plough and has received grant/research support from GlaxoSmithKline and Pfizer. Dr Buchanan has served as a consultant to Abbott and ClaxoSmithKline; has received grant/research support from Novartis and Janssen; has served on advisory boards for AstraZeneca, Wyeth, Schering Plough, Solvay and Pfizer, and has received other material or financial support from Bristol-Myers Squibb, Otsuka, Pfizer and Cephalon. Drs Weiner and McMahon and Ms Buchholz report no financial or other relationship relevant to the subject of this article.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Random assignments made by the statistician." Comment: no further information given
Allocation concealment (selection bias)	Unclear risk	Quote: "Random assignments made by the statistician." Comment: no further information given

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Weiner 2012 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Quote: “double-blind, placebo-controlled clinical trial." Comment: no further information given
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 8/24 (33.3%) in the bupropion group; 6/22 (27.3%) in the placebo group. Therefore overall dropout was less than 50% and similar between groups.
Other bias	Unclear risk	“While the target completion number was 40 there was insufficient study drug available to meet this goal." It is unclear how this was dealt with and whether it is accounted for in the dropouts reported in the flow diagram. However loss to follow-up was similar between arms.

White 2005

Study characteristics	
Methods	Study design: RCT Country: Canada Setting: university Recruitment method: local media
Participants	36 participants randomized; 61.1% female; average age 41.9; average cigarettes per day 24.0; mean FT-ND 7.2
Interventions	• Bupropion 150 mg on days 1–3, then 150 mg twice daily for the remainder of the 6-week study • Gabapentin started at 300 mg daily, with titration to 1800 mg daily by day 6 All participants each week received 15-minute one-to-one smoking cessation counselling with a study investigator, using the Mayo Clinic workbook ‘"Smoke-Free and Living It" for a total of 1 hour and 30 minutes
Outcomes	• Smoking cessation: 6 weeks - too short a follow-up for this outcome to be considered as part of this review • Adverse events: measured for 6 weeks
Funding Source	Calgary Centre for Advancement of Health. Gabapentin (Neurontin) samples were donated through an informal arrangement with a local representative of Pfizer Canada Inc.
Author conflicts of interest	None detailed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: “we conducted a randomized, open-label pilot trial." Comment: no further information given
Allocation concealment (selection bias)	Unclear risk	Quote: “we conducted a randomized, open-label pilot trial." Comment: no further information given

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White 2005 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	High risk	Quote: “we conducted a randomized, open-label pilot trial” Comment: open-label
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout rates are as follows: 9/19 (47.4%) in the bupropion group; 6/17 (35.3%) in the gabapentin group. Therefore overall attrition was less than 50% and similar between arms.

Wittchen 2011

Study characteristics	
Methods	Study design: RCT Country: Germany Setting: 167 primary care clinics Recruitment: patients at participating primary care clinics
Participants	467 "current regular smokers"; 52% female; average age 43; average cigarettes per day 20
Interventions	• CBT 4-5 one-on-one counselling sessions for 20-30 mins • CBT and bupropion SR. CBT as above. Bupropion SR (9-12 weeks, 150 mg; 1/day for first 6 days; 2/day thereafter) • CBT and NRT. CBT as above. NRT for 9-12 weeks, patient's choice of patch (7 mg to 52.5 mg), gum (2 or 4 mg) or spray (10 mg/mL) • Minimal intervention (not used in review)
Outcomes	• Smoking cessation: abstinence at 12 months (from EoT). Validation method not specified • Adverse events: measured for 12 weeks
Funding Source	Patients covered all costs for pharmaceutical treatments. Sponsored by the Federal Ministry of Education and Research; additional support provided by GlaxoSmithKline GmbH & Co and Pharmacia GmbH
Author conflicts of interest	None specified
Notes	New for 2013 update 3 versus 2 included in primary analyses. 2 versus 4 included in Analysis 1.7 comparison of NRT with bupropion. 1 not used as results versus bupropion would be confounded with CBT

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Generated by the study center"; used to put 4 different coloured questionnaires in random order
Allocation concealment (selection bias)	High risk	Quote: "questionnaires were distributed consecutively to all attending patients on the target days by nurses. Thus, the assignment of patients was entirely dependent on the consecutive attendance of patients and the random assignment of a color. Doctors were not allowed to interfere with this study procedure." But numbers allocated to groups very uneven and discussion states: "Random checks of this procedure [randomization] and quality assur-

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Wittchen 2011 *(Continued)*

		ance tests by study monitors revealed that in some cases in the latter part of the study treatment was based on patient and physician preferences." Comment: therefore no concealment
Blinding (performance bias and detection bias) All outcomes	High risk	Neither participants nor providers were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar number of dropouts between groups; participants lost to follow-up considered smokers for meta-analysis

Zellweger 2005

Study characteristics	
Methods	Study design: RCT Countries: 12 European countries Setting: 26 clinical trial centres Recruitment: volunteers, healthcare professionals (qualified practising physician or nurse)
Participants	667 smokers (excludes 1 centre enrolling 20 people, and 3 people who took no medication); 64% female; average age 40; average cigarettes per day 23; 32% doctor, 68% nurse
Interventions	• Bupropion SR. 300 mg/day for 7 weeks • Placebo Common components: Brief (10-15 min) motivational support at weekly clinic visits and telephone support one day before TQD, 3 days after TQD, monthly during follow-up
Outcomes	• Smoking cessation. Prolonged abstinence at 52 weeks (starting from week 4). Validated by CO ≤ 10 ppm
Funding Source	GlaxoSmithKline
Author conflicts of interest	None specified
Notes	Continuous abstinence rates and information on adverse events from GlaxoSmithKline data. One centre excluded

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomization method not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Double-blind but further detail not provided

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Zellweger 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number lost to follow-up not stated. Participants with missing assessments or dropouts considered to be smoking

Zincir 2013

Study characteristics	
Methods	Study design: naturalistic clinical follow-up study Country: Turkey Setting: outpatient smoking cessation clinic in a hospital Recruitment method: patients who presented at the smoking cessation outpatient clinic were included in the study on a voluntary basis
Participants	300 participants randomized; average age: 45.8 in those who stopped smoking and 40.8 in those who continued smoking; average boxes of cigarettes per year: 23.62 in those who stopped smoking and 23.26 in those who continued smoking; mean FTND: 5.9 in those who stopped smoking and 6.7 in those who continued smoking
Interventions	• Bupropion 150 mg/day, started a week before the quit day and continued from day 1-3, raised to 300 mg daily on day 4, with this dose maintained until the end of week 12 • Varenicline 0.5 mg daily, raised to 1 mg daily at day 4, then to 2 mg daily at day 8, with this dose maintained until the end of week 12 • Nicotine replacement therapy. Administered using either a nicotine patch or nicotine gum, or a combination of both. Nicotine patches were used in their three forms containing 21, 14 and 7 mg of nicotine, and in cases of excessive nicotine craving, 2 mg nicotine gum was used. For each dose of nicotine patches, 4 weeks of administration in decreasing doses was recommended. The nicotine gum was started between 12 and 24 doses (2 mg) a day and gradually decreased.
Outcomes	• Smoking cessation: not specified • Adverse events: measured for unspecified period
Funding Source	None specified
Author conflicts of interest	None detailed
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "…they were randomized to the pharmacological therapy groups" Comment: No further information given
Allocation concealment (selection bias)	Unclear risk	Quote: "…they were randomized to the pharmacological therapy groups" Comment: no further information given
Blinding (performance bias and detection bias) All outcomes	High risk	Quote: "This was a naturalistic clinical follow-up study." Comment: those involved in the study were therefore unblinded

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Zincir 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	300 participants were randomized and 251 completed the study. Therefore 49/300 (16.3%) were lost to follow-up overall. However, it is impossible to establish the number lost to follow-up by group.
Other bias	High risk	Quote: "no adverse event was reported during the study". This is highly unlikely to be correct. Additionally, there is no explanation of how adverse events were assessed.

AE: adverse event
CBGT: cognitive behavioral group therapy
CBT: cognitive behavioural therapy
CES-D: Center for Epidemiologic Studies Depression Scale
CO: carbon monoxide (in exhaled breath)
COPD: chronic obstructive pulmonary disease
CVD: cardiovascular disease
EOT: end of treatment
FTND: Fagerstrom Test for Nicotine Dependence
FTQ: Fagerstrom Tolerance Questionnaire
ITT: intention-to-treat
MDD: major depressive disorder
MI: myocardial infarction
mins: minutes
NRT: nicotine replacement therapy
ppa: point prevalence abstinence
ppm: parts per million
RCT: randomized controlled trial
RP: relapse prevention
Rx: treatment
SAE: serious adverse event
SAMe: S-Adenosyl-L-Methionine
S-H: self-help
SR: sustained release
TQD: target quit date
VAMC: Veterans Affairs Medical Center

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

Study	Reason for exclusion
Akbarpour 2010	Bupropion - short follow-up
Aryanpur 2016	Arms not matched - different behavioural interventions in each
Banham 2010	Not RCT - review of smoking cessation treatment for people with severe mental illness
Becker 2003	St John's wort - short follow-up (1 month)
Berlin 2005	Befloxatone (reversible monoamine oxidase-B inhibitor) - data not published, treatment reported to have had no effect on abstinence rates
Bloch 2010	Bupropion - trial in people with schizophrenia, short follow-up and cessation not reported
Bowen 1991	Tryptophan - short follow-up Tryptophan 50 mg/kg/day, with high carbohydrate low protein diet (7/1 ratio), versus placebo and low carbohydrate high protein diet (1/1 ratio) for two weeks

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Study	Reason for exclusion
Brauer 2000	Selegiline - only preliminary short-term results available. Six month follow-up planned
Breitling 2008	Trial of practitioner education and financial incentives, or cessation drug costs reimbursement
Brody 2013	Ineligible outcomes - less than six months follow-up and no safety data reported
Carrão 2007	Sertraline - combined with buspirone so effect of sertraline could not be isolated
Chan 2005	Bupropion - case control study in pregnant women
Chandrashekar 2015	Short-term follow-up and no safety assessment
Christenhusz 2012	Not randomized to treatments, only treatment strategies
Cornelius 1997	Fluoxetine - cessation not an outcome. Fluoxetine reduced the amount smoked by depressed alcoholic smokers
Cornelius 1999	Fluoxetine - short-term outcome in a study of depressed alcoholic participants not attempting to quit
Covey 2007	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Croghan 2007	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Cropsey 2015	Randomization to treatment strategy, not actual treatment
Dalack 1995	Fluoxetine - refers to, but does not report on a cessation study
Dale 2002	Bupropion - used for smokeless tobacco cessation, not smoking cessation
Dale 2007	Bupropion - for smokeless tobacco cessation, see Ebbert 2011
Daniela 2008	Sertraline and buspirone - effect of antidepressant confounded with that of anxiolytic
Edwards 1989	Doxepin - short follow-up (2 months)
EUCTR2005-006189-32-AT	Arms not matched
Evins 2008	Bupropion - long-term results not presented due to high loss to follow-up
Fatemi 2005	Bupropion - short-term cross-over trial
Frederick 1997	Venlafaxine - short follow-up (8 weeks)
Gawin 1989	Buspirone - open trial
Gifford 2011	Bupropion - test of behavioural therapy, all participants received bupropion
Glover 2002	Bupropion - used for smokeless tobacco cessation, not smoking cessation
Gold 2002	Bupropion - non-random assignment, participant preference
Grandi 2011	Bupropion - not RCT, review of bupropion use in patients with CVD

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Study	Reason for exclusion
Grassi 2009	Not a RCT, pre-post study of influence of smoking ban on people's selection of smoking cessation treatment
Hall 2009	Bupropion - all participants received bupropion for quitting, test of extended CBT or NRT
Hall 2011	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Hatsukami 2004	Previously included. Harm reduction study. See Lindson-Hawley 2016
Hawk 2008	Bupropion - short follow-up (12 weeks). Compares 1 week to 4 week pre-quit use
Hawk 2015	Interventions not matched - same intervention post-quit date
Hays 2001	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Hays 2009	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Hilberink 2005	Bupropion - test of NRT + counselling, one cluster received bupropion but is not a test of bupropion
Hitsman 1999	Fluoxetine - the majority of participants in this study were also part of the multicentre trial reported in Niaura 2002
Houtsmuller 2002	Selegiline - short-term laboratory study
Hurt 2003	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Hussain 2010	Bupropion - short follow-up, trial in unmotivated smokers
Isgro 2015	Topiramate not an antidepressant
Jacobs 1971	Imipramine - short follow-up. Outcome was reduction in smoking to less than 10% of baseline
Kalman 2004	Bupropion - short follow-up (12 weeks)
Khunrong 2016	Ineligible outcomes
Killen 2006	Previously included. Relapse prevention study. See Livingstone-Banks 2019
Kotz 2009	Nortriptyline - pharmacotherapy was confounded with additional counselling from nurse (control group 1), compared to usual care
Kras 2010	St John's wort - short follow-up
Lawvere 2006	St John's wort - uncontrolled study
Li 2009	Bupropion - short follow-up
Miller 2003	Bupropion - short follow-up (8 weeks)
Monuteaux 2007	Bupropion - participants were adolescent non-smokers, not for cessation
Mooney 2008	Bupropion - short follow-up, bupropion for opioid and tobacco dependence
Mooney 2016	Bupropion same in both arms

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Study	Reason for exclusion
Naranjo 1990	Fluoxetine - study of short-term smoking behaviour
NCT00032084	Trial terminated before completion
NCT00119210	Trial terminated before completion
NCT00136747	Smoking cessation not measured
NCT00136786	Smoking cessation not measured
NCT00158171	Cessation not measured - harm reduction study
NCT00248118	Bupropion - trial was terminated prior to completion
NCT00320697	Pharmacotherpaies not matched
NCT00390923	Selegiline - study terminated early due to lack of efficacy, results available at 9 weeks only
NCT00484692	Bupropion - used as an active control to a psychosocial intervention, cannot estimate pharmacotherapy effect
NCT00580853	Does not measure smoking cessation - ability to resist smoking
NCT00670904	No randomization - participants chose their medication
NCT00936299	Bupropion - no abstinence outcome reported and follow-up only 16 weeks
NCT01850589	Behavioural intervention and pharmacotherapy is different between arms
NCT01965405	All participants in all arms receive the same bupropion treatment
NCT02736474	Both naltrexone and bupropion given together in same arm
NCT03471767	Bupropion given in both arms
NCT03920319	Wrong outcomes
Neumann 2000	Bupropion - smokers randomized to 1 or 2 months of medication (300 mg/day). 91/165 randomized were not included in the analysis, including some 1-month group participants who requested further medication.
Neumann 2002	Bupropion - short-term follow-up. Comparison of 300 mg and 150 mg doses
Niederhofer 2004	Participants are required to be abstinent for at least five days prior to enrolment to trial
Olmstead 1999	Bupropion - all participants received bupropion. Short-term follow-up
Paluck 2006	Bupropion - uncontrolled prospective observational study
Pomerleau 1991	Fluoxetine - no cessation data reported
Raynor 2005	Bupropion - short (90 day) follow-up. Substudy within a larger trial with long-term follow-up, not yet published
Robinson 1991	Buspirone - case series

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Study	Reason for exclusion
Rovina 2003	Bupropion - abstract only, trial report not available. Insufficient information to determine inclusion
Schepis 2006	Bupropion - abstract only, trial report not available. Insufficient information to determine inclusion
Sellers 1987	Zimelidine or citalopram (SSRIs) - placebo-controlled cross-over design study of smoking behaviour and alcohol use in non-depressed heavy drinkers
Sherman 2008	Bupropion - trial of NRT as adjunct to bupropion
Shiffman 2000	Bupropion - placebo-controlled short-term study of effects on craving and withdrawal in participants not wanting to quit smoking permanently
Shoptaw 2008	Bupropion - tested for methamphetamine dependence. Reduction in smoking was a secondary outcome. Only 48/73 participants smoked, quitting not reported.
Sittipunt 2007	Nortriptyline - only 3-month follow-up
Sonntag 2003	Bupropion - abstract only, trial report not available. Insufficient information to determine inclusion
Spring 1995	Fluoxetine - 6-month cessation not reported. Primarily a study of post-cessation weight gain
Stein 1993	Fluoxetine - does not report outcomes from a double-blind study
Steinberg 2009	Bupropion - confounded with nicotine inhaler and treatment duration in comparison with nicotine patch alone
Strayer 2004	Bupropion - all participants prescribed bupropion. Test of behavioural interventions, not bupropion. Adverse event data from author used
Swanson 2003	Bupropion +/- nicotine patch. Unable to confirm correct denominators
Tidey 2009	Bupropion - laboratory study, outcomes included urge to smoke, not cessation
Toll 2007	Bupropion - all participants had same pharmacotherapy
Weinberger 2008	Bupropion for people with bipolar disorder. Short follow-up (8 weeks). Only 5 participants
Weiner 2001	Bupropion - no control group
Winhusen 2012	Bupropion confounded by other agents
Zernig 2008	Bupropion - used as an active control to a psychosocial intervention, cannot estimate pharmacotherapy effect
ZYB30011	Bupropion - follow-up only to end of treatment (7 weeks)

CBT: cognitive behavioural therapy; NRT: nicotine replacement therapy; CVD: cardiovascular disease; RCT: randomized controlled trial; SSRI: selective serotonin reuptake inhibitor

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

NCT03326128

Study name	High dose bupropion for smoking cessation

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NCT03326128 *(Continued)*

Methods	Triple-blind randomized trial
Participants	300 heavy smokers who also experience psychiatric symptoms
Interventions	• Bupropion 300 mg 4 weeks before and 4 weeks after TQD • Bupropion 450 mg 4 weeks before and 4 weeks after TQD Common components: standard smoking cessation counselling for 8 weeks
Outcomes	• Smoking cessation: point prevalence abstinence at 26 weeks post-quit date. Validated by self-report • Self report of smoking status
Starting date	May 2019
Contact information	Lauren Whitted, 323-442-1197, lwhitted@usc.edulwhitted@usc.edu
Notes	

NCT03342027

Study name	Smoking cessation interventions for people living with HIV in Nairobi, Kenya
Methods	2 x 2 factorial, double-blind randomized controlled trial
Participants	300 participants people living with HIV, who smoke and who are receiving care in a methadone maintenance program will be randomized
Interventions	• Bupropion and positively smoke free (an 8-session tailored behavioural intervention for smokers living with HIV) • Bupropion and standard of care (brief advice to quit) • Placebo and positively smoke free • Placebo and standard of care
Outcomes	Smoking cessation: 7-day point prevalence abstinence at 36 weeks. Validated by expired CO < 7 ppm
Starting date	20 August 2019
Contact information	Wendy Potts, (410) 706-2490, wpotts@som.umaryland.edu
Notes	

Zawertailo 2018

Study name	The Medication Aids for Tobacco Cessation and Health (MATCH) Study
Methods	Randomized, open-label, parallel-arm trial
Participants	968 smokers motivated to quit

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Zawertailo 2018 *(Continued)*

Interventions	• Bupropion 150 mg once daily for first three days, then twice daily for the remainder of 12 weeks. Starting 7 days prior to TQD • Varenicline 0.5 mg once daily for first three days, then 0.5 mg twice daily for next four days, then 1 mg twice daily for the remainder of 12 weeks. Starting 7 days prior to TQD Common components: weekly motivational emails
Outcomes	Smoking cessation: continuous abstinence at 52 weeks. Validated by saliva cotinine
Starting date	1 May 2014
Contact information	Laurie Zawertailo, 1 416 535 8501 ext 77422, laurie.zawertailo@camh.ca
Notes	

TQD: target quit date

DATA AND ANALYSES

Comparison 1. Bupropion versus placebo/no pharmacotherapy control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Smoking cessation	46	17866	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.77]
1.2 Smoking cessation - subgroup by level of behavioural support	46	17866	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.77]
1.2.1 Multisession group behavioural support	10	2001	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.44, 2.16]
1.2.2 Multisession individual counselling	31	15033	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.50, 1.77]
1.2.3 Low-intensity support	1	47	Risk Ratio (M-H, Fixed, 95% CI)	2.88 [0.32, 25.68]
1.2.4 Not specified	4	785	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.00, 2.00]
1.3 Smoking cessation - subgroup by mental health disorders	46	17866	Risk Ratio (M-H, Fixed, 95% CI)	1.64 [1.52, 1.77]
1.3.1 Psychiatric conditions	5	2180	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.30, 2.15]
1.3.2 Non-psychiatric	42	15686	Risk Ratio (M-H, Fixed, 95% CI)	1.63 [1.51, 1.77]
1.4 Adverse events	19	10893	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.11, 1.18]
1.5 Serious adverse events	21	10625	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.90, 1.48]
1.6 Psychiatric adverse events	6	4439	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.15, 1.37]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Seizures	13	7344	Risk Ratio (M-H, Fixed, 95% CI)	2.93 [0.64, 13.37]
1.8 Overdoses	5	5585	Risk Ratio (M-H, Fixed, 95% CI)	2.15 [0.23, 19.86]
1.9 Suicide attempts	10	6484	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.29, 8.92]
1.10 Death by suicide	14	8822	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.26]
1.11 All-cause mortality	21	11403	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.42, 1.87]
1.12 Anxiety	11	7406	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.21, 1.67]
1.13 Insomnia	22	11077	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.62, 1.96]
1.14 Dropouts due to drug	25	12340	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.21, 1.56]

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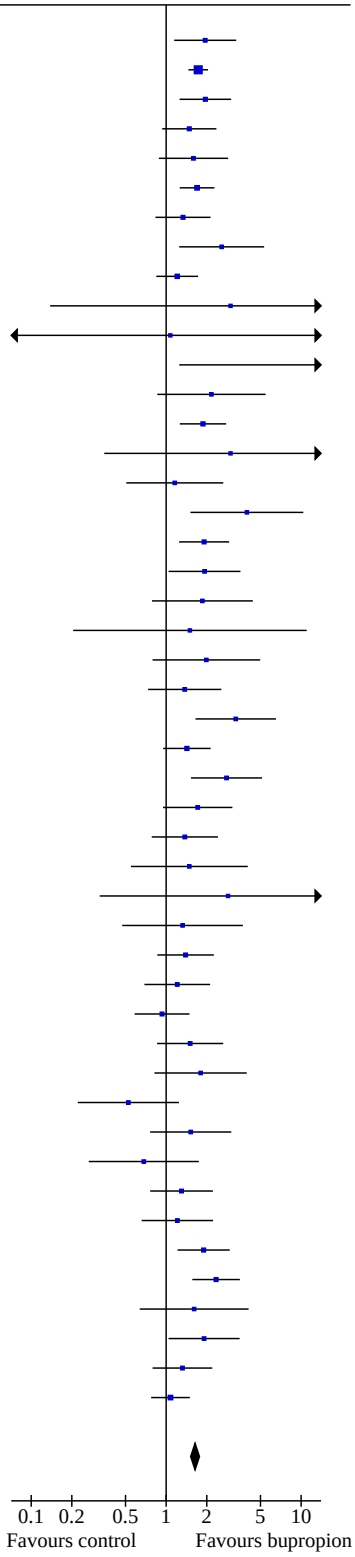
Analysis 1.1. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 1: Smoking cessation

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahluwalia 2002	37	300	19	300	2.0%	1.95 [1.15 , 3.31]
Anthenelli 2016	330	2034	191	2035	19.9%	1.73 [1.46 , 2.04]
Aubin 2004	85	340	21	164	3.0%	1.95 [1.26 , 3.03]
Brown 2007	38	255	27	269	2.7%	1.48 [0.93 , 2.36]
Cinciripini 2013	23	102	15	106	1.5%	1.59 [0.88 , 2.88]
Collins 2004	93	285	52	270	5.6%	1.69 [1.26 , 2.28]
Cox 2012	36	270	27	270	2.8%	1.33 [0.83 , 2.13]
Dalsgarð 2004	40	221	8	114	1.1%	2.58 [1.25 , 5.32]
Eisenberg 2013	49	183	43	194	4.4%	1.21 [0.85 , 1.73]
Evins 2001	1	9	0	9	0.1%	3.00 [0.14 , 65.16]
Evins 2005	1	27	1	29	0.1%	1.07 [0.07 , 16.33]
Ferry 1992	10	23	0	22	0.1%	20.13 [1.25 , 324.00]
Ferry 1994	13	95	6	95	0.6%	2.17 [0.86 , 5.46]
Fossati 2007	101	400	26	193	3.7%	1.87 [1.26 , 2.78]
George 2002	3	16	1	16	0.1%	3.00 [0.35 , 25.87]
Gilbert 2019	9	34	8	35	0.8%	1.16 [0.51 , 2.65]
Gonzales 2001	20	226	5	224	0.5%	3.96 [1.51 , 10.38]
Gonzales 2006	53	329	29	344	3.0%	1.91 [1.25 , 2.93]
Haggström 2006	22	53	11	51	1.2%	1.92 [1.04 , 3.55]
Hall 2002	13	73	7	73	0.7%	1.86 [0.79 , 4.39]
Hertzberg 2001	3	10	1	5	0.1%	1.50 [0.20 , 11.00]
Holt 2005	19	88	5	46	0.7%	1.99 [0.79 , 4.98]
Hurt 1997	21	156	15	153	1.6%	1.37 [0.74 , 2.56]
Jorenby 1999	45	244	9	160	1.1%	3.28 [1.65 , 6.52]
Jorenby 2006	50	342	35	341	3.7%	1.42 [0.95 , 2.14]
Levine 2010	42	195	12	156	1.4%	2.80 [1.53 , 5.13]
McCarthy 2008 (1)	24	113	15	121	1.5%	1.71 [0.95 , 3.10]
McCarthy 2008 (2)	24	116	17	113	1.8%	1.38 [0.78 , 2.42]
Muramoto 2007	9	104	6	103	0.6%	1.49 [0.55 , 4.02]
Myles 2004	3	24	1	23	0.1%	2.88 [0.32 , 25.68]
Nides 2006	8	128	6	127	0.6%	1.32 [0.47 , 3.70]
Piper 2007	42	224	21	156	2.6%	1.39 [0.86 , 2.26]
Piper 2009	84	264	10	38	1.8%	1.21 [0.69 , 2.12]
Planer 2011	23	75	25	76	2.6%	0.93 [0.58 , 1.49]
Rigotti 2006	25	124	17	127	1.8%	1.51 [0.86 , 2.65]
Rovina 2009	14	40	7	36	0.8%	1.80 [0.82 , 3.96]
Schmitz 2007	7	78	13	76	1.4%	0.52 [0.22 , 1.24]
Selby 2003	18	141	12	143	1.2%	1.52 [0.76 , 3.04]
Simon 2009	6	41	9	42	0.9%	0.68 [0.27 , 1.75]
SMK20001	26	143	20	143	2.1%	1.30 [0.76 , 2.22]
Tashkin 2001	21	204	17	200	1.8%	1.21 [0.66 , 2.23]
Tonnesen 2003	111	527	20	180	3.1%	1.90 [1.21 , 2.96]
Tonstad 2003	68	313	29	313	3.0%	2.34 [1.56 , 3.52]
Uyar 2007	13	50	5	31	0.6%	1.61 [0.64 , 4.08]
Wagena 2005	24	86	13	89	1.3%	1.91 [1.04 , 3.50]
Wittchen 2011	22	108	27	175	2.2%	1.32 [0.79 , 2.20]
Zellweger 2005	117	501	36	166	5.6%	1.08 [0.77 , 1.50]
Total (95% CI)		**9714**		**8152**	**100.0%**	**1.64 [1.52 , 1.77]**
Total events:	1846		900			

Heterogeneity: Chi² = 54.22, df = 46 (P = 0.19); I² = 15%
Test for overall effect: Z = 12.91 (P < 0.00001)
Test for subgroup differences: Not applicable



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Analysis 1.1. (Continued)

Test for overall effect: Z = 12.91 (P < 0.00001)
Test for subgroup differences: Not applicable

Favours control Favours bupropion

Footnotes

(1) Counselling arms

(2) Pscyhoeducation arms

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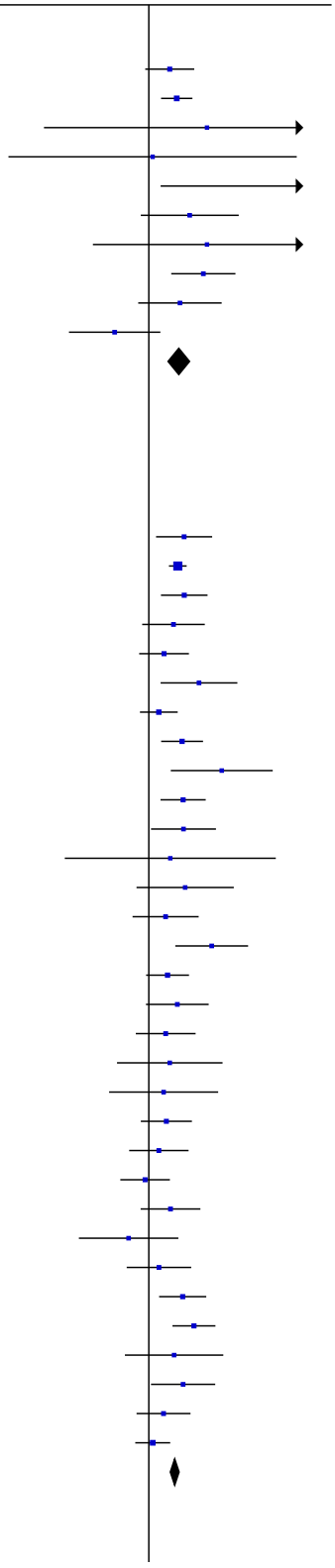
Analysis 1.2. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 2: Smoking cessation - subgroup by level of behavioural support

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Multisession group behavioural support						
Brown 2007	38	255	27	269	2.7%	1.48 [0.93 , 2.36]
Collins 2004	93	285	52	270	5.6%	1.69 [1.26 , 2.28]
Evins 2001	1	9	0	9	0.1%	3.00 [0.14 , 65.16]
Evins 2005	1	27	1	29	0.1%	1.07 [0.07 , 16.33]
Ferry 1992	10	23	0	22	0.1%	20.13 [1.25 , 324.00]
Ferry 1994	13	95	6	95	0.6%	2.17 [0.86 , 5.46]
George 2002	3	16	1	16	0.1%	3.00 [0.35 , 25.87]
Levine 2010	42	195	12	156	1.4%	2.80 [1.53 , 5.13]
Rovina 2009	14	40	7	36	0.8%	1.80 [0.82 , 3.96]
Schmitz 2007	7	78	13	76	1.4%	0.52 [0.22 , 1.24]
Subtotal (95% CI)		**1023**		**978**	**12.8%**	**1.76 [1.44 , 2.16]**
Total events:	222		119			
Heterogeneity: Chi² = 14.03, df = 9 (P = 0.12); I² = 36%						
Test for overall effect: Z = 5.47 (P < 0.00001)						
1.2.2 Multisession individual counselling						
Ahluwalia 2002	37	300	19	300	2.0%	1.95 [1.15 , 3.31]
Anthenelli 2016	330	2034	191	2035	19.9%	1.73 [1.46 , 2.04]
Aubin 2004	85	340	21	164	3.0%	1.95 [1.26 , 3.03]
Cinciripini 2013	23	102	15	106	1.5%	1.59 [0.88 , 2.88]
Cox 2012	36	270	27	270	2.8%	1.33 [0.83 , 2.13]
Dalsgarð 2004	40	221	8	114	1.1%	2.58 [1.25 , 5.32]
Eisenberg 2013	49	183	43	194	4.4%	1.21 [0.85 , 1.73]
Fossati 2007	101	400	26	193	3.7%	1.87 [1.26 , 2.78]
Gonzales 2001	20	226	5	224	0.5%	3.96 [1.51 , 10.38]
Gonzales 2006	53	329	29	344	3.0%	1.91 [1.25 , 2.93]
Haggsträm 2006	22	53	11	51	1.2%	1.92 [1.04 , 3.55]
Hertzberg 2001	3	10	1	5	0.1%	1.50 [0.20 , 11.00]
Holt 2005	19	88	5	46	0.7%	1.99 [0.79 , 4.98]
Hurt 1997	21	156	15	153	1.6%	1.37 [0.74 , 2.56]
Jorenby 1999	45	244	9	160	1.1%	3.28 [1.65 , 6.52]
Jorenby 2006	50	342	35	341	3.7%	1.42 [0.95 , 2.14]
McCarthy 2008 (1)	24	113	15	121	1.5%	1.71 [0.95 , 3.10]
McCarthy 2008 (2)	24	116	17	113	1.8%	1.38 [0.78 , 2.42]
Muramoto 2007	9	104	6	103	0.6%	1.49 [0.55 , 4.02]
Nides 2006	8	128	6	127	0.6%	1.32 [0.47 , 3.70]
Piper 2007	42	224	21	156	2.6%	1.39 [0.86 , 2.26]
Piper 2009	84	264	10	38	1.8%	1.21 [0.69 , 2.12]
Planer 2011	23	75	25	76	2.6%	0.93 [0.58 , 1.49]
Rigotti 2006	25	124	17	127	1.8%	1.51 [0.86 , 2.65]
Simon 2009	6	41	9	42	0.9%	0.68 [0.27 , 1.75]
Tashkin 2001	21	204	17	200	1.8%	1.21 [0.66 , 2.23]
Tonnesen 2003	111	527	20	180	3.1%	1.90 [1.21 , 2.96]
Tonstad 2003	68	313	29	313	3.0%	2.34 [1.56 , 3.52]
Uyar 2007	13	50	5	31	0.6%	1.61 [0.64 , 4.08]
Wagena 2005	24	86	13	89	1.3%	1.91 [1.04 , 3.50]
Wittchen 2011	22	108	27	175	2.2%	1.32 [0.79 , 2.20]
Zellweger 2005	117	501	36	166	5.6%	1.08 [0.77 , 1.50]
Subtotal (95% CI)		**8276**		**6757**	**82.2%**	**1.63 [1.50 , 1.77]**
Total events:	1555		733			
Heterogeneity: Chi² = 38.32, df = 31 (P = 0.17); I² = 19%						
Test for overall effect: Z = 11.55 (P < 0.00001)						



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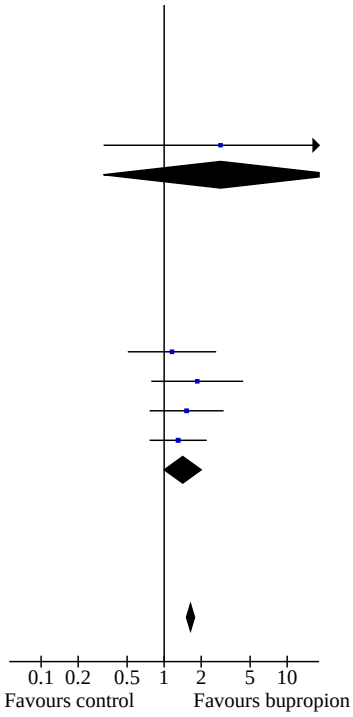
Analysis 1.2. (Continued)

Heterogeneity: Chi² = 38.32, df = 31 (P = 0.17); I² = 19%
Test for overall effect: Z = 11.55 (P < 0.00001)

1.2.3 Low-intensity support						
Myles 2004	3	24	1	23	0.1%	2.88 [0.32 , 25.68]
Subtotal (95% CI)		**24**		**23**	**0.1%**	**2.88 [0.32 , 25.68]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.2.4 Not specified						
Gilbert 2019	9	34	8	35	0.8%	1.16 [0.51 , 2.65]
Hall 2002	13	73	7	73	0.7%	1.86 [0.79 , 4.39]
Selby 2003	18	141	12	143	1.2%	1.52 [0.76 , 3.04]
SMK20001	26	143	20	143	2.1%	1.30 [0.76 , 2.22]
Subtotal (95% CI)		**391**		**394**	**4.9%**	**1.42 [1.00 , 2.00]**
Total events:	66		47			
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
Total (95% CI)		**9714**		**8152**	**100.0%**	**1.64 [1.52 , 1.77]**
Total events:	1846		900			
Heterogeneity: Chi² = 54.22, df = 46 (P = 0.19); I² = 15%						
Test for overall effect: Z = 12.91 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.45, df = 3 (P = 0.70), I² = 0%						



Footnotes
(1) Counselling arms
(2) Pscyhoeducation arms

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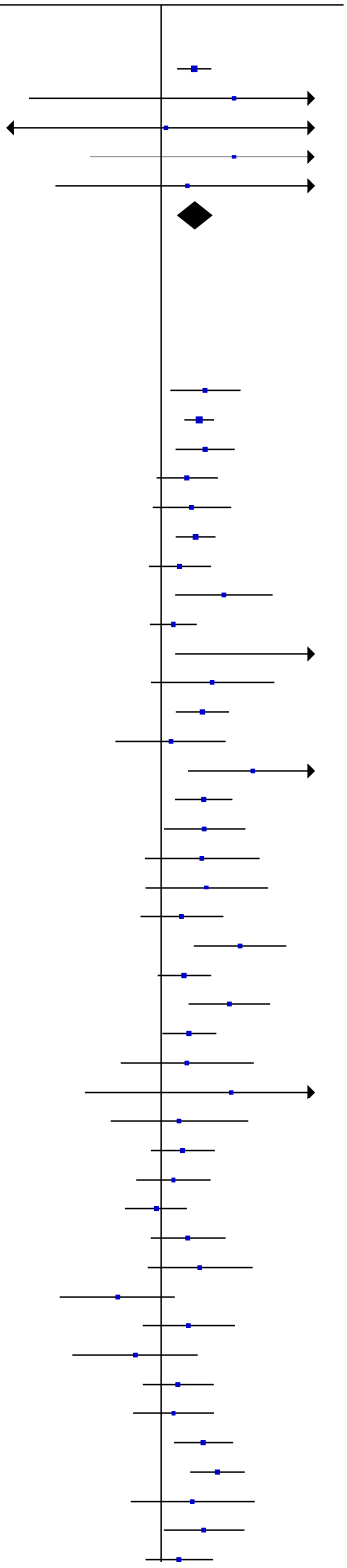
Analysis 1.3. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 3: Smoking cessation - subgroup by mental health disorders

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Psychiatric conditions						
Anthenelli 2016 (1)	142	1033	85	1026	8.9%	1.66 [1.29 , 2.14]
Evins 2001 (2)	1	9	0	9	0.1%	3.00 [0.14 , 65.16]
Evins 2005 (2)	1	27	1	29	0.1%	1.07 [0.07 , 16.33]
George 2002 (2)	3	16	1	16	0.1%	3.00 [0.35 , 25.87]
Hertzberg 2001 (3)	3	10	1	5	0.1%	1.50 [0.20 , 11.00]
Subtotal (95% CI)		**1095**		**1085**	**9.3%**	**1.67 [1.30 , 2.15]**
Total events:	150		88			
Heterogeneity: Chi² = 0.54, df = 4 (P = 0.97); I² = 0%						
Test for overall effect: Z = 4.06 (P < 0.0001)						
1.3.2 Non-psychiatric						
Ahluwalia 2002	37	300	19	300	2.0%	1.95 [1.15 , 3.31]
Anthenelli 2016 (4)	188	1001	106	1009	11.0%	1.79 [1.43 , 2.23]
Aubin 2004	85	340	21	164	3.0%	1.95 [1.26 , 3.03]
Brown 2007	38	255	27	269	2.7%	1.48 [0.93 , 2.36]
Cinciripini 2013	23	102	15	106	1.5%	1.59 [0.88 , 2.88]
Collins 2004	93	285	52	270	5.6%	1.69 [1.26 , 2.28]
Cox 2012	36	270	27	270	2.8%	1.33 [0.83 , 2.13]
Dalsgarð 2004	40	221	8	114	1.1%	2.58 [1.25 , 5.32]
Eisenberg 2013	49	183	43	194	4.4%	1.21 [0.85 , 1.73]
Ferry 1992	10	23	0	22	0.1%	20.13 [1.25 , 324.00]
Ferry 1994	13	95	6	95	0.6%	2.17 [0.86 , 5.46]
Fossati 2007	101	400	26	193	3.7%	1.87 [1.26 , 2.78]
Gilbert 2019	9	34	8	35	0.8%	1.16 [0.51 , 2.65]
Gonzales 2001	20	226	5	224	0.5%	3.96 [1.51 , 10.38]
Gonzales 2006	53	329	29	344	3.0%	1.91 [1.25 , 2.93]
Haggsträm 2006	22	53	11	51	1.2%	1.92 [1.04 , 3.55]
Hall 2002	13	73	7	73	0.7%	1.86 [0.79 , 4.39]
Holt 2005	19	88	5	46	0.7%	1.99 [0.79 , 4.98]
Hurt 1997	21	156	15	153	1.6%	1.37 [0.74 , 2.56]
Jorenby 1999	45	244	9	160	1.1%	3.28 [1.65 , 6.52]
Jorenby 2006	50	342	35	341	3.7%	1.42 [0.95 , 2.14]
Levine 2010	42	195	12	156	1.4%	2.80 [1.53 , 5.13]
McCarthy 2008	48	229	32	234	3.3%	1.53 [1.02 , 2.31]
Muramoto 2007	9	104	6	103	0.6%	1.49 [0.55 , 4.02]
Myles 2004	3	24	1	23	0.1%	2.88 [0.32 , 25.68]
Nides 2006	8	128	6	127	0.6%	1.32 [0.47 , 3.70]
Piper 2007	42	224	21	156	2.6%	1.39 [0.86 , 2.26]
Piper 2009	84	264	10	38	1.8%	1.21 [0.69 , 2.12]
Planer 2011	23	75	25	76	2.6%	0.93 [0.58 , 1.49]
Rigotti 2006	25	124	17	127	1.8%	1.51 [0.86 , 2.65]
Rovina 2009	14	40	7	36	0.8%	1.80 [0.82 , 3.96]
Schmitz 2007	7	78	13	76	1.4%	0.52 [0.22 , 1.24]
Selby 2003	18	141	12	143	1.2%	1.52 [0.76 , 3.04]
Simon 2009	6	41	9	42	0.9%	0.68 [0.27 , 1.75]
SMK20001	26	143	20	143	2.1%	1.30 [0.76 , 2.22]
Tashkin 2001	21	204	17	200	1.8%	1.21 [0.66 , 2.23]
Tonnesen 2003	111	527	20	180	3.1%	1.90 [1.21 , 2.96]
Tonstad 2003	68	313	29	313	3.0%	2.34 [1.56 , 3.52]
Uyar 2007	13	50	5	31	0.6%	1.61 [0.64 , 4.08]
Wagena 2005	24	86	13	89	1.3%	1.91 [1.04 , 3.50]
Wittchen 2011	22	108	27	175	2.2%	1.32 [0.79 , 2.20]



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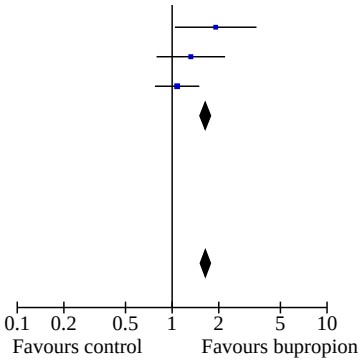
Analysis 1.3. (Continued)

Wagena 2005	24	86	13	89	1.3%	1.91 [1.04 , 3.50]
Wittchen 2011	22	108	27	175	2.2%	1.32 [0.79 , 2.20]
Zellweger 2005	117	501	36	166	5.6%	1.08 [0.77 , 1.50]
Subtotal (95% CI)		**8619**		**7067**	**90.7%**	**1.63 [1.51 , 1.77]**
Total events:	1696		812			
Heterogeneity: Chi² = 53.52, df = 41 (P = 0.09); I² = 23%						
Test for overall effect: Z = 12.27 (P < 0.00001)						
Total (95% CI)		**9714**		**8152**	**100.0%**	**1.64 [1.52 , 1.77]**
Total events:	1846		900			
Heterogeneity: Chi² = 54.15, df = 46 (P = 0.19); I² = 15%						
Test for overall effect: Z = 12.92 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						



Footnotes

(1) Psychiatric cohort

(2) Schizophrenia

(3) PTSD

(4) Non-psychiatric cohort

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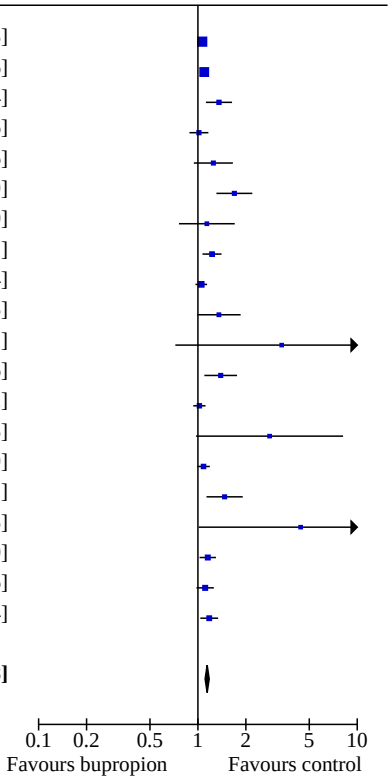
Analysis 1.4. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 4: Adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	742	1017	696	1015	23.4%	1.06 [1.01 , 1.13]
Anthenelli 2016 (2)	704	989	649	999	21.7%	1.10 [1.03 , 1.16]
Aubin 2004	208	340	74	164	3.4%	1.36 [1.12 , 1.64]
Cinciripini 2013	82	102	84	106	2.8%	1.01 [0.88 , 1.16]
Cox 2012	80	270	64	270	2.2%	1.25 [0.94 , 1.66]
Fossati 2007	179	400	51	193	2.3%	1.69 [1.31 , 2.19]
Gilbert 2019	21	34	19	35	0.6%	1.14 [0.76 , 1.70]
Gonzales 2001	162	226	131	224	4.4%	1.23 [1.07 , 1.41]
Gonzales 2006	258	329	257	344	8.4%	1.05 [0.97 , 1.14]
Gray 2011	47	73	29	61	1.1%	1.35 [0.99 , 1.85]
Kalman 2011	7	73	2	70	0.1%	3.36 [0.72 , 15.61]
McCarthy 2008	102	229	75	234	2.5%	1.39 [1.10 , 1.76]
Nides 2006	113	126	108	123	3.7%	1.02 [0.93 , 1.12]
Simon 2009	11	42	4	43	0.1%	2.82 [0.97 , 8.15]
SMK20001	129	143	119	143	4.0%	1.08 [0.99 , 1.19]
Tashkin 2001	90	204	60	200	2.0%	1.47 [1.13 , 1.91]
Tidey 2011	7	23	2	29	0.1%	4.41 [1.01 , 19.25]
Tonnesen 2003	395	527	117	180	5.9%	1.15 [1.02 , 1.30]
Tonstad 2003	201	313	181	313	6.1%	1.11 [0.98 , 1.26]
Zellweger 2005	379	518	105	169	5.3%	1.18 [1.04 , 1.34]
Total (95% CI)		**5978**		**4915**	**100.0%**	**1.14 [1.11 , 1.18]**
Total events:	3917		2827			

Heterogeneity: Chi² = 51.53, df = 19 (P < 0.0001); I² = 63%
Test for overall effect: Z = 8.99 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

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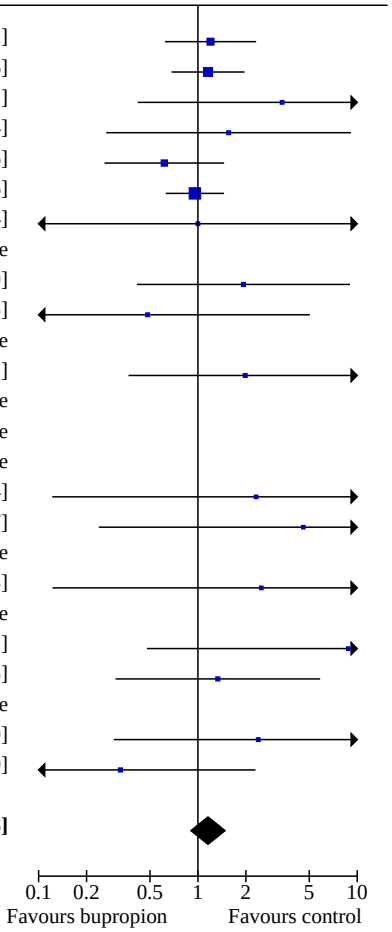
Analysis 1.5. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 5: Serious adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	19	989	16	999	14.3%	1.20 [0.62 , 2.32]
Anthenelli 2016 (2)	29	1017	25	1015	22.5%	1.16 [0.68 , 1.96]
Aubin 2004	7	340	1	164	1.2%	3.38 [0.42 , 27.22]
Cinciripini 2013	3	102	2	106	1.8%	1.56 [0.27 , 9.14]
Cox 2012	8	270	13	270	11.7%	0.62 [0.26 , 1.46]
Eisenberg 2013	34	192	37	200	32.6%	0.96 [0.63 , 1.46]
Ferry 1992	1	23	1	23	0.9%	1.00 [0.07 , 15.04]
Ferry 1994	0	94	0	93		Not estimable
Fossati 2007	8	400	2	193	2.4%	1.93 [0.41 , 9.00]
George 2008	1	30	2	29	1.8%	0.48 [0.05 , 5.05]
Gilbert 2019	0	34	0	35		Not estimable
Gonzales 2001	4	226	2	224	1.8%	1.98 [0.37 , 10.71]
Haggsträm 2006	0	53	0	51		Not estimable
Hurt 1997 (3)	0	153	0	51		Not estimable
Hurt 1997 (4)	0	153	0	51		Not estimable
Hurt 1997 (5)	3	156	0	51	0.7%	2.32 [0.12 , 44.14]
Jorenby 1999	3	243	0	159	0.5%	4.59 [0.24 , 88.27]
Kalman 2011	0	73	0	70		Not estimable
Muramoto 2007 (6)	2	105	0	52	0.6%	2.50 [0.12 , 51.15]
Muramoto 2007 (7)	0	104	0	51		Not estimable
Nides 2006	4	126	0	123	0.5%	8.79 [0.48 , 161.51]
SMK20001	4	143	3	143	2.7%	1.33 [0.30 , 5.85]
Tidey 2011	0	23	0	29		Not estimable
Tonnesen 2003	7	527	1	180	1.3%	2.39 [0.30 , 19.30]
Zellweger 2005	2	518	2	169	2.7%	0.33 [0.05 , 2.30]
Total (95% CI)		**6094**		**4531**	**100.0%**	**1.16 [0.90 , 1.48]**
Total events:	139		107			

Heterogeneity: Chi² = 10.59, df = 16 (P = 0.83); I² = 0%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



Footnotes

(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(6) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control grou
(7) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control grou

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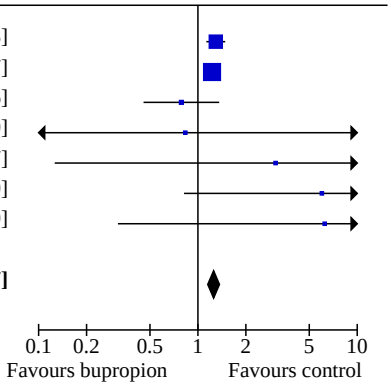
Analysis 1.6. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 6: Psychiatric adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	332	989	259	999	40.8%	1.29 [1.13 , 1.48]
Anthenelli 2016 (2)	435	1017	354	1015	56.1%	1.23 [1.10 , 1.37]
Gilbert 2019	13	34	17	35	2.7%	0.79 [0.46 , 1.36]
Karam-Hage 2011	1	6	1	5	0.2%	0.83 [0.07 , 10.20]
Sheng 2013	1	127	0	130	0.1%	3.07 [0.13 , 74.67]
Singh 2010	6	15	1	15	0.2%	6.00 [0.82 , 44.00]
Tidey 2011	2	23	0	29	0.1%	6.25 [0.31 , 124.10]
Total (95% CI)		**2211**		**2228**	**100.0%**	**1.25 [1.15 , 1.37]**
Total events:	790		632			

Heterogeneity: Chi² = 7.05, df = 6 (P = 0.32); I² = 15%
Test for overall effect: Z = 5.25 (P < 0.00001)
Test for subgroup differences: Not applicable

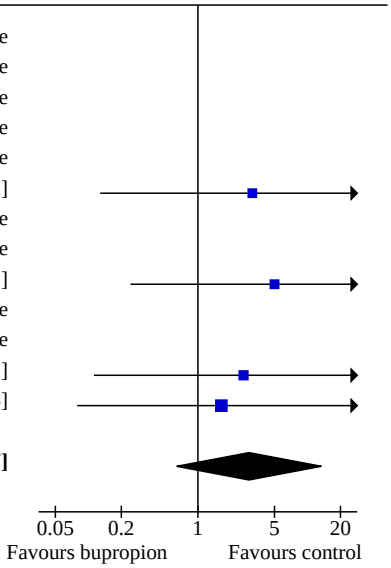


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

Analysis 1.7. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 7: Seizures

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	0	2006	0	2014		Not estimable
Cinciripini 2013	0	102	0	106		Not estimable
Dalsgarð 2004	0	221	0	114		Not estimable
Eisenberg 2013	0	192	0	200		Not estimable
Gonzales 2001	0	226	0	224		Not estimable
Gonzales 2006	1	329	0	344	21.5%	3.14 [0.13 , 76.72]
Gray 2011	0	73	0	61		Not estimable
Myles 2004	0	14	0	10		Not estimable
Nides 2006	2	126	0	126	22.0%	5.00 [0.24 , 103.11]
Rovina 2009	0	40	0	36		Not estimable
Tidey 2011	0	23	0	29		Not estimable
Weiner 2012	1	22	0	19	23.5%	2.61 [0.11 , 60.51]
Zellweger 2005	2	518	0	169	33.1%	1.64 [0.08 , 33.95]
Total (95% CI)		**3892**		**3452**	**100.0%**	**2.93 [0.64 , 13.37]**
Total events:	6		0			

Heterogeneity: Chi² = 0.27, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric and non-psychiatric cohorts combined

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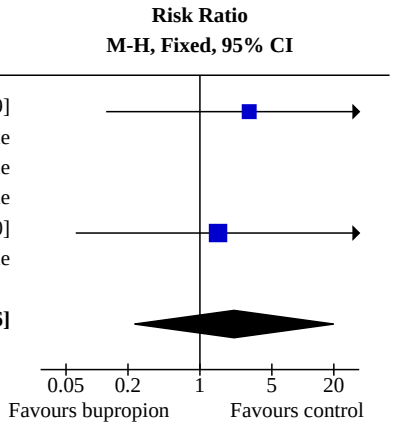
Analysis 1.8. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 8: Overdoses

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	2006	0	2014	42.8%	3.01 [0.12 , 73.89]
Cinciripini 2013	0	102	0	106		Not estimable
Fossati 2007	0	400	0	193		Not estimable
Gonzales 2001	0	226	0	224		Not estimable
Muramoto 2007 (2)	1	105	0	52	57.2%	1.50 [0.06 , 36.20]
Muramoto 2007 (3)	0	105	0	52		Not estimable
Total (95% CI)		**2944**		**2641**	**100.0%**	**2.15 [0.23 , 19.86]**
Total events:	2		0			

Heterogeneity: Chi² = 0.09, df = 1 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Footnotes

(1) Psychiatric and non-psychiatric cohort combined
(2) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control group
(3) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control group

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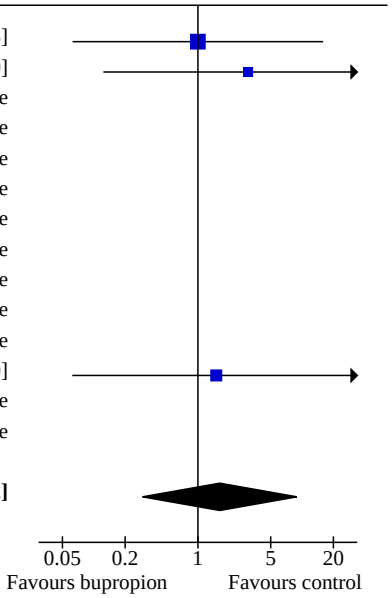
Analysis 1.9. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 9: Suicide attempts

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	1017	1	1015	46.2%	1.00 [0.06 , 15.93]
Anthenelli 2016 (2)	1	989	0	999	23.0%	3.03 [0.12 , 74.30]
Cinciripini 2013	0	102	0	106		Not estimable
Gonzales 2001	0	226	0	224		Not estimable
Gray 2011	0	73	0	61		Not estimable
Hurt 1997 (3)	0	153	0	51		Not estimable
Hurt 1997 (4)	0	156	0	51		Not estimable
Hurt 1997 (5)	0	153	0	51		Not estimable
Jorenby 1999	0	243	0	159		Not estimable
Kalman 2011	0	73	0	70		Not estimable
Muramoto 2007 (6)	0	105	0	51		Not estimable
Muramoto 2007 (7)	1	105	0	52	30.8%	1.50 [0.06 , 36.20]
Planer 2011	0	73	0	74		Not estimable
Tidey 2011	0	23	0	29		Not estimable
Total (95% CI)		**3491**		**2993**	**100.0%**	**1.62 [0.29 , 8.92]**
Total events:	3		1			

Heterogeneity: Chi² = 0.27, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable



Footnotes

(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(6) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control group
(7) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control group

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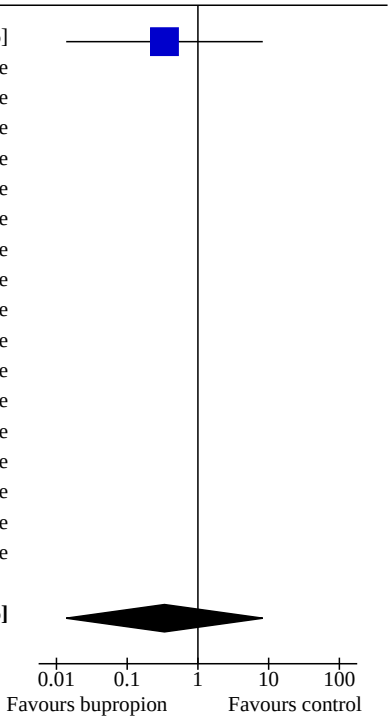
Analysis 1.10. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 10: Death by suicide

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	0	989	1	999	100.0%	0.34 [0.01 , 8.26]
Anthenelli 2016 (2)	0	1017	0	1015		Not estimable
Cinciripini 2013	0	102	0	106		Not estimable
Eisenberg 2013	0	192	0	200		Not estimable
Fossati 2007	0	400	0	193		Not estimable
Gonzales 2001	0	226	0	224		Not estimable
Gonzales 2006	0	329	0	344		Not estimable
Gray 2011	0	73	0	61		Not estimable
Hurt 1997 (3)	0	153	0	51		Not estimable
Hurt 1997 (4)	0	153	0	51		Not estimable
Hurt 1997 (5)	0	156	0	51		Not estimable
Jorenby 1999	0	243	0	159		Not estimable
Jorenby 2006	0	340	0	340		Not estimable
Kalman 2011	0	73	0	70		Not estimable
Muramoto 2007 (6)	0	105	0	52		Not estimable
Muramoto 2007 (7)	0	105	0	51		Not estimable
Planer 2011	0	73	0	74		Not estimable
Tidey 2011	0	23	0	29		Not estimable
Total (95% CI)		**4752**		**4070**	**100.0%**	**0.34 [0.01 , 8.26]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(6) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control grou
(7) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control grou

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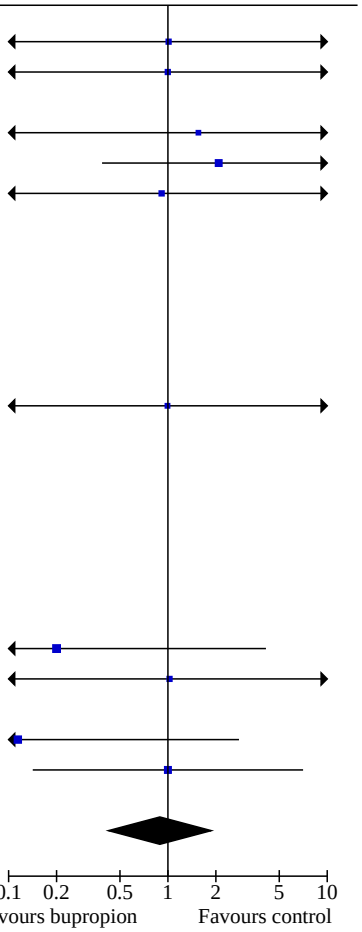
Analysis 1.11. Comparison 1: Bupropion versus placebo/ no pharmacotherapy control, Outcome 11: All-cause mortality

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	989	1	999	7.0%	1.01 [0.06 , 16.13]
Anthenelli 2016 (2)	1	1017	1	1015	7.1%	1.00 [0.06 , 15.93]
Cinciripini 2013	0	102	0	106		Not estimable
Dalsgarð 2004	1	221	0	114	4.7%	1.55 [0.06 , 37.85]
Eisenberg 2013	4	192	2	200	13.9%	2.08 [0.39 , 11.24]
Ferry 1992	1	23	1	21	7.4%	0.91 [0.06 , 13.69]
Ferry 1994	0	94	0	93		Not estimable
Fossati 2007	0	400	0	193		Not estimable
Gonzales 2001	0	226	0	224		Not estimable
Gonzales 2006	0	329	0	344		Not estimable
Hurt 1997 (3)	0	153	0	51		Not estimable
Hurt 1997 (4)	0	153	0	51		Not estimable
Hurt 1997 (5)	1	156	0	51	5.3%	0.99 [0.04 , 24.02]
Jorenby 1999	0	243	0	159		Not estimable
Jorenby 2006	0	340	0	340		Not estimable
Kalman 2011	0	73	0	70		Not estimable
Muramoto 2007 (6)	0	105	0	52		Not estimable
Muramoto 2007 (7)	0	105	0	51		Not estimable
Nides 2006	0	126	0	123		Not estimable
Planer 2011	0	73	0	74		Not estimable
Rigotti 2006	0	124	2	124	17.7%	0.20 [0.01 , 4.12]
Simon 2009	1	42	1	43	7.0%	1.02 [0.07 , 15.84]
SMK20001	0	143	0	143		Not estimable
Tonnesen 2003	0	527	1	180	15.8%	0.11 [0.00 , 2.79]
Tonstad 2003	2	313	2	313	14.2%	1.00 [0.14 , 7.05]
Total (95% CI)		**6269**		**5134**	**100.0%**	**0.89 [0.42 , 1.87]**
Total events:	12		11			



Heterogeneity: Chi² = 3.66, df = 9 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.76)
Test for subgroup differences: Not applicable

Footnotes

(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(6) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control group
(7) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control group

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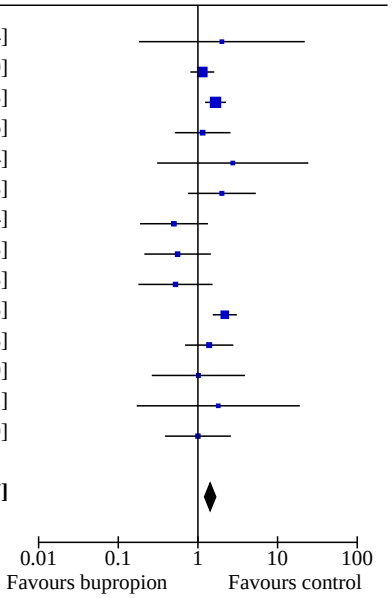
Analysis 1.12. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 12: Anxiety

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahluwalia 2002	2	300	1	300	0.4%	2.00 [0.18 , 21.94]
Anthenelli 2016 (1)	64	989	57	999	25.1%	1.13 [0.80 , 1.60]
Anthenelli 2016 (2)	105	1017	63	1015	27.9%	1.66 [1.23 , 2.25]
Aubin 2004	19	340	8	164	4.8%	1.15 [0.51 , 2.56]
Ferry 1992	3	23	1	21	0.5%	2.74 [0.31 , 24.34]
George 2002	8	16	4	16	1.8%	2.00 [0.75 , 5.33]
Hurt 1997 (3)	9	153	6	51	4.0%	0.50 [0.19 , 1.34]
Hurt 1997 (4)	10	153	6	51	4.0%	0.56 [0.21 , 1.45]
Hurt 1997 (5)	8	156	5	51	3.3%	0.52 [0.18 , 1.53]
Jorenby 1999	103	243	31	159	16.6%	2.17 [1.53 , 3.08]
Jorenby 2006	18	340	13	340	5.8%	1.38 [0.69 , 2.78]
Planer 2011	4	73	4	74	1.8%	1.01 [0.26 , 3.90]
Rovina 2009	2	40	1	36	0.5%	1.80 [0.17 , 19.02]
SMK20001	8	143	8	143	3.5%	1.00 [0.39 , 2.59]
Total (95% CI)		**3986**		**3420**	**100.0%**	**1.42 [1.21 , 1.67]**
Total events:	363		208			

Heterogeneity: Chi² = 21.74, df = 13 (P = 0.06); I² = 40%
Test for overall effect: Z = 4.31 (P < 0.0001)
Test for subgroup differences: Not applicable



Footnotes

(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control

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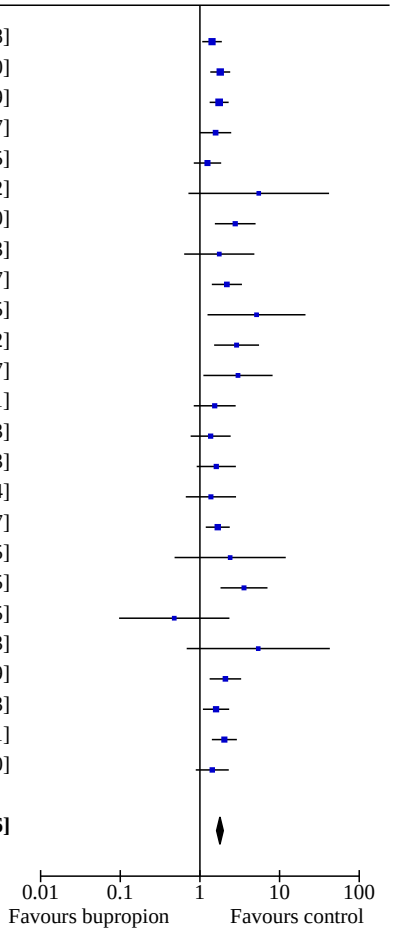
Analysis 1.13. Comparison 1: Bupropion versus placebo/no pharmacotherapy control, Outcome 13: Insomnia

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahluwalia 2002	88	300	62	300	11.0%	1.42 [1.07 , 1.88]
Anthenelli 2016 (1)	119	1017	66	1015	11.7%	1.80 [1.35 , 2.40]
Anthenelli 2016 (2)	126	989	73	999	12.8%	1.74 [1.32 , 2.29]
Dalsgarð 2004	61	221	20	114	4.7%	1.57 [1.00 , 2.47]
Eisenberg 2013	43	192	36	200	6.2%	1.24 [0.84 , 1.85]
Ferry 1992	6	23	1	21	0.2%	5.48 [0.72 , 41.82]
Fossati 2007	69	400	12	193	2.9%	2.77 [1.54 , 5.00]
George 2002	7	16	4	16	0.7%	1.75 [0.63 , 4.83]
Gonzales 2001	55	226	25	224	4.4%	2.18 [1.41 , 3.37]
Grant 2007	11	30	2	28	0.4%	5.13 [1.25 , 21.15]
Haggsträm 2006	27	53	9	51	1.6%	2.89 [1.51 , 5.52]
Holt 2005	23	88	4	46	0.9%	3.01 [1.11 , 8.17]
Hurt 1997 (3)	46	153	10	51	2.7%	1.53 [0.84 , 2.81]
Hurt 1997 (4)	45	153	11	51	2.9%	1.36 [0.76 , 2.43]
Hurt 1997 (5)	54	156	11	51	2.9%	1.60 [0.91 , 2.83]
Jorenby 1999	21	243	10	159	2.1%	1.37 [0.66 , 2.84]
Jorenby 2006	72	340	43	340	7.6%	1.67 [1.18 , 2.37]
Kalman 2011	5	73	2	70	0.4%	2.40 [0.48 , 11.95]
McCarthy 2008	35	229	10	234	1.7%	3.58 [1.81 , 7.05]
Myles 2004	2	14	3	10	0.6%	0.48 [0.10 , 2.35]
Rovina 2009	6	40	1	36	0.2%	5.40 [0.68 , 42.73]
Tashkin 2001	49	204	23	200	4.1%	2.09 [1.32 , 3.29]
Tonnesen 2003	126	527	27	180	7.1%	1.59 [1.09 , 2.33]
Tonstad 2003	75	313	37	313	6.5%	2.03 [1.41 , 2.91]
Wagena 2005	29	86	21	89	3.6%	1.43 [0.89 , 2.30]
Total (95% CI)		**6086**		**4991**	**100.0%**	**1.78 [1.62 , 1.96]**
Total events:	1200		523			

Heterogeneity: Chi² = 27.31, df = 24 (P = 0.29); I² = 12%
Test for overall effect: Z = 11.84 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control

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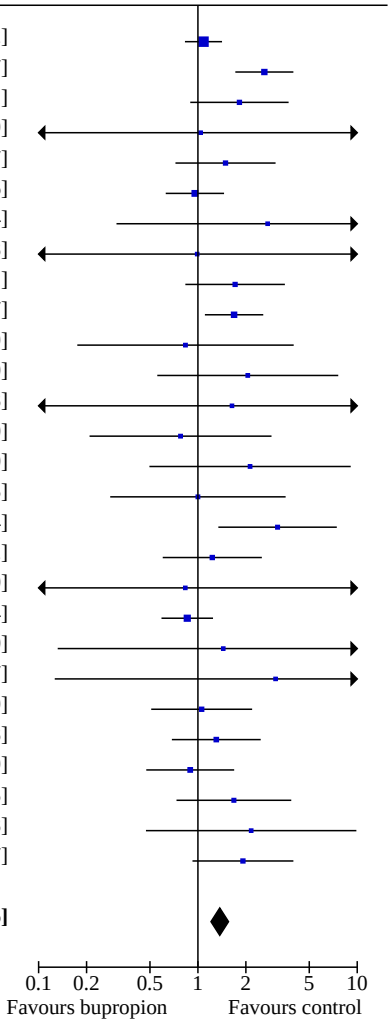
Analysis 1.14. Comparison 1: Bupropion versus placebo/ no pharmacotherapy control, Outcome 14: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	101	1017	93	1015	24.5%	1.08 [0.83 , 1.42]
Anthenelli 2016 (2)	75	989	29	999	7.6%	2.61 [1.72 , 3.97]
Aubin 2004	34	340	9	164	3.2%	1.82 [0.90 , 3.71]
Cinciripini 2013	1	102	1	106	0.3%	1.04 [0.07 , 16.39]
Dalsgarð 2004	26	221	9	114	3.1%	1.49 [0.72 , 3.07]
Eisenberg 2013	34	192	37	200	9.5%	0.96 [0.63 , 1.46]
Ferry 1992	3	23	1	21	0.3%	2.74 [0.31 , 24.34]
Ferry 1994	1	94	1	93	0.3%	0.99 [0.06 , 15.58]
Gonzales 2001	19	226	11	224	2.9%	1.71 [0.83 , 3.51]
Gonzales 2006	50	329	31	344	8.0%	1.69 [1.11 , 2.57]
Gray 2011	3	73	3	61	0.9%	0.84 [0.17 , 3.99]
Hall 2002	6	36	3	37	0.8%	2.06 [0.56 , 7.60]
Hertzberg 2001	1	10	0	5	0.2%	1.64 [0.08 , 34.28]
Hurt 1997 (3)	7	153	3	51	1.2%	0.78 [0.21 , 2.90]
Hurt 1997 (4)	13	156	2	51	0.8%	2.13 [0.50 , 9.10]
Hurt 1997 (5)	9	153	3	51	1.2%	1.00 [0.28 , 3.55]
Jorenby 1999	29	243	6	159	1.9%	3.16 [1.34 , 7.44]
Jorenby 2006	16	340	13	340	3.4%	1.23 [0.60 , 2.52]
Karam-Hage 2011	1	6	1	5	0.3%	0.83 [0.07 , 10.20]
Nides 2006	36	126	41	123	10.9%	0.86 [0.59 , 1.24]
Piper 2009	2	262	1	189	0.3%	1.44 [0.13 , 15.80]
Sheng 2013	1	127	0	130	0.1%	3.07 [0.13 , 74.67]
Tashkin 2001	14	204	13	200	3.4%	1.06 [0.51 , 2.19]
Tonnesen 2003	42	527	11	180	4.3%	1.30 [0.69 , 2.48]
Tonstad 2003	17	313	19	313	5.0%	0.89 [0.47 , 1.69]
Wagena 2005	13	86	8	89	2.1%	1.68 [0.73 , 3.85]
Weiner 2012	5	22	2	19	0.6%	2.16 [0.47 , 9.88]
Zellweger 2005	47	518	8	169	3.2%	1.92 [0.92 , 3.97]
Total (95% CI)		**6888**		**5452**	**100.0%**	**1.37 [1.21 , 1.56]**
Total events:	606		359			

Heterogeneity: Chi² = 33.22, df = 27 (P = 0.19); I² = 19%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control

Comparison 2. Bupropion plus nicotine replacement therapy (NRT) versus NRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Smoking cessation	12	3487	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.94, 1.51]
2.1.1 Patch alone	9	1774	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.84, 1.84]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.2 Lozenge alone	2	1051	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.81, 1.81]
2.1.3 Choice of NRT	1	662	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.73, 1.28]
2.2 Adverse events	2	313	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.02, 1.43]
2.3 Serious adverse events	3	607	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 8.89]
2.4 Seizures	1	527	Odds Ratio (M-H, Fixed, 95% CI)	2.93 [0.12, 72.31]
2.5 Suicide attempts	1	487	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.6 Death by suicide	1	487	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.7 All-cause mortality	2	731	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.98]
2.8 Insomnia	2	556	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.24, 1.93]
2.9 Anxiety	3	1218	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.97, 2.56]
2.10 Dropouts due to drug	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.95, 2.92]

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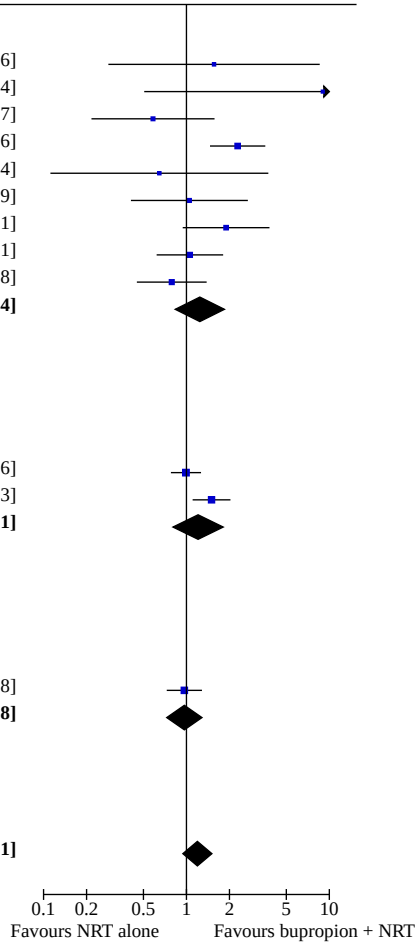
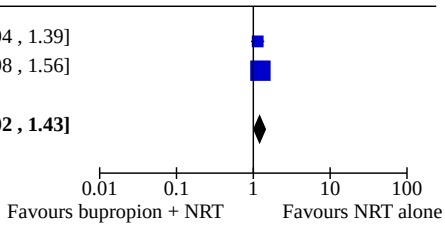
Analysis 2.1. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 1: Smoking cessation

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Patch alone						
Evins 2007	3	25	2	26	1.7%	1.56 [0.28 , 8.56]
George 2008	4	29	0	29	0.6%	9.00 [0.51 , 159.94]
Grant 2007	5	30	8	28	4.4%	0.58 [0.22 , 1.57]
Jorenby 1999	55	245	24	244	11.9%	2.28 [1.46 , 3.56]
Kalman 2011	2	66	3	64	1.6%	0.65 [0.11 , 3.74]
Killen 2004	8	103	8	108	4.8%	1.05 [0.41 , 2.69]
Rose 2013	20	143	11	149	7.3%	1.89 [0.94 , 3.81]
Schnoll 2010	21	114	23	132	9.9%	1.06 [0.62 , 1.81]
Simon 2004	18	119	23	120	9.4%	0.79 [0.45 , 1.38]
Subtotal (95% CI)		**874**		**900**	**51.7%**	**1.24 [0.84 , 1.84]**
Total events:	136		102			
Heterogeneity: Tau² = 0.16; Chi² = 16.01, df = 8 (P = 0.04); I² = 50%						
Test for overall effect: Z = 1.07 (P = 0.29)						
2.1.2 Lozenge alone						
Piper 2009	87	262	87	260	17.0%	0.99 [0.78 , 1.26]
Smith 2009	80	268	52	261	15.4%	1.50 [1.10 , 2.03]
Subtotal (95% CI)		**530**		**521**	**32.4%**	**1.21 [0.81 , 1.81]**
Total events:	167		139			
Heterogeneity: Tau² = 0.07; Chi² = 4.32, df = 1 (P = 0.04); I² = 77%						
Test for overall effect: Z = 0.91 (P = 0.36)						
2.1.3 Choice of NRT						
Stapleton 2013	57	244	101	418	15.9%	0.97 [0.73 , 1.28]
Subtotal (95% CI)		**244**		**418**	**15.9%**	**0.97 [0.73 , 1.28]**
Total events:	57		101			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**1648**		**1839**	**100.0%**	**1.19 [0.94 , 1.51]**
Total events:	360		342			
Heterogeneity: Tau² = 0.07; Chi² = 23.10, df = 11 (P = 0.02); I² = 52%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%						



Analysis 2.2. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 2: Adverse events

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rose 2013	31	34	28	35	31.7%	1.14 [0.94 , 1.39]
Simon 2004	73	121	60	123	68.3%	1.24 [0.98 , 1.56]
Total (95% CI)		**155**		**158**	**100.0%**	**1.21 [1.02 , 1.43]**
Total events:	104		88			
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
Test for subgroup differences: Not applicable						



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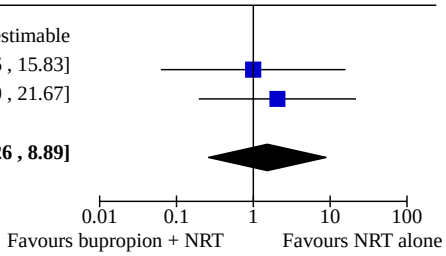
Analysis 2.3. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 3: Serious adverse events

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Evins 2007	0	25	0	26		Not estimable
Jorenby 1999	1	244	1	243	50.4%	1.00 [0.06 , 15.83]
Rose 2013	2	34	1	35	49.6%	2.06 [0.20 , 21.67]
Total (95% CI)		**303**		**304**	**100.0%**	**1.52 [0.26 , 8.89]**
Total events:	3		2			

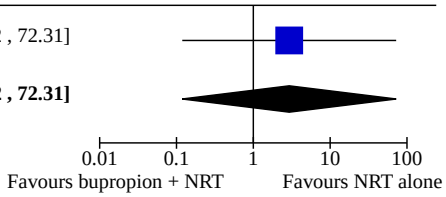
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.47 (P = 0.64)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 4: Seizures

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Piper 2009	1	267	0	260	100.0%	2.93 [0.12 , 72.31]
Total (95% CI)		**267**		**260**	**100.0%**	**2.93 [0.12 , 72.31]**
Total events:	1		0			

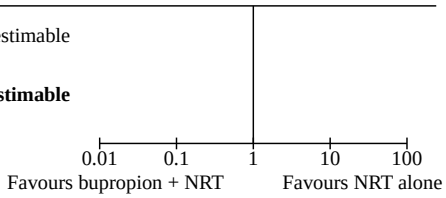
Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 5: Suicide attempts

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorenby 1999	0	244	0	243		Not estimable
Total (95% CI)		**244**		**243**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



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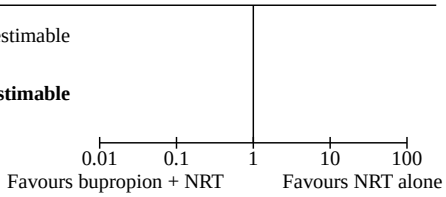
Analysis 2.6. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 6: Death by suicide

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorenby 1999	0	244	0	243		Not estimable
Total (95% CI)		**244**		**243**		**Not estimable**
Total events:	0		0			

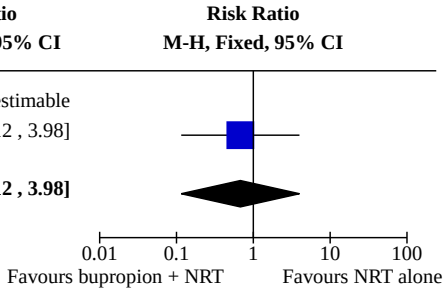
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 7: All-cause mortality

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorenby 1999	0	244	0	243		Not estimable
Simon 2004	2	121	3	123	100.0%	0.68 [0.12 , 3.98]
Total (95% CI)		**365**		**366**	**100.0%**	**0.68 [0.12 , 3.98]**
Total events:	2		3			

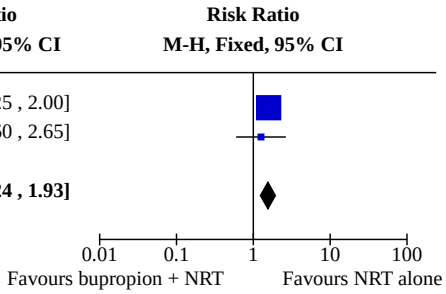
Heterogeneity: Not applicable
Test for overall effect: Z = 0.43 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 8: Insomnia

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorenby 1999	116	244	73	243	89.2%	1.58 [1.25 , 2.00]
Rose 2013	11	34	9	35	10.8%	1.26 [0.60 , 2.65]
Total (95% CI)		**278**		**278**	**100.0%**	**1.55 [1.24 , 1.93]**
Total events:	127		82			

Heterogeneity: $Chi^2 = 0.33$, df = 1 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = 3.85 (P = 0.0001)
Test for subgroup differences: Not applicable



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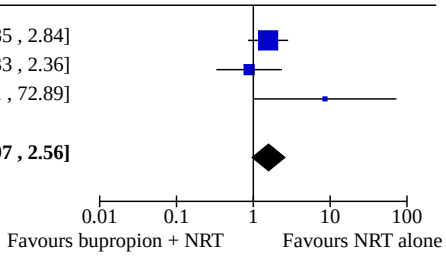
Analysis 2.9. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 9: Anxiety

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Jorenby 1999	25	244	16	243	67.7%	1.56 [0.85 , 2.84]
Rose 2013	6	34	7	35	29.1%	0.88 [0.33 , 2.36]
Stapleton 2013	5	244	1	418	3.1%	8.57 [1.01 , 72.89]
Total (95% CI)		**522**		**696**	**100.0%**	**1.58 [0.97 , 2.56]**
Total events:	36		24			

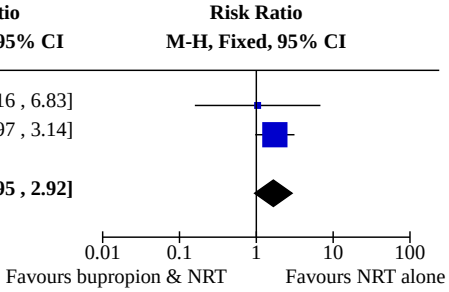
Heterogeneity: Chi² = 3.74, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 1.85 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Bupropion plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 10: Dropouts due to drug

Study or Subgroup	Bupropion & NRT Events	Bupropion & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Evins 2007	2	25	2	26	10.9%	1.04 [0.16 , 6.83]
Jorenby 1999	28	244	16	243	89.1%	1.74 [0.97 , 3.14]
Total (95% CI)		**269**		**269**	**100.0%**	**1.67 [0.95 , 2.92]**
Total events:	30		18			

Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.79 (P = 0.07)
Test for subgroup differences: Not applicable



Comparison 3. Bupropion plus varenicline versus varenicline alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Smoking cessation	3	1057	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.95, 1.55]
3.2 Adverse events	4	1043	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.02, 1.17]
3.3 Serious adverse events	5	1268	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.63, 2.42]
3.4 Psychiatric adverse events	2	835	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.03, 1.30]
3.5 Seizures	1	221	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.6 Overdoses	2	550	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.27]
3.7 Suicide attempts	3	1056	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.27]
3.8 Death by suicide	2	727	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.9 All-cause mortality	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.40]

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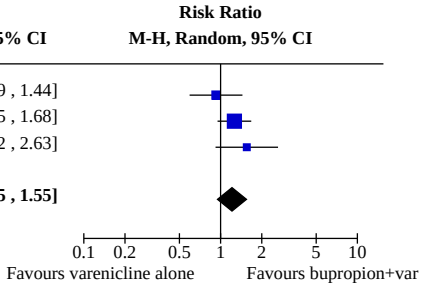
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.10 Anxiety	2	499	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.01, 2.38]
3.11 Insomnia	2	499	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [1.14, 1.84]
3.12 Dropouts due to drug	4	1230	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.45]

Analysis 3.1. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 1: Smoking cessation

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Cinciripini 2018	30	163	33	166	26.2%	0.93 [0.59 , 1.44]
Ebbert 2014	77	249	63	257	54.3%	1.26 [0.95 , 1.68]
Rose 2014	29	113	18	109	19.4%	1.55 [0.92 , 2.63]
Total (95% CI)		**525**		**532**	**100.0%**	**1.21 [0.95 , 1.55]**
Total events:	136		114			

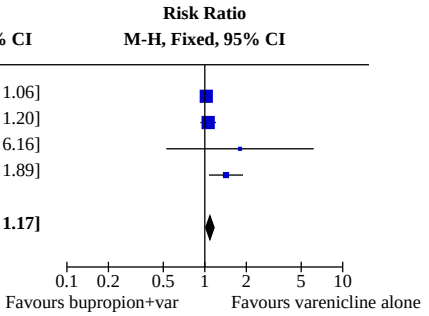
Heterogeneity: Tau² = 0.01; Chi² = 2.34, df = 2 (P = 0.31); I² = 15%
Test for overall effect: Z = 1.54 (P = 0.12)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 2: Adverse events

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	160	163	159	166	44.1%	1.02 [0.99 , 1.06]
Ebbert 2014	165	249	161	257	44.4%	1.06 [0.93 , 1.20]
NCT01406223	6	20	3	18	0.9%	1.80 [0.53 , 6.16]
Rose 2017	53	83	39	87	10.7%	1.42 [1.07 , 1.89]
Total (95% CI)		**515**		**528**	**100.0%**	**1.09 [1.02 , 1.17]**
Total events:	384		362			

Heterogeneity: Chi² = 13.95, df = 3 (P = 0.003); I² = 78%
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



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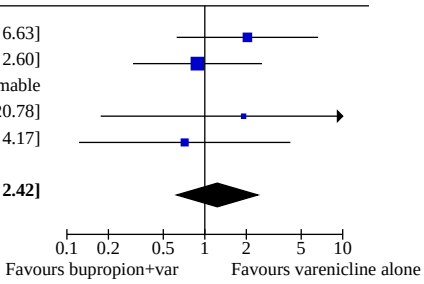
Analysis 3.3. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 3: Serious adverse events

Study or Subgroup	Bupropion & varenicline Events	Total	Varenicline alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	8	163	4	166	26.8%	2.04 [0.63 , 6.63]
Ebbert 2014	6	249	7	257	46.6%	0.88 [0.30 , 2.60]
NCT01406223	0	20	0	18		Not estimable
Rose 2014	2	113	1	108	6.9%	1.91 [0.18 , 20.78]
Rose 2017	2	84	3	90	19.6%	0.71 [0.12 , 4.17]
Total (95% CI)		**629**		**639**	**100.0%**	**1.23 [0.63 , 2.42]**
Total events:	18		15			

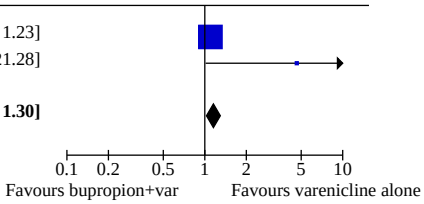
Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 4: Psychiatric adverse events

Study or Subgroup	Bupropion & varenicline Events	Total	Varenicline alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	136	163	126	166	98.4%	1.10 [0.99 , 1.23]
Ebbert 2014	9	249	2	257	1.6%	4.64 [1.01 , 21.28]
Total (95% CI)		**412**		**423**	**100.0%**	**1.15 [1.03 , 1.30]**
Total events:	145		128			

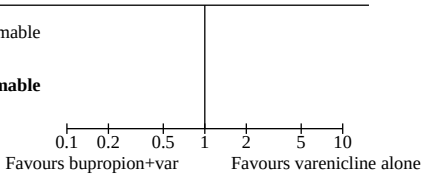
Heterogeneity: Chi² = 3.98, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 2.43 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 5: Seizures

Study or Subgroup	Bupropion & varenicline Events	Total	Varenicline alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rose 2014	0	113	0	108		Not estimable
Total (95% CI)		**113**		**108**		**Not estimable**
Total events:	0		0			

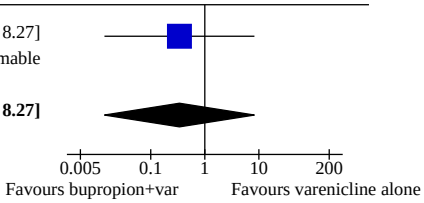
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.6. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 6: Overdoses

Study or Subgroup	Bupropion & varenicline Events	Total	Varenicline alone Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	0	163	1	166	100.0%	0.34 [0.01 , 8.27]
Rose 2014	0	113	0	108		Not estimable
Total (95% CI)		**276**		**274**	**100.0%**	**0.34 [0.01 , 8.27]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



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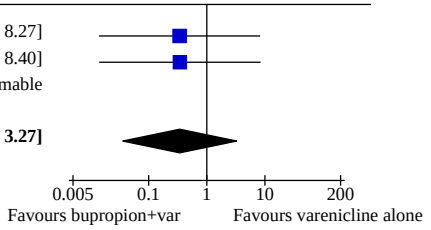
Analysis 3.7. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 7: Suicide attempts

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	0	163	1	166	50.2%	0.34 [0.01 , 8.27]
Ebbert 2014	0	249	1	257	49.8%	0.34 [0.01 , 8.40]
Rose 2014	0	113	0	108		Not estimable
Total (95% CI)		**525**		**531**	**100.0%**	**0.34 [0.04 , 3.27]**
Total events:	0		2			

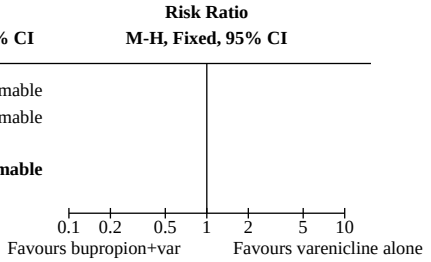
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 8: Death by suicide

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ebbert 2014	0	249	0	257		Not estimable
Rose 2014	0	113	0	108		Not estimable
Total (95% CI)		**362**		**365**		**Not estimable**
Total events:	0		0			

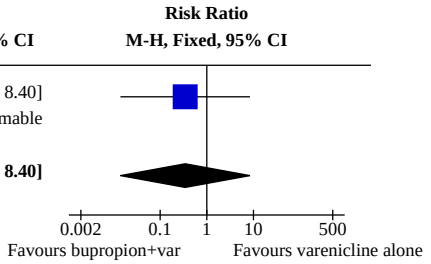
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 3.9. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 9: All-cause mortality

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ebbert 2014	0	249	1	257	100.0%	0.34 [0.01 , 8.40]
Rose 2014	0	113	0	108		Not estimable
Total (95% CI)		**362**		**365**	**100.0%**	**0.34 [0.01 , 8.40]**
Total events:	0		1			

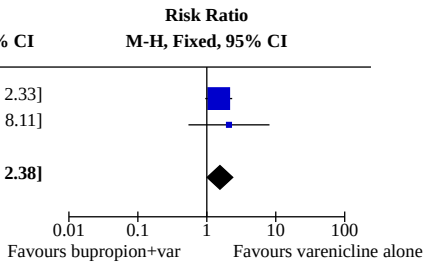
Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 10: Anxiety

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	38	163	26	166	89.8%	1.49 [0.95 , 2.33]
Rose 2017	6	83	3	87	10.2%	2.10 [0.54 , 8.11]
Total (95% CI)		**246**		**253**	**100.0%**	**1.55 [1.01 , 2.38]**
Total events:	44		29			

Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)
Test for subgroup differences: Not applicable



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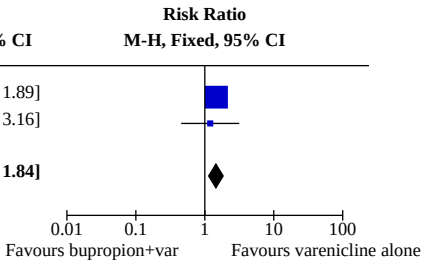
Analysis 3.11. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 11: Insomnia

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	87	163	60	166	89.7%	1.48 [1.15 , 1.89]
Rose 2017	8	83	7	87	10.3%	1.20 [0.45 , 3.16]
Total (95% CI)		**246**		**253**	**100.0%**	**1.45 [1.14 , 1.84]**
Total events:	95		67			

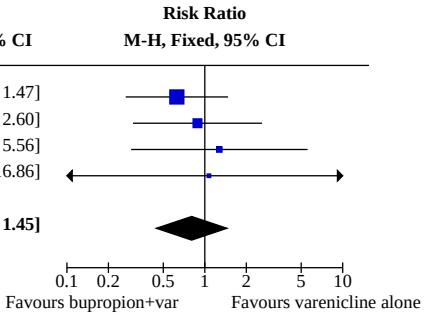
Heterogeneity: Chi² = 0.17, df = 1 (P = 0.68); I² = 0%
Test for overall effect: Z = 2.99 (P = 0.003)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Bupropion plus varenicline versus varenicline alone, Outcome 12: Dropouts due to drug

Study or Subgroup	Bupropion & varenicline Events	Bupropion & varenicline Total	Varenicline alone Events	Varenicline alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2018	8	163	13	166	54.1%	0.63 [0.27 , 1.47]
Ebbert 2014	6	249	7	257	28.9%	0.88 [0.30 , 2.60]
Rose 2014	4	113	3	108	12.9%	1.27 [0.29 , 5.56]
Rose 2017	1	84	1	90	4.1%	1.07 [0.07 , 16.86]
Total (95% CI)		**609**		**621**	**100.0%**	**0.80 [0.45 , 1.45]**
Total events:	19		24			

Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)
Test for subgroup differences: Not applicable



Comparison 4. Exploratory safety analysis: effects of bupropion only across comparisons

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Adverse events	25	12249	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.11, 1.17]
4.1.1 Bupropion versus control	19	10893	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [1.11, 1.18]
4.1.2 Bupropion + NRT versus NRT	2	313	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.02, 1.43]
4.1.3 Bupropion + varenicline versus varenicline	4	1043	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.02, 1.17]
4.2 Psychiatric adverse events	8	5274	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.15, 1.33]
4.2.1 Bupropion versus control	6	4439	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.15, 1.37]
4.2.2 Bupropion + varenicline versus varenicline	2	835	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.03, 1.30]
4.3 Serious adverse events	28	12500	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.93, 1.47]
4.3.1 Bupropion versus control	21	10625	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.90, 1.48]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3.2 Bupropion + NRT versus NRT	3	607	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.26, 8.89]
4.3.3 Bupropion + varenicline versus varenicline	5	1268	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.63, 2.42]
4.4 Dropouts due to drug	30	14108	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [1.20, 1.52]
4.4.1 Bupropion versus control	25	12340	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [1.21, 1.56]
4.4.2 Bupropion + NRT versus NRT	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.95, 2.92]
4.4.3 Bupropion + varenicline versus varenicline	4	1230	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.45, 1.45]

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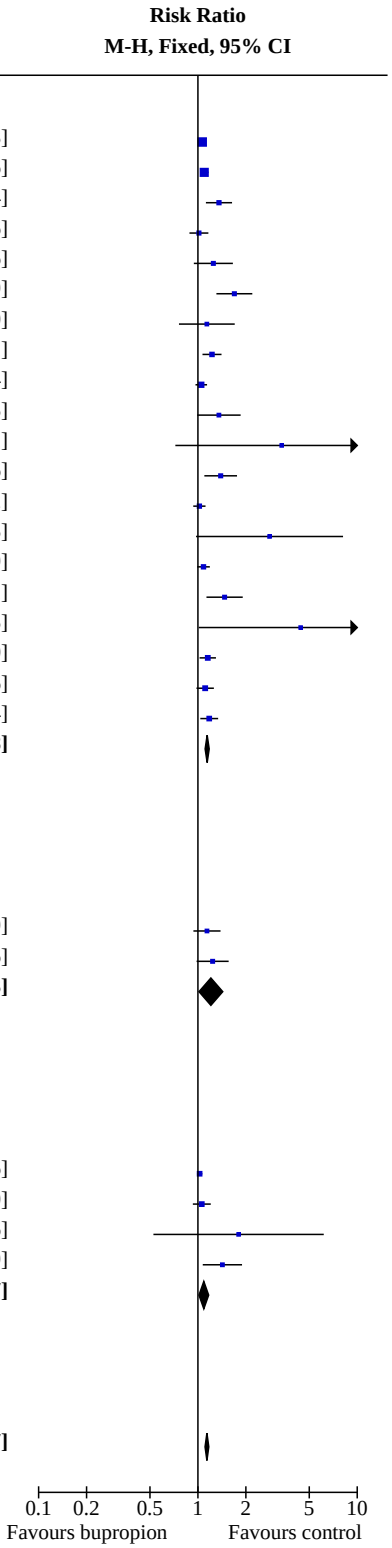
Analysis 4.1. Comparison 4: Exploratory safety analysis: effects of bupropion only across comparisons, Outcome 1: Adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Bupropion versus control						
Anthenelli 2016 (1)	742	1017	696	1015	20.4%	1.06 [1.01 , 1.13]
Anthenelli 2016 (2)	704	989	649	999	18.9%	1.10 [1.03 , 1.16]
Aubin 2004	208	340	74	164	2.9%	1.36 [1.12 , 1.64]
Cinciripini 2013	82	102	84	106	2.4%	1.01 [0.88 , 1.16]
Cox 2012	80	270	64	270	1.9%	1.25 [0.94 , 1.66]
Fossati 2007	179	400	51	193	2.0%	1.69 [1.31 , 2.19]
Gilbert 2019	21	34	19	35	0.5%	1.14 [0.76 , 1.70]
Gonzales 2001	162	226	131	224	3.8%	1.23 [1.07 , 1.41]
Gonzales 2006	258	329	257	344	7.3%	1.05 [0.97 , 1.14]
Gray 2011	47	73	29	61	0.9%	1.35 [0.99 , 1.85]
Kalman 2011	7	73	2	70	0.1%	3.36 [0.72 , 15.61]
McCarthy 2008	102	229	75	234	2.2%	1.39 [1.10 , 1.76]
Nides 2006	113	126	108	123	3.2%	1.02 [0.93 , 1.12]
Simon 2009	11	42	4	43	0.1%	2.82 [0.97 , 8.15]
SMK20001	129	143	119	143	3.5%	1.08 [0.99 , 1.19]
Tashkin 2001	90	204	60	200	1.8%	1.47 [1.13 , 1.91]
Tidey 2011	7	23	2	29	0.1%	4.41 [1.01 , 19.25]
Tonnesen 2003	395	527	117	180	5.1%	1.15 [1.02 , 1.30]
Tonstad 2003	201	313	181	313	5.3%	1.11 [0.98 , 1.26]
Zellweger 2005	379	518	105	169	4.6%	1.18 [1.04 , 1.34]
Subtotal (95% CI)		**5978**		**4915**	**87.0%**	**1.14 [1.11 , 1.18]**
Total events:	3917		2827			
Heterogeneity: Chi² = 51.53, df = 19 (P < 0.0001); I² = 63%						
Test for overall effect: Z = 8.99 (P < 0.00001)						
4.1.2 Bupropion + NRT versus NRT						
Rose 2013	31	34	28	35	0.8%	1.14 [0.94 , 1.39]
Simon 2004	73	121	60	123	1.7%	1.24 [0.98 , 1.56]
Subtotal (95% CI)		**155**		**158**	**2.5%**	**1.21 [1.02 , 1.43]**
Total events:	104		88			
Heterogeneity: Chi² = 0.37, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 2.14 (P = 0.03)						
4.1.3 Bupropion + varenicline versus varenicline						
Cinciripini 2018	160	163	159	166	4.6%	1.02 [0.99 , 1.06]
Ebbert 2014	165	249	161	257	4.6%	1.06 [0.93 , 1.20]
NCT01406223	6	20	3	18	0.1%	1.80 [0.53 , 6.16]
Rose 2017	53	83	39	87	1.1%	1.42 [1.07 , 1.89]
Subtotal (95% CI)		**515**		**528**	**10.4%**	**1.09 [1.02 , 1.17]**
Total events:	384		362			
Heterogeneity: Chi² = 13.95, df = 3 (P = 0.003); I² = 78%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Total (95% CI)		**6648**		**5601**	**100.0%**	**1.14 [1.11 , 1.17]**
Total events:	4405		3277			
Heterogeneity: Chi² = 84.30, df = 25 (P < 0.00001); I² = 70%						
Test for overall effect: Z = 9.53 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.05, df = 2 (P = 0.36), I² = 2.6%						



Footnotes

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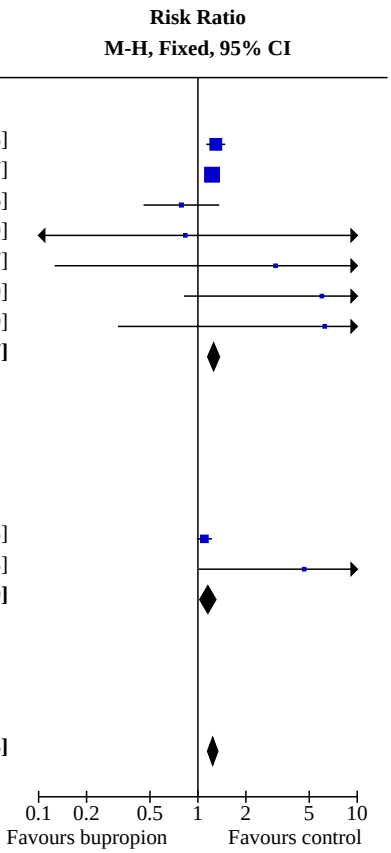
Analysis 4.1. (Continued)

Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

Analysis 4.2. Comparison 4: Exploratory safety analysis: effects of bupropion only across comparisons, Outcome 2: Psychiatric adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Bupropion versus control						
Anthenelli 2016 (1)	332	989	259	999	34.0%	1.29 [1.13 , 1.48]
Anthenelli 2016 (2)	435	1017	354	1015	46.7%	1.23 [1.10 , 1.37]
Gilbert 2019	13	34	17	35	2.2%	0.79 [0.46 , 1.36]
Karam-Hage 2011	1	6	1	5	0.1%	0.83 [0.07 , 10.20]
Sheng 2013	1	127	0	130	0.1%	3.07 [0.13 , 74.67]
Singh 2010	6	15	1	15	0.1%	6.00 [0.82 , 44.00]
Tidey 2011	2	23	0	29	0.1%	6.25 [0.31 , 124.10]
Subtotal (95% CI)		**2211**		**2228**	**83.3%**	**1.25 [1.15 , 1.37]**
Total events:	790		632			
Heterogeneity: Chi² = 7.05, df = 6 (P = 0.32); I² = 15%						
Test for overall effect: Z = 5.25 (P < 0.00001)						
4.2.2 Bupropion + varenicline versus varenicline						
Cinciripini 2018	136	163	126	166	16.5%	1.10 [0.99 , 1.23]
Ebbert 2014	9	249	2	257	0.3%	4.64 [1.01 , 21.28]
Subtotal (95% CI)		**412**		**423**	**16.7%**	**1.15 [1.03 , 1.30]**
Total events:	145		128			
Heterogeneity: Chi² = 3.98, df = 1 (P = 0.05); I² = 75%						
Test for overall effect: Z = 2.43 (P = 0.01)						
Total (95% CI)		**2623**		**2651**	**100.0%**	**1.24 [1.15 , 1.33]**
Total events:	935		760			
Heterogeneity: Chi² = 14.42, df = 8 (P = 0.07); I² = 45%						
Test for overall effect: Z = 5.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.30, df = 1 (P = 0.25), I² = 23.0%						



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

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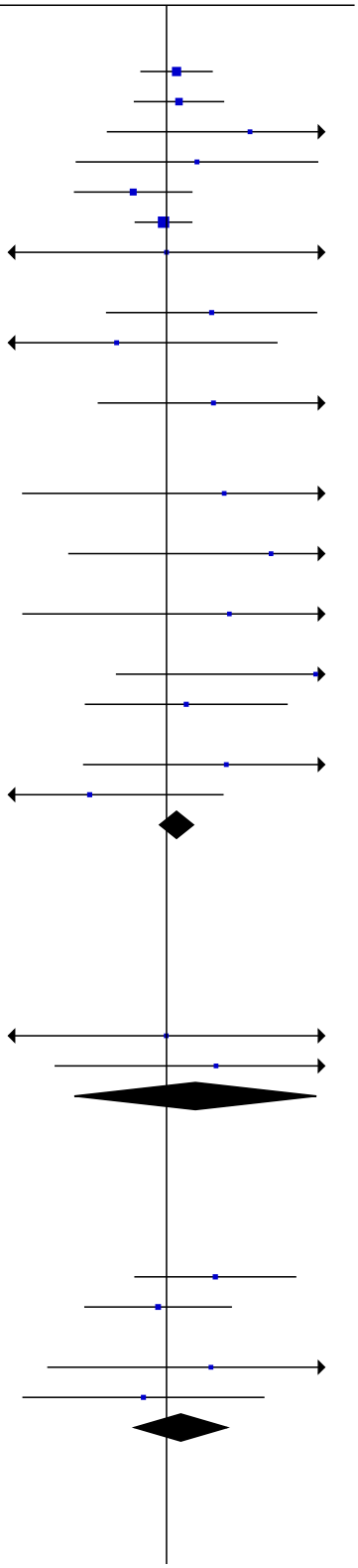
Analysis 4.3. Comparison 4: Exploratory safety analysis: effects of bupropion only across comparisons, Outcome 3: Serious adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Bupropion versus control						
Anthenelli 2016 (1)	29	1017	25	1015	19.5%	1.16 [0.68 , 1.96]
Anthenelli 2016 (2)	19	989	16	999	12.4%	1.20 [0.62 , 2.32]
Aubin 2004	7	340	1	164	1.1%	3.38 [0.42 , 27.22]
Cinciripini 2013	3	102	2	106	1.5%	1.56 [0.27 , 9.14]
Cox 2012	8	270	13	270	10.2%	0.62 [0.26 , 1.46]
Eisenberg 2013	34	192	37	200	28.3%	0.96 [0.63 , 1.46]
Ferry 1992	1	23	1	23	0.8%	1.00 [0.07 , 15.04]
Ferry 1994	0	94	0	93		Not estimable
Fossati 2007	8	400	2	193	2.1%	1.93 [0.41 , 9.00]
George 2008	1	30	2	29	1.6%	0.48 [0.05 , 5.05]
Gilbert 2019	0	34	0	35		Not estimable
Gonzales 2001	4	226	2	224	1.6%	1.98 [0.37 , 10.71]
Haggsträm 2006	0	53	0	51		Not estimable
Hurt 1997 (3)	0	153	0	51		Not estimable
Hurt 1997 (4)	3	156	0	51	0.6%	2.32 [0.12 , 44.14]
Hurt 1997 (5)	0	153	0	51		Not estimable
Jorenby 1999	3	243	0	159	0.5%	4.59 [0.24 , 88.27]
Kalman 2011	0	73	0	70		Not estimable
Muramoto 2007 (6)	2	105	0	52	0.5%	2.50 [0.12 , 51.15]
Muramoto 2007 (7)	0	104	0	51		Not estimable
Nides 2006	4	126	0	123	0.4%	8.79 [0.48 , 161.51]
SMK20001	4	143	3	143	2.3%	1.33 [0.30 , 5.85]
Tidey 2011	0	23	0	29		Not estimable
Tonnesen 2003	7	527	1	180	1.2%	2.39 [0.30 , 19.30]
Zellweger 2005	2	518	2	169	2.4%	0.33 [0.05 , 2.30]
Subtotal (95% CI)		**6094**		**4531**	**86.9%**	**1.16 [0.90 , 1.48]**
Total events:	139		107			
Heterogeneity: Chi² = 10.59, df = 16 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
4.3.2 Bupropion + NRT versus NRT						
Evins 2007	0	25	0	26		Not estimable
Jorenby 1999	1	244	1	243	0.8%	1.00 [0.06 , 15.83]
Rose 2013	2	34	1	35	0.8%	2.06 [0.20 , 21.67]
Subtotal (95% CI)		**303**		**304**	**1.6%**	**1.52 [0.26 , 8.89]**
Total events:	3		2			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
4.3.3 Bupropion + varenicline versus varenicline						
Cinciripini 2018	8	163	4	166	3.1%	2.04 [0.63 , 6.63]
Ebbert 2014	6	249	7	257	5.4%	0.88 [0.30 , 2.60]
NCT01406223	0	20	0	18		Not estimable
Rose 2014	2	113	1	108	0.8%	1.91 [0.18 , 20.78]
Rose 2017	2	84	3	90	2.3%	0.71 [0.12 , 4.17]
Subtotal (95% CI)		**629**		**639**	**11.5%**	**1.23 [0.63 , 2.42]**
Total events:	18		15			
Heterogeneity: Chi² = 1.56, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						



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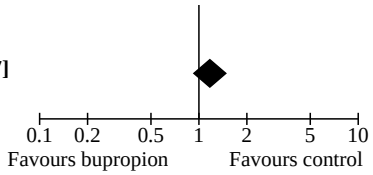
Analysis 4.3. (Continued)

Test for overall effect: Z = 0.60 (P = 0.55)

Total (95% CI)	**7026**	**5474**	**100.0%**	**1.17 [0.93 , 1.47]**	
Total events:	160	124			

Heterogeneity: Chi² = 12.48, df = 22 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)
Test for subgroup differences: Chi² = 0.12, df = 2 (P = 0.94), I² = 0%



Footnotes

(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(6) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with half the placebo control grou
(7) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with half the placebo control grou

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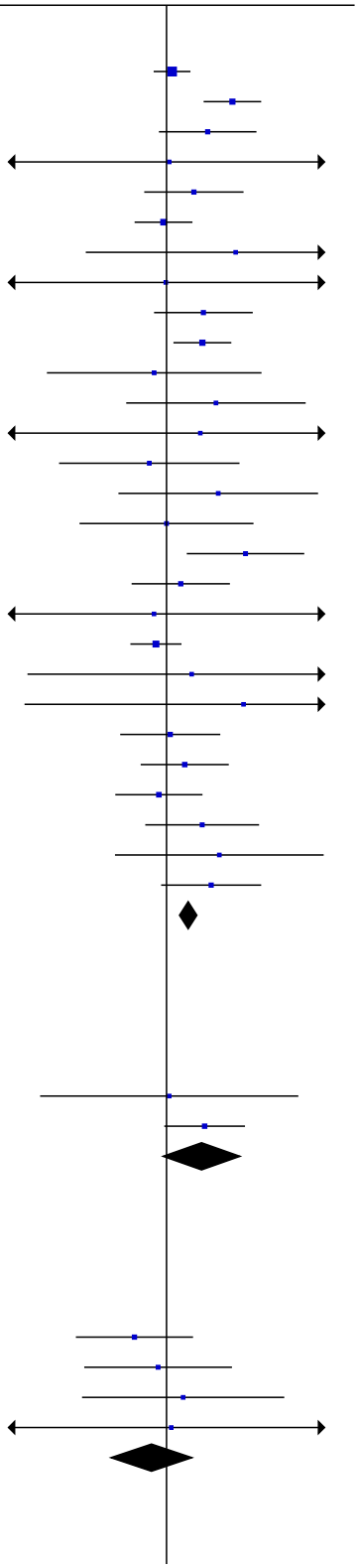
Analysis 4.4. Comparison 4: Exploratory safety analysis: effects of bupropion only across comparisons, Outcome 4: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Bupropion versus control						
Anthenelli 2016 (1)	101	1017	93	1015	22.0%	1.08 [0.83 , 1.42]
Anthenelli 2016 (2)	75	989	29	999	6.8%	2.61 [1.72 , 3.97]
Aubin 2004	34	340	9	164	2.9%	1.82 [0.90 , 3.71]
Cinciripini 2013	1	102	1	106	0.2%	1.04 [0.07 , 16.39]
Dalsgarð 2004	26	221	9	114	2.8%	1.49 [0.72 , 3.07]
Eisenberg 2013	34	192	37	200	8.6%	0.96 [0.63 , 1.46]
Ferry 1992	3	23	1	21	0.2%	2.74 [0.31 , 24.34]
Ferry 1994	1	94	1	93	0.2%	0.99 [0.06 , 15.58]
Gonzales 2001	19	226	11	224	2.6%	1.71 [0.83 , 3.51]
Gonzales 2006	50	329	31	344	7.2%	1.69 [1.11 , 2.57]
Gray 2011	3	73	3	61	0.8%	0.84 [0.17 , 3.99]
Hall 2002	6	36	3	37	0.7%	2.06 [0.56 , 7.60]
Hertzberg 2001	1	10	0	5	0.2%	1.64 [0.08 , 34.28]
Hurt 1997 (3)	7	153	3	51	1.1%	0.78 [0.21 , 2.90]
Hurt 1997 (4)	13	156	2	51	0.7%	2.13 [0.50 , 9.10]
Hurt 1997 (5)	9	153	3	51	1.1%	1.00 [0.28 , 3.55]
Jorenby 1999	29	243	6	159	1.7%	3.16 [1.34 , 7.44]
Jorenby 2006	16	340	13	340	3.1%	1.23 [0.60 , 2.52]
Karam-Hage 2011	1	6	1	5	0.3%	0.83 [0.07 , 10.20]
Nides 2006	36	126	41	123	9.8%	0.86 [0.59 , 1.24]
Piper 2009	2	262	1	189	0.3%	1.44 [0.13 , 15.80]
Sheng 2013	1	127	0	130	0.1%	3.07 [0.13 , 74.67]
Tashkin 2001	14	204	13	200	3.1%	1.06 [0.51 , 2.19]
Tonnesen 2003	42	527	11	180	3.9%	1.30 [0.69 , 2.48]
Tonstad 2003	17	313	19	313	4.5%	0.89 [0.47 , 1.69]
Wagena 2005	13	86	8	89	1.9%	1.68 [0.73 , 3.85]
Weiner 2012	5	22	2	19	0.5%	2.16 [0.47 , 9.88]
Zellweger 2005	47	518	8	169	2.9%	1.92 [0.92 , 3.97]
Subtotal (95% CI)		**6888**		**5452**	**90.1%**	**1.37 [1.21 , 1.56]**
Total events:	606		359			
Heterogeneity: Chi² = 33.22, df = 27 (P = 0.19); I² = 19%						
Test for overall effect: Z = 4.90 (P < 0.00001)						
4.4.2 Bupropion + NRT versus NRT						
Evins 2007	2	25	2	26	0.5%	1.04 [0.16 , 6.83]
Jorenby 1999	28	244	16	243	3.8%	1.74 [0.97 , 3.14]
Subtotal (95% CI)		**269**		**269**	**4.3%**	**1.67 [0.95 , 2.92]**
Total events:	30		18			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.79 (P = 0.07)						
4.4.3 Bupropion + varenicline versus varenicline						
Cinciripini 2018	8	163	13	166	3.0%	0.63 [0.27 , 1.47]
Ebbert 2014	6	249	7	257	1.6%	0.88 [0.30 , 2.60]
Rose 2014	4	113	3	108	0.7%	1.27 [0.29 , 5.56]
Rose 2017	1	84	1	90	0.2%	1.07 [0.07 , 16.86]
Subtotal (95% CI)		**609**		**621**	**5.6%**	**0.80 [0.45 , 1.45]**
Total events:	19		24			
Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						



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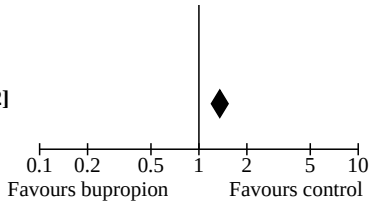
Analysis 4.4. (Continued)

Heterogeneity: Chi² = 0.77, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.47)

Total (95% CI)		**7766**	**6342**	**100.0%**	**1.35 [1.20 , 1.52]**
Total events:	655	401			

Heterogeneity: Chi² = 37.53, df = 33 (P = 0.27); I² = 12%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Chi² = 3.59, df = 2 (P = 0.17), I² = 44.2%



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares 150mg bupropion with a third of the placebo control
(4) This study has been split into two comparisons for this analysis – this comparison compares 300mg bupropion with a third of the placebo control
(5) This study has been split into two comparisons for this analysis – this comparison compares 100mg bupropion with a third of the placebo control

Comparison 5. Bupropion versus varenicline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Smoking cessation	6	6286	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.64, 0.79]
5.2 Adverse events	5	5780	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.00]
5.3 Serious adverse events	4	4742	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.94, 2.04]
5.4 Psychiatric adverse events	2	4051	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.99, 1.16]
5.5 Seizures	4	5389	Risk Ratio (M-H, Fixed, 95% CI)	7.16 [0.92, 55.42]
5.6 Overdoses	2	4210	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.14, 6.25]
5.7 Suicide attempts	3	4239	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.31, 28.96]
5.8 Death by suicide	5	5600	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.9 All-cause mortality	5	6074	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.31, 28.96]
5.10 Insomnia	3	5208	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.22, 1.60]
5.11 Anxiety	2	4705	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.07, 1.53]
5.12 Dropouts due to drug	6	6103	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.96, 1.31]

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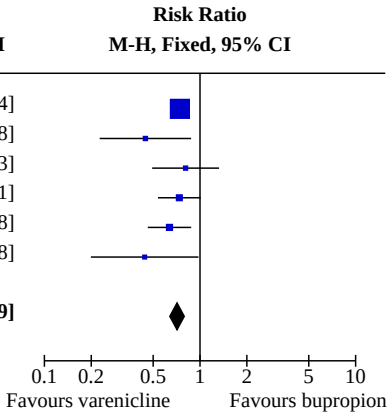
Analysis 5.1. Comparison 5: Bupropion versus varenicline, Outcome 1: Smoking cessation

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016	330	2034	445	2037	66.5%	0.74 [0.65 , 0.84]
Benli 2017	10	161	34	244	4.0%	0.45 [0.23 , 0.88]
Cinciripini 2013	23	102	24	86	3.9%	0.81 [0.49 , 1.33]
Gonzales 2006	53	329	77	352	11.1%	0.74 [0.54 , 1.01]
Jorenby 2006	50	342	79	344	11.8%	0.64 [0.46 , 0.88]
Nides 2006	8	128	18	127	2.7%	0.44 [0.20 , 0.98]
Total (95% CI)		**3096**		**3190**	**100.0%**	**0.71 [0.64 , 0.79]**
Total events:	474		677			

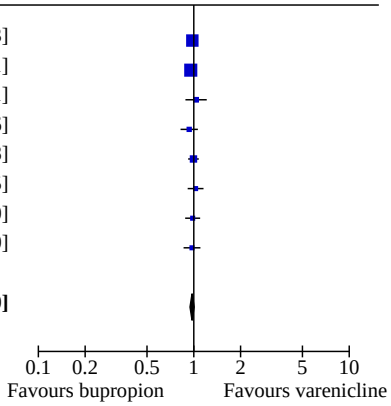
Heterogeneity: Chi² = 4.41, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 6.26 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5: Bupropion versus varenicline, Outcome 2: Adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	704	989	720	990	33.8%	0.98 [0.93 , 1.03]
Anthenelli 2016 (2)	742	1017	783	1026	36.6%	0.96 [0.91 , 1.01]
Benli 2017	98	155	143	234	5.3%	1.03 [0.88 , 1.21]
Cinciripini 2013	82	102	74	86	3.8%	0.93 [0.82 , 1.06]
Gonzales 2006	258	329	275	349	12.5%	1.00 [0.92 , 1.08]
Nides 2006 (3)	38	42	111	126	2.6%	1.03 [0.91 , 1.15]
Nides 2006 (4)	38	42	115	125	2.7%	0.98 [0.88 , 1.10]
Nides 2006 (5)	37	42	114	126	2.7%	0.97 [0.86 , 1.10]
Total (95% CI)		**2718**		**3062**	**100.0%**	**0.98 [0.95 , 1.00]**
Total events:	1997		2335			

Heterogeneity: Chi² = 2.61, df = 7 (P = 0.92); I² = 0%
Test for overall effect: Z = 1.64 (P = 0.10)
Test for subgroup differences: Not applicable



Footnotes

(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 1 n
(4) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 2 n
(5) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 0.3

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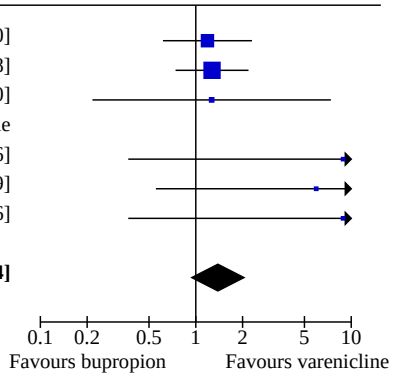
Analysis 5.3. Comparison 5: Bupropion versus varenicline, Outcome 3: Serious adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	19	989	16	990	38.0%	1.19 [0.61 , 2.30]
Anthenelli 2016 (2)	29	1017	23	1026	54.4%	1.27 [0.74 , 2.18]
Cinciripini 2013	3	102	2	86	5.2%	1.26 [0.22 , 7.40]
Gray 2012	0	14	0	15		Not estimable
Nides 2006 (3)	1	42	0	126	0.6%	8.86 [0.37 , 213.46]
Nides 2006 (4)	2	42	1	125	1.2%	5.95 [0.55 , 63.99]
Nides 2006 (5)	1	42	0	126	0.6%	8.86 [0.37 , 213.46]
Total (95% CI)		**2248**		**2494**	**100.0%**	**1.39 [0.94 , 2.04]**
Total events:	55		42			

Heterogeneity: Chi² = 4.37, df = 5 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable

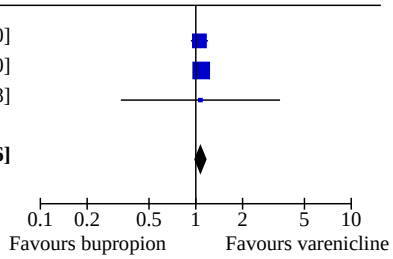


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 0.3
(4) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 2 n
(5) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 1 n

Analysis 5.4. Comparison 5: Bupropion versus varenicline, Outcome 4: Psychiatric adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	332	989	315	990	43.6%	1.06 [0.93 , 1.20]
Anthenelli 2016 (2)	435	1017	405	1026	55.9%	1.08 [0.98 , 1.20]
Gray 2012	4	14	4	15	0.5%	1.07 [0.33 , 3.48]
Total (95% CI)		**2020**		**2031**	**100.0%**	**1.07 [0.99 , 1.16]**
Total events:	771		724			

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

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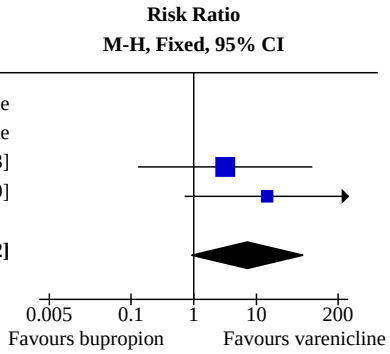
Analysis 5.5. Comparison 5: Bupropion versus varenicline, Outcome 5: Seizures

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016	0	2006	0	2016		Not estimable
Cinciripini 2013	0	102	0	86		Not estimable
Gonzales 2006	1	329	0	349	65.8%	3.18 [0.13 , 77.83]
Nides 2006	2	126	0	375	34.2%	14.80 [0.72 , 306.29]
Total (95% CI)		**2563**		**2826**	**100.0%**	**7.16 [0.92 , 55.42]**
Total events:	3		0			

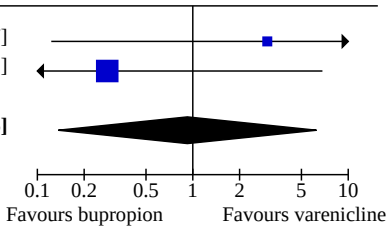
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



Analysis 5.6. Comparison 5: Bupropion versus varenicline, Outcome 6: Overdoses

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016	1	2006	0	2016	23.5%	3.01 [0.12 , 73.97]
Cinciripini 2013	0	102	1	86	76.5%	0.28 [0.01 , 6.82]
Total (95% CI)		**2108**		**2102**	**100.0%**	**0.92 [0.14 , 6.25]**
Total events:	1		1			

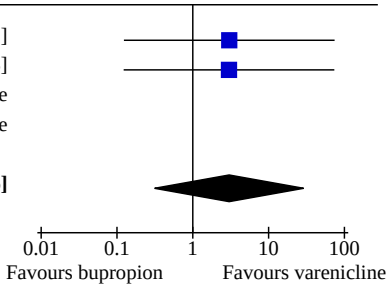
Heterogeneity: Chi² = 1.06, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 0.08 (P = 0.93)
Test for subgroup differences: Not applicable



Analysis 5.7. Comparison 5: Bupropion versus varenicline, Outcome 7: Suicide attempts

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	1017	0	1026	49.9%	3.03 [0.12 , 74.21]
Anthenelli 2016 (2)	1	989	0	990	50.1%	3.00 [0.12 , 73.63]
Cinciripini 2013	0	102	0	86		Not estimable
Gray 2012	0	14	0	15		Not estimable
Total (95% CI)		**2122**		**2117**	**100.0%**	**3.01 [0.31 , 28.96]**
Total events:	2		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

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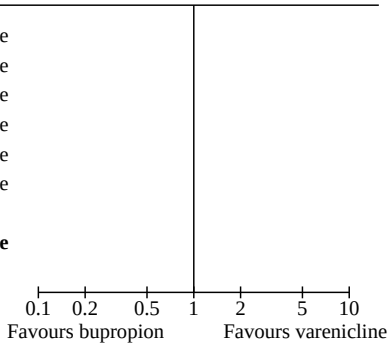
Analysis 5.8. Comparison 5: Bupropion versus varenicline, Outcome 8: Death by suicide

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	0	1017	0	1026		Not estimable
Anthenelli 2016 (2)	0	989	0	990		Not estimable
Cinciripini 2013	0	102	0	86		Not estimable
Gonzales 2006	0	329	0	349		Not estimable
Gray 2012	0	14	0	15		Not estimable
Jorenby 2006	0	340	0	343		Not estimable
Total (95% CI)		**2791**		**2809**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

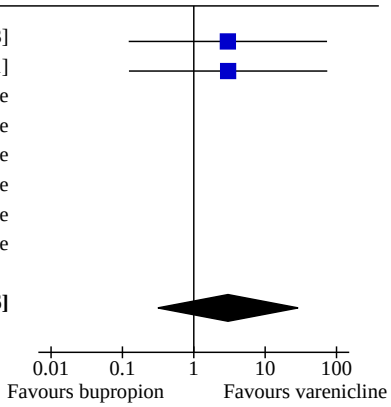


Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

Analysis 5.9. Comparison 5: Bupropion versus varenicline, Outcome 9: All-cause mortality

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	989	0	990	50.1%	3.00 [0.12 , 73.63]
Anthenelli 2016 (2)	1	1017	0	1026	49.9%	3.03 [0.12 , 74.21]
Cinciripini 2013	0	102	0	86		Not estimable
Gonzales 2006	0	329	0	349		Not estimable
Jorenby 2006	0	340	0	343		Not estimable
Nides 2006 (3)	0	42	0	125		Not estimable
Nides 2006 (4)	0	42	0	126		Not estimable
Nides 2006 (5)	0	42	0	126		Not estimable
Total (95% CI)		**2903**		**3171**	**100.0%**	**3.01 [0.31 , 28.96]**
Total events:	2		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.34)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 2 n
(4) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 0.3
(5) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 1 n

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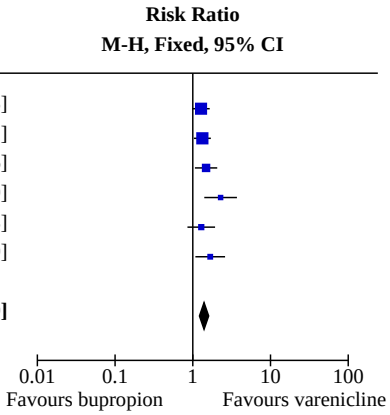
Analysis 5.10. Comparison 5: Bupropion versus varenicline, Outcome 10: Insomnia

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	119	1017	94	1026	32.4%	1.28 [0.99 , 1.65]
Anthenelli 2016 (2)	126	989	95	990	32.9%	1.33 [1.03 , 1.71]
Jorenby 2006	72	340	49	343	16.9%	1.48 [1.07 , 2.06]
Nides 2006 (3)	19	42	25	126	4.3%	2.28 [1.41 , 3.70]
Nides 2006 (4)	19	42	44	125	7.7%	1.29 [0.85 , 1.93]
Nides 2006 (5)	19	42	34	126	5.9%	1.68 [1.08 , 2.60]
Total (95% CI)		**2472**		**2736**	**100.0%**	**1.40 [1.22 , 1.60]**
Total events:	374		341			

Heterogeneity: Chi² = 5.52, df = 5 (P = 0.36); I² = 9%
Test for overall effect: Z = 4.80 (P < 0.00001)
Test for subgroup differences: Not applicable

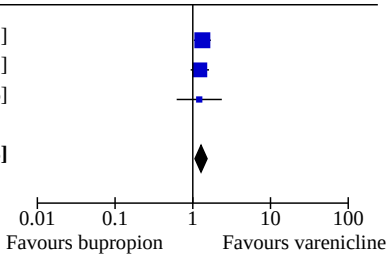


Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 0.3
(4) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 2 n
(5) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 1 n

Analysis 5.11. Comparison 5: Bupropion versus varenicline, Outcome 11: Anxiety

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	126	989	95	990	48.6%	1.33 [1.03 , 1.71]
Anthenelli 2016 (2)	105	1017	86	1026	43.8%	1.23 [0.94 , 1.62]
Jorenby 2006	18	340	15	343	7.6%	1.21 [0.62 , 2.36]
Total (95% CI)		**2346**		**2359**	**100.0%**	**1.28 [1.07 , 1.53]**
Total events:	249		196			

Heterogeneity: Chi² = 0.18, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.69 (P = 0.007)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

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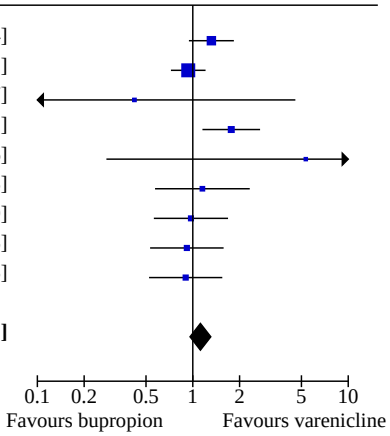
Analysis 5.12. Comparison 5: Bupropion versus varenicline, Outcome 12: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	75	989	57	990	21.2%	1.32 [0.94 , 1.84]
Anthenelli 2016 (2)	101	1017	109	1026	40.3%	0.93 [0.72 , 1.21]
Cinciripini 2013	1	102	2	86	0.8%	0.42 [0.04 , 4.57]
Gonzales 2006	50	329	30	349	10.8%	1.77 [1.15 , 2.71]
Gray 2012	2	14	0	15	0.2%	5.33 [0.28 , 102.26]
Jorenby 2006	16	340	14	343	5.2%	1.15 [0.57 , 2.33]
Nides 2006 (3)	12	42	37	126	6.9%	0.97 [0.56 , 1.69]
Nides 2006 (4)	12	42	39	125	7.3%	0.92 [0.53 , 1.58]
Nides 2006 (5)	12	42	40	126	7.4%	0.90 [0.52 , 1.55]
Total (95% CI)		**2917**		**3186**	**100.0%**	**1.12 [0.96 , 1.31]**
Total events:	281		328			

Heterogeneity: Chi² = 10.34, df = 8 (P = 0.24); I² = 23%
Test for overall effect: Z = 1.44 (P = 0.15)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort
(3) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 1 n
(4) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 2 n
(5) This study has been split into two comparisons for this analysis – this comparison compares one third of the bupropion group with the varenicline 0.3

Comparison 6. Bupropion versus nicotine replacement therapy (NRT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Smoking cessation	10	8230	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.09]
6.1.1 Patch	8	5778	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.16]
6.1.2 Lozenge	2	694	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.67, 1.22]
6.1.3 Patch + lozenge	2	720	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 0.98]
6.1.4 Choice of NRT	2	1038	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.33]
6.2 Adverse events	2	4097	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
6.3 Serious adverse events	5	5624	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.83, 1.80]
6.4 Psychiatric adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.5 Seizures	1	4028	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.24]
6.6 Overdoses	1	4028	Risk Ratio (M-H, Fixed, 95% CI)	3.02 [0.12, 74.19]
6.7 Suicide attempts	2	4514	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.22, 12.75]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.8 Death by suicide	2	4514	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.9 All-cause mortality	3	5313	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.38, 4.84]
6.10 Insomnia	2	4128	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.10, 1.55]
6.11 Anxiety	2	4855	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.06, 1.62]
6.12 Dropouts due to drug	4	4825	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.95, 1.38]

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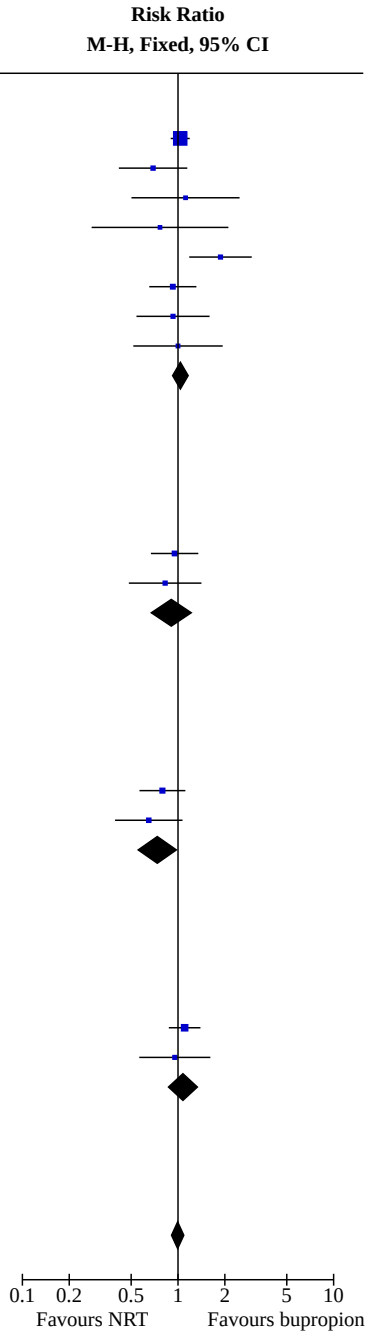
Analysis 6.1. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 1: Smoking cessation

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 Patch						
Anthenelli 2016	330	2034	320	2038	42.6%	1.03 [0.90 , 1.19]
Gariti 2009	21	133	29	127	4.0%	0.69 [0.42 , 1.15]
Gilbert 2019	9	34	9	38	1.1%	1.12 [0.50 , 2.49]
Górecka 2003	5	31	8	38	1.0%	0.77 [0.28 , 2.11]
Jorenby 1999	45	244	24	244	3.2%	1.88 [1.18 , 2.98]
Piper 2009 (1)	28	88	90	262	6.0%	0.93 [0.65 , 1.31]
Smith 2009	14	85	50	282	3.1%	0.93 [0.54 , 1.60]
Uyar 2007	13	50	13	50	1.7%	1.00 [0.52 , 1.94]
Subtotal (95% CI)		**2699**		**3079**	**62.7%**	**1.04 [0.92 , 1.16]**
Total events:	465		543			
Heterogeneity: Chi² = 9.71, df = 7 (P = 0.21); I² = 28%						
Test for overall effect: Z = 0.60 (P = 0.55)						
6.1.2 Lozenge						
Piper 2009	28	88	87	260	5.9%	0.95 [0.67 , 1.35]
Smith 2009	14	85	52	261	3.4%	0.83 [0.48 , 1.41]
Subtotal (95% CI)		**173**		**521**	**9.3%**	**0.91 [0.67 , 1.22]**
Total events:	42		139			
Heterogeneity: Chi² = 0.19, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 0.66 (P = 0.51)						
6.1.3 Patch + lozenge						
Piper 2009	28	88	107	267	7.1%	0.79 [0.57 , 1.11]
Smith 2009	15	86	75	279	4.7%	0.65 [0.39 , 1.07]
Subtotal (95% CI)		**174**		**546**	**11.8%**	**0.74 [0.55 , 0.98]**
Total events:	43		182			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 2.13 (P = 0.03)						
6.1.4 Choice of NRT						
Stapleton 2013	109	409	101	418	13.3%	1.10 [0.87 , 1.39]
Wittchen 2011	22	108	22	103	3.0%	0.95 [0.56 , 1.61]
Subtotal (95% CI)		**517**		**521**	**16.3%**	**1.08 [0.87 , 1.33]**
Total events:	131		123			
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**3563**		**4667**	**100.0%**	**0.99 [0.91 , 1.09]**
Total events:	681		987			
Heterogeneity: Chi² = 15.85, df = 13 (P = 0.26); I² = 18%						
Test for overall effect: Z = 0.11 (P = 0.91)						
Test for subgroup differences: Chi² = 5.75, df = 3 (P = 0.12), I² = 47.8%						



Footnotes

(1) Bupropion arm divided between 3 subgroups to avoid multiple counting in overall effect

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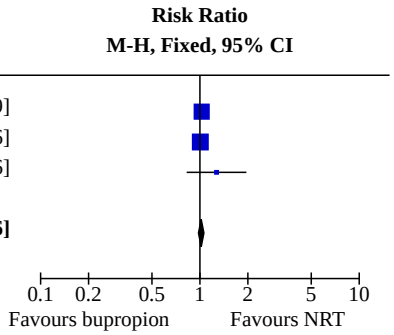
Analysis 6.2. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 2: Adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	704	989	698	1006	47.9%	1.03 [0.97 , 1.09]
Anthenelli 2016 (2)	742	1017	737	1016	51.0%	1.01 [0.95 , 1.06]
Gilbert 2019	21	34	17	35	1.2%	1.27 [0.83 , 1.96]
Total (95% CI)		**2040**		**2057**	**100.0%**	**1.02 [0.98 , 1.06]**
Total events:	1467		1452			

Heterogeneity: Chi² = 1.29, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
Test for subgroup differences: Not applicable

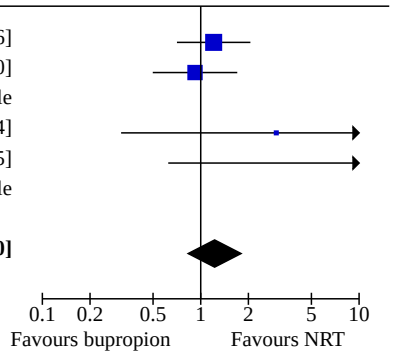


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

Analysis 6.3. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 3: Serious adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	29	1017	24	1016	51.8%	1.21 [0.71 , 2.06]
Anthenelli 2016 (2)	19	989	21	1006	44.9%	0.92 [0.50 , 1.70]
Gilbert 2019	0	34	0	38		Not estimable
Jorenby 1999	3	243	1	243	2.2%	3.00 [0.31 , 28.64]
Stapleton 2013	5	409	0	418	1.1%	11.24 [0.62 , 202.65]
Wittchen 2011	0	108	0	103		Not estimable
Total (95% CI)		**2800**		**2824**	**100.0%**	**1.22 [0.83 , 1.80]**
Total events:	56		46			

Heterogeneity: Chi² = 3.70, df = 3 (P = 0.30); I² = 19%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

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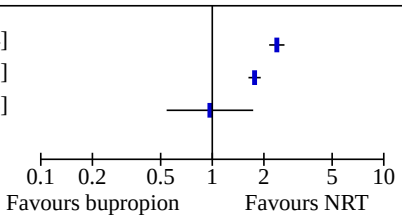
Analysis 6.4. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 4: Psychiatric adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	704	989	301	1006	2.38 [2.15 , 2.64]
Anthenelli 2016 (2)	742	1017	420	1016	1.76 [1.63 , 1.92]
Gilbert 2019	13	34	15	38	0.97 [0.54 , 1.73]



Footnotes

(1) Non-psychiatric cohort

(2) Psychiatric cohort

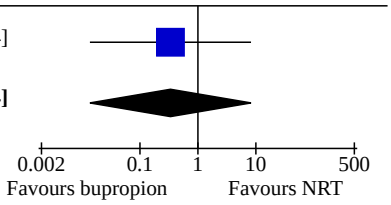
Analysis 6.5. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 5: Seizures

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016	0	2006	1	2022	100.0%	0.34 [0.01 , 8.24]
Total (95% CI)		**2006**		**2022**	**100.0%**	**0.34 [0.01 , 8.24]**
Total events:	0		1			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



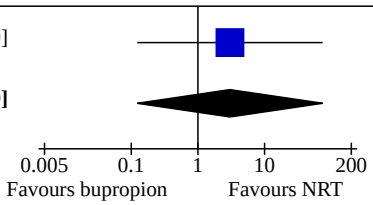
Analysis 6.6. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 6: Overdoses

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016	1	2006	0	2022	100.0%	3.02 [0.12 , 74.19]
Total (95% CI)		**2006**		**2022**	**100.0%**	**3.02 [0.12 , 74.19]**
Total events:	1		0			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.68 (P = 0.50)

Test for subgroup differences: Not applicable



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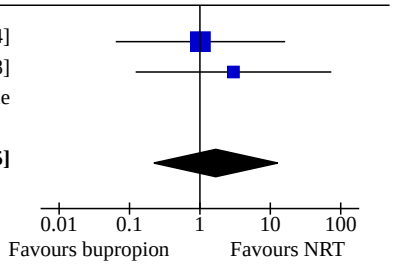
Analysis 6.7. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 7: Suicide attempts

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	989	1	1006	66.5%	1.02 [0.06 , 16.24]
Anthenelli 2016 (2)	1	1017	0	1016	33.5%	3.00 [0.12 , 73.48]
Jorenby 1999	0	243	0	243		Not estimable
Total (95% CI)		**2249**		**2265**	**100.0%**	**1.68 [0.22 , 12.75]**
Total events:	2		1			

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable

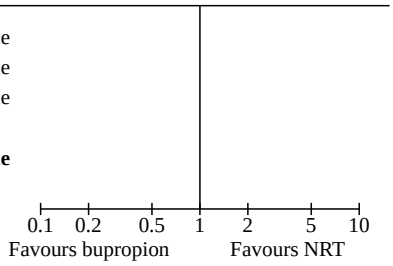


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

Analysis 6.8. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 8: Death by suicide

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	0	989	0	1006		Not estimable
Anthenelli 2016 (2)	0	1017	0	1016		Not estimable
Jorenby 1999	0	243	0	243		Not estimable
Total (95% CI)		**2249**		**2265**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

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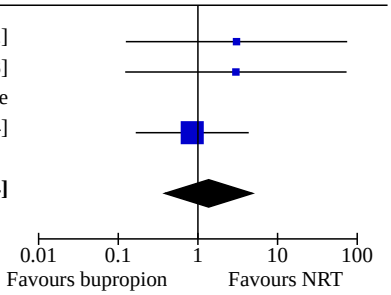
Analysis 6.9. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 9: All-cause mortality

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	1	989	0	1006	11.8%	3.05 [0.12 , 74.82]
Anthenelli 2016 (2)	1	1017	0	1016	11.9%	3.00 [0.12 , 73.48]
Jorenby 1999	0	243	0	243		Not estimable
Smith 2009	2	256	5	543	76.3%	0.85 [0.17 , 4.34]
Total (95% CI)		**2505**		**2808**	**100.0%**	**1.36 [0.38 , 4.84]**
Total events:	4		5			

Heterogeneity: Chi² = 0.80, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable

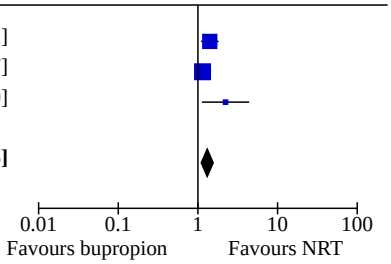


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

Analysis 6.10. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 10: Insomnia

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	126	989	91	1006	44.4%	1.41 [1.09 , 1.82]
Anthenelli 2016 (2)	119	1017	104	1016	51.2%	1.14 [0.89 , 1.47]
Uyar 2007	20	50	9	50	4.4%	2.22 [1.12 , 4.40]
Total (95% CI)		**2056**		**2072**	**100.0%**	**1.31 [1.10 , 1.55]**
Total events:	265		204			

Heterogeneity: Chi² = 3.77, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 3.07 (P = 0.002)
Test for subgroup differences: Not applicable



Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

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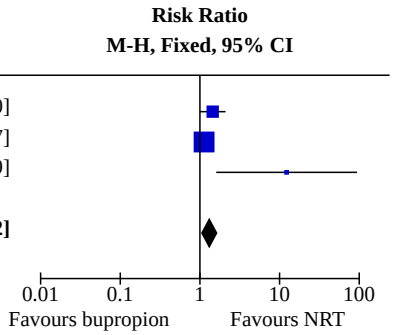
Analysis 6.11. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 11: Anxiety

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	64	989	45	1006	32.2%	1.45 [1.00 , 2.10]
Anthenelli 2016 (2)	105	1017	93	1016	67.1%	1.13 [0.87 , 1.47]
Stapleton 2013	12	409	1	418	0.7%	12.26 [1.60 , 93.89]
Total (95% CI)		**2415**		**2440**	**100.0%**	**1.31 [1.06 , 1.62]**
Total events:	181		139			

Heterogeneity: Chi² = 6.14, df = 2 (P = 0.05); I² = 67%
Test for overall effect: Z = 2.49 (P = 0.01)
Test for subgroup differences: Not applicable

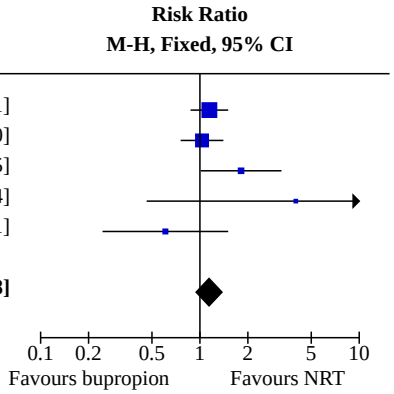


Footnotes
(1) Non-psychiatric cohort
(2) Psychiatric cohort

Analysis 6.12. Comparison 6: Bupropion versus nicotine replacement therapy (NRT), Outcome 12: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anthenelli 2016 (1)	101	1017	88	1016	46.4%	1.15 [0.87 , 1.51]
Anthenelli 2016 (2)	75	989	74	1006	38.7%	1.03 [0.76 , 1.40]
Jorenby 1999	29	243	16	243	8.4%	1.81 [1.01 , 3.25]
Uyar 2007	4	50	1	50	0.5%	4.00 [0.46 , 34.54]
Wittchen 2011	7	108	11	103	5.9%	0.61 [0.24 , 1.51]
Total (95% CI)		**2407**		**2418**	**100.0%**	**1.14 [0.95 , 1.38]**
Total events:	216		190			

Heterogeneity: Chi² = 5.98, df = 4 (P = 0.20); I² = 33%
Test for overall effect: Z = 1.39 (P = 0.17)
Test for subgroup differences: Not applicable



Footnotes
(1) Psychiatric cohort
(2) Non-psychiatric cohort

Comparison 7. Bupropion versus nortriptyline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Smoking cessation	3	417	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.93, 1.82]
7.2 Serious adverse events	1	105	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.3 Insomnia	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.4 Dropouts due to drug	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.47, 1.44]

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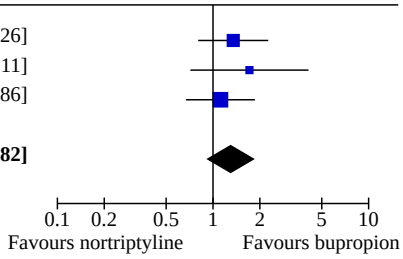
Analysis 7.1. Comparison 7: Bupropion versus nortriptyline, Outcome 1: Smoking cessation

Study or Subgroup	Bupropion Events	Bupropion Total	Nortriptyline Events	Nortriptyline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haggsträm 2006	22	53	16	52	36.8%	1.35 [0.80 , 2.26]
Hall 2002	12	73	7	73	16.0%	1.71 [0.72 , 4.11]
Wagena 2005	24	86	20	80	47.2%	1.12 [0.67 , 1.86]
Total (95% CI)		**212**		**205**	**100.0%**	**1.30 [0.93 , 1.82]**
Total events:	58		43			

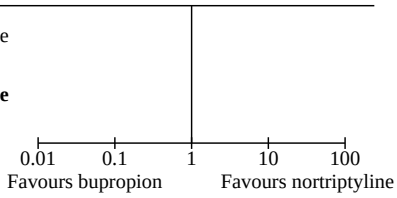
Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 7.2. Comparison 7: Bupropion versus nortriptyline, Outcome 2: Serious adverse events

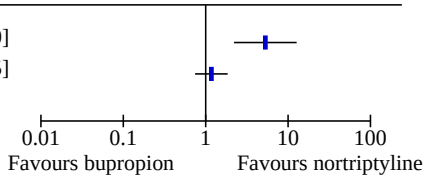
Study or Subgroup	Bupropion Events	Bupropion Total	Nortriptyline Events	Nortriptyline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haggsträm 2006	0	53	0	52		Not estimable
Total (95% CI)		**53**		**52**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 7.3. Comparison 7: Bupropion versus nortriptyline, Outcome 3: Insomnia

Study or Subgroup	Bupropion Events	Bupropion Total	Nortriptyline Events	Nortriptyline Total	Risk Ratio M-H, Fixed, 95% CI
Haggsträm 2006	27	53	5	52	5.30 [2.21 , 12.70]
Wagena 2005	29	86	23	80	1.17 [0.74 , 1.85]



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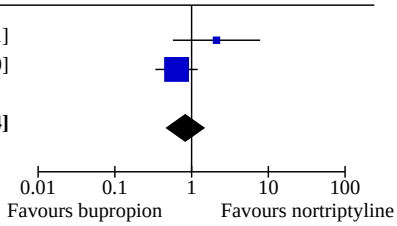
Analysis 7.4. Comparison 7: Bupropion versus nortriptyline, Outcome 4: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	Nortriptyline Events	Nortriptyline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hall 2002	6	36	3	38	12.9%	2.11 [0.57 , 7.81]
Wagena 2005	13	86	19	80	87.1%	0.64 [0.34 , 1.20]
Total (95% CI)		**122**		**118**	**100.0%**	**0.83 [0.47 , 1.44]**
Total events:	19		22			

Heterogeneity: Chi² = 2.62, df = 1 (P = 0.11); I² = 62%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



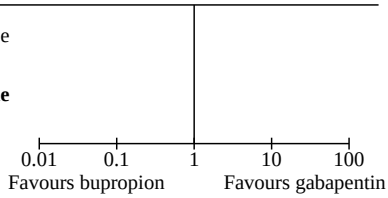
Comparison 8. Bupropion versus gabapentin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Serious adverse events	1	36	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.2 Dropouts due to drug	1	36	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [0.50, 10.06]

Analysis 8.1. Comparison 8: Bupropion versus gabapentin, Outcome 1: Serious adverse events

Study or Subgroup	Bupropion Events	Bupropion Total	Gabapentin Events	Gabapentin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
White 2005	0	19	0	17		Not estimable
Total (95% CI)		**19**		**17**		**Not estimable**
Total events:	0		0			

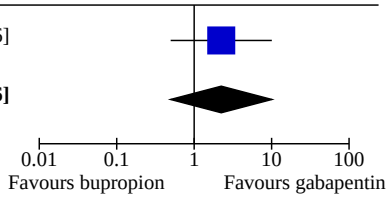
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8: Bupropion versus gabapentin, Outcome 2: Dropouts due to drug

Study or Subgroup	Bupropion Events	Bupropion Total	Gabapentin Events	Gabapentin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
White 2005	5	19	2	17	100.0%	2.24 [0.50 , 10.06]
Total (95% CI)		**19**		**17**	**100.0%**	**2.24 [0.50 , 10.06]**
Total events:	5		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.05 (P = 0.29)
Test for subgroup differences: Not applicable



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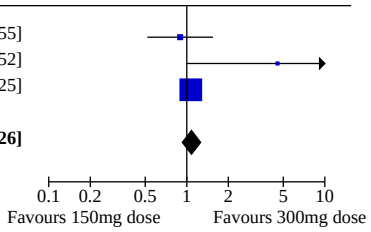
Comparison 9. Bupropion (different doses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Smoking cessation	3	2042	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.93, 1.26]
9.2 Serious adverse events	2	518	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.30, 5.94]
9.3 Overdoses	1	209	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.17]
9.4 Suicide attempts	2	518	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.17]
9.5 Death by suicide	2	518	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.6 All-cause mortality	2	518	Risk Ratio (M-H, Fixed, 95% CI)	2.94 [0.12, 71.68]
9.7 Insomnia	1	309	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.85, 1.63]
9.8 Anxiety	1	309	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.35, 2.20]
9.9 Dropouts due to drug	1	309	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.75, 4.44]

Analysis 9.1. Comparison 9: Bupropion (different doses), Outcome 1: Smoking cessation

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	21	156	23	153	9.9%	0.90 [0.52 , 1.55]
Muramoto 2007	9	104	2	105	0.8%	4.54 [1.01 , 20.52]
Swan 2003	224	761	210	763	89.3%	1.07 [0.91 , 1.25]
Total (95% CI)		**1021**		**1021**	**100.0%**	**1.08 [0.93 , 1.26]**
Total events:	254		235			

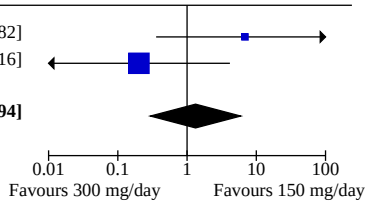
Heterogeneity: Chi² = 3.96, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Analysis 9.2. Comparison 9: Bupropion (different doses), Outcome 2: Serious adverse events

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	3	156	0	153	16.9%	6.87 [0.36 , 131.82]
Muramoto 2007	0	104	2	105	83.1%	0.20 [0.01 , 4.16]
Total (95% CI)		**260**		**258**	**100.0%**	**1.33 [0.30 , 5.94]**
Total events:	3		2			

Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



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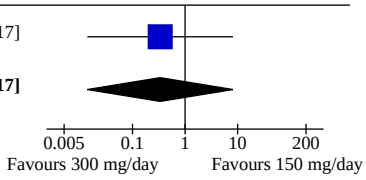
Analysis 9.3. Comparison 9: Bupropion (different doses), Outcome 3: Overdoses

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Muramoto 2007	0	104	1	105	100.0%	0.34 [0.01 , 8.17]
Total (95% CI)		**104**		**105**	**100.0%**	**0.34 [0.01 , 8.17]**
Total events:	0		1			

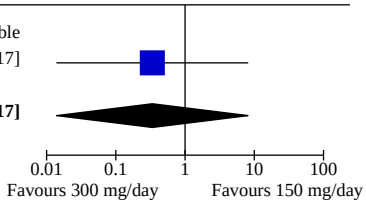
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9: Bupropion (different doses), Outcome 4: Suicide attempts

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	0	156	0	153		Not estimable
Muramoto 2007	0	104	1	105	100.0%	0.34 [0.01 , 8.17]
Total (95% CI)		**260**		**258**	**100.0%**	**0.34 [0.01 , 8.17]**
Total events:	0		1			

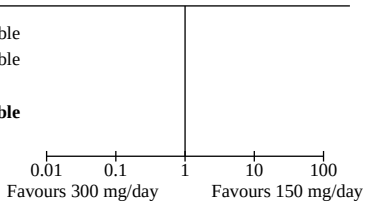
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 9.5. Comparison 9: Bupropion (different doses), Outcome 5: Death by suicide

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	0	156	0	153		Not estimable
Muramoto 2007	0	104	0	105		Not estimable
Total (95% CI)		**260**		**258**		**Not estimable**
Total events:	0		0			

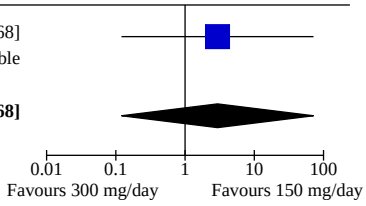
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 9.6. Comparison 9: Bupropion (different doses), Outcome 6: All-cause mortality

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	1	156	0	153	100.0%	2.94 [0.12 , 71.68]
Muramoto 2007	0	104	0	105		Not estimable
Total (95% CI)		**260**		**258**	**100.0%**	**2.94 [0.12 , 71.68]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



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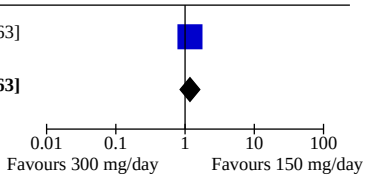
Analysis 9.7. Comparison 9: Bupropion (different doses), Outcome 7: Insomnia

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	54	156	45	153	100.0%	1.18 [0.85 , 1.63]
Total (95% CI)		**156**		**153**	**100.0%**	**1.18 [0.85 , 1.63]**
Total events:	54		45			

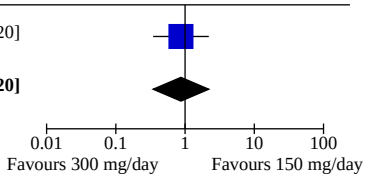
Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



Analysis 9.8. Comparison 9: Bupropion (different doses), Outcome 8: Anxiety

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	8	156	9	153	100.0%	0.87 [0.35 , 2.20]
Total (95% CI)		**156**		**153**	**100.0%**	**0.87 [0.35 , 2.20]**
Total events:	8		9			

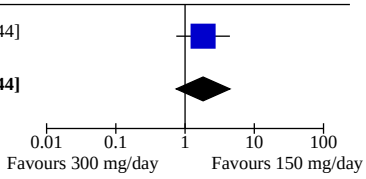
Heterogeneity: Not applicable
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 9.9. Comparison 9: Bupropion (different doses), Outcome 9: Dropouts due to drug

Study or Subgroup	300 mg/day bupropion Events	300 mg/day bupropion Total	150 mg/day bupropion Events	150 mg/day bupropion Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hurt 1997	13	156	7	153	100.0%	1.82 [0.75 , 4.44]
Total (95% CI)		**156**		**153**	**100.0%**	**1.82 [0.75 , 4.44]**
Total events:	13		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable



Comparison 10. Nortriptyline versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Smoking cessation	6	975	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.48, 2.78]
10.2 Serious adverse events	1	103	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3 Insomnia	2	247	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.28, 1.21]
10.4 Anxiety	1	144	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.34, 1.20]
10.5 Dropouts due to drug	4	537	Risk Ratio (M-H, Fixed, 95% CI)	1.99 [1.18, 3.36]

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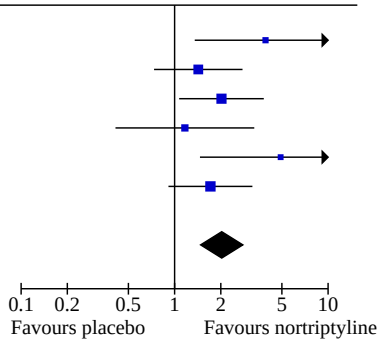
Analysis 10.1. Comparison 10: Nortriptyline versus placebo, Outcome 1: Smoking cessation

Study or Subgroup	Nortriptyline Events	Nortriptyline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Da Costa 2002	14	68	4	76	7.8%	3.91 [1.35 , 11.31]
Haggsträm 2006	16	52	11	51	23.1%	1.43 [0.73 , 2.77]
Hall 1998	24	99	12	100	24.8%	2.02 [1.07 , 3.81]
Hall 2002	7	73	6	73	12.5%	1.17 [0.41 , 3.30]
Prochazka 1998	15	108	3	106	6.3%	4.91 [1.46 , 16.46]
Wagena 2005	20	80	13	89	25.6%	1.71 [0.91 , 3.21]
Total (95% CI)		**480**		**495**	**100.0%**	**2.03 [1.48 , 2.78]**
Total events:	96		49			

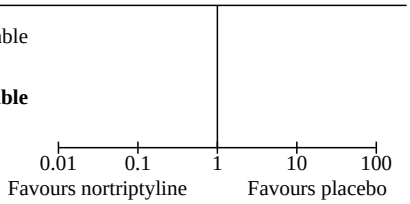
Heterogeneity: Chi² = 5.96, df = 5 (P = 0.31); I² = 16%
Test for overall effect: Z = 4.38 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 10.2. Comparison 10: Nortriptyline versus placebo, Outcome 2: Serious adverse events

Study or Subgroup	Nortriptyline Events	Nortriptyline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haggsträm 2006	0	52	0	51		Not estimable
Total (95% CI)		**52**		**51**		**Not estimable**
Total events:	0		0			

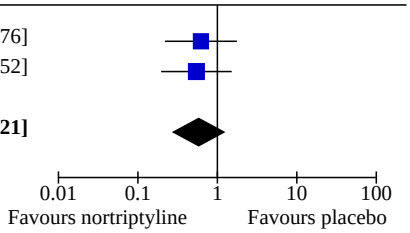
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Nortriptyline versus placebo, Outcome 3: Insomnia

Study or Subgroup	Nortriptyline Events	Nortriptyline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Da Costa 2002	5	68	9	76	48.3%	0.62 [0.22 , 1.76]
Haggsträm 2006	5	52	9	51	51.7%	0.54 [0.20 , 1.52]
Total (95% CI)		**120**		**127**	**100.0%**	**0.58 [0.28 , 1.21]**
Total events:	10		18			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.86); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



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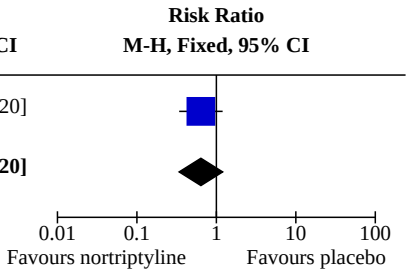
Analysis 10.4. Comparison 10: Nortriptyline versus placebo, Outcome 4: Anxiety

Study or Subgroup	Nortriptyline Events	Nortriptyline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Da Costa 2002	12	68	21	76	100.0%	0.64 [0.34 , 1.20]
Total (95% CI)		**68**		**76**	**100.0%**	**0.64 [0.34 , 1.20]**
Total events:	12		21			

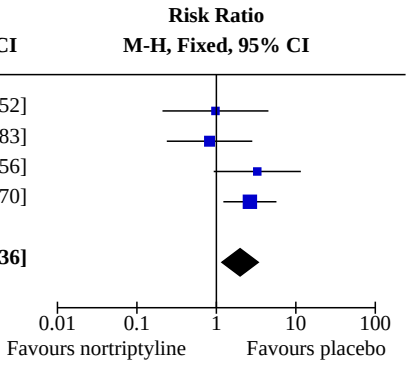
Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10: Nortriptyline versus placebo, Outcome 5: Dropouts due to drug

Study or Subgroup	Nortriptyline Events	Nortriptyline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Haggsträm 2006	3	38	3	37	16.4%	0.97 [0.21 , 4.52]
Hall 2004	4	39	5	40	26.6%	0.82 [0.24 , 2.83]
Prochazka 1998	10	108	3	106	16.3%	3.27 [0.93 , 11.56]
Wagena 2005	19	80	8	89	40.8%	2.64 [1.22 , 5.70]
Total (95% CI)		**265**		**272**	**100.0%**	**1.99 [1.18 , 3.36]**
Total events:	36		19			

Heterogeneity: Chi² = 3.92, df = 3 (P = 0.27); I² = 23%
Test for overall effect: Z = 2.56 (P = 0.01)
Test for subgroup differences: Not applicable



Comparison 11. Selective serotonin reuptake inhibitors (SSRIs) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Smoking cessation	4	1594	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.71, 1.22]
11.1.1 Fluoxetine	2	1236	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.65, 1.30]
11.1.2 Paroxetine	1	224	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.64, 1.82]
11.1.3 Sertraline	1	134	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.30, 1.64]
11.2 Adverse events	1	206	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.11, 67.40]
11.2.1 Fluoxetine	1	206	Risk Ratio (M-H, Fixed, 95% CI)	2.78 [0.11, 67.40]
11.3 Dropouts due to drug	3	1270	Risk Ratio (M-H, Fixed, 95% CI)	2.59 [1.70, 3.94]
11.3.1 Fluoxetine	2	1136	Risk Ratio (M-H, Fixed, 95% CI)	2.72 [1.75, 4.23]
11.3.2 Sertraline	1	134	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.30, 5.56]

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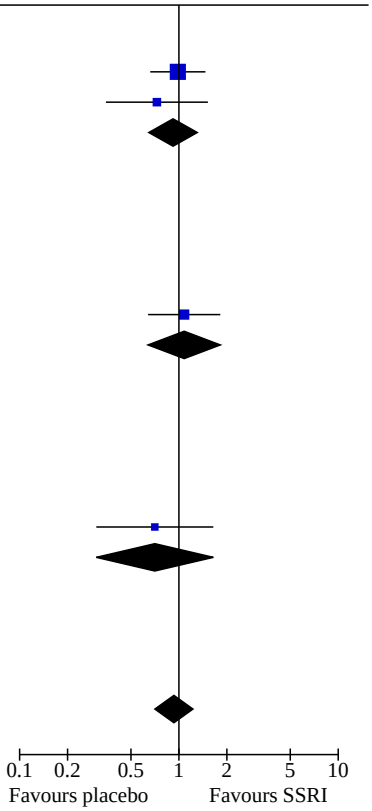
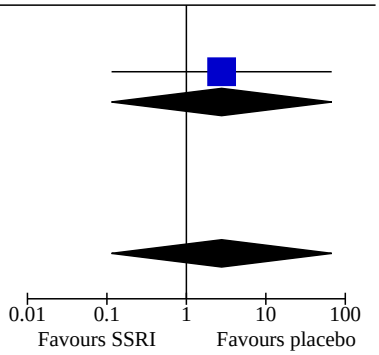
Analysis 11.1. Comparison 11: Selective serotonin reuptake inhibitors (SSRIs) versus placebo, Outcome 1: Smoking cessation

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 Fluoxetine						
Niaura 2002	64	656	33	333	47.9%	0.98 [0.66 , 1.47]
Spring 2007	11	124	15	123	16.5%	0.73 [0.35 , 1.52]
Subtotal (95% CI)		**780**		**456**	**64.4%**	**0.92 [0.65 , 1.30]**
Total events:	75		48			
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.63)						
11.1.2 Paroxetine						
Killen 2000	35	150	16	74	23.4%	1.08 [0.64 , 1.82]
Subtotal (95% CI)		**150**		**74**	**23.4%**	**1.08 [0.64 , 1.82]**
Total events:	35		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
11.1.3 Sertraline						
Covey 2002	8	68	11	66	12.2%	0.71 [0.30 , 1.64]
Subtotal (95% CI)		**68**		**66**	**12.2%**	**0.71 [0.30 , 1.64]**
Total events:	8		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Total (95% CI)		**998**		**596**	**100.0%**	**0.93 [0.71 , 1.22]**
Total events:	118		75			
Heterogeneity: Chi² = 1.23, df = 3 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.61)						
Test for subgroup differences: Chi² = 0.72, df = 2 (P = 0.70), I² = 0%						



Analysis 11.2. Comparison 11: Selective serotonin reuptake inhibitors (SSRIs) versus placebo, Outcome 2: Adverse events

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.2.1 Fluoxetine						
NCT00578669	1	107	0	99	100.0%	2.78 [0.11 , 67.40]
Subtotal (95% CI)		**107**		**99**	**100.0%**	**2.78 [0.11 , 67.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**107**		**99**	**100.0%**	**2.78 [0.11 , 67.40]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Not applicable						



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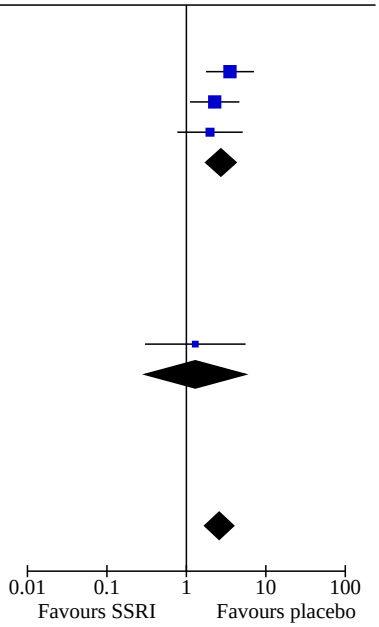
Analysis 11.3. Comparison 11: Selective serotonin reuptake inhibitors (SSRIs) versus placebo, Outcome 3: Dropouts due to drug

Study or Subgroup	SSRI Events	SSRI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.3.1 Fluoxetine						
Niaura 2002 (1)	80	328	8	116	36.2%	3.54 [1.76 , 7.09]
Niaura 2002 (2)	51	328	8	117	36.1%	2.27 [1.11 , 4.65]
Spring 2007	12	124	6	123	18.4%	1.98 [0.77 , 5.12]
Subtotal (95% CI)		**780**		**356**	**90.7%**	**2.72 [1.75 , 4.23]**
Total events:	143		22			
Heterogeneity: Chi² = 1.21, df = 2 (P = 0.54); I² = 0%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
11.3.2 Sertraline						
Covey 2002	4	68	3	66	9.3%	1.29 [0.30 , 5.56]
Subtotal (95% CI)		**68**		**66**	**9.3%**	**1.29 [0.30 , 5.56]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.35 (P = 0.73)						
Total (95% CI)		**848**		**422**	**100.0%**	**2.59 [1.70 , 3.94]**
Total events:	147		25			
Heterogeneity: Chi² = 2.07, df = 3 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%						



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 60 mg fluoxetine with half the placebo control group

(2) This study has been split into two comparisons for this analysis – this comparison compares 30 mg fluoxetine with half the placebo control group

Comparison 12. Monoamine oxidase inhibitor (MAOI) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 Smoking cessation	6	827	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.93, 1.79]
12.1.1 Moclobemide	1	88	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.67, 3.68]
12.1.2 Selegiline	5	739	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.88, 1.78]
12.2 Adverse events	2	391	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
12.2.1 Selegeline	1	101	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.91, 1.16]
12.2.2 EVT302	1	290	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
12.3 Psychiatric adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.3.1 Selegeline	1	5	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.02, 3.74]
12.4 Serious adverse events	4	804	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.37, 3.68]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.4.1 Moclobemide	1	87	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.4.2 Selegeline	1	101	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.4.3 Lazabemide	1	326	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.12, 2.32]
12.4.4 EVT302	1	290	Risk Ratio (M-H, Fixed, 95% CI)	7.00 [0.36, 134.32]
12.5 Insomnia	5	752	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.15, 1.97]
12.5.1 Moclobemide	1	87	Risk Ratio (M-H, Fixed, 95% CI)	5.21 [1.64, 16.61]
12.5.2 Selegeline	3	339	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.91, 1.60]
12.5.3 Lazabemide	1	326	Risk Ratio (M-H, Fixed, 95% CI)	2.66 [0.78, 9.00]
12.6 Anxiety	2	427	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.48, 2.22]
12.6.1 Selegeline	1	101	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.42, 2.27]
12.6.2 Lazabemide	1	326	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.19, 8.32]
12.7 Dropouts due to drug	5	910	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.07, 2.86]
12.7.1 Moclobemide	1	87	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.38, 10.12]
12.7.2 Selegeline	2	203	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.94, 3.85]
12.7.3 Lazabemide	1	330	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.69, 3.62]
12.7.4 EVT302	1	290	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.25, 8.84]

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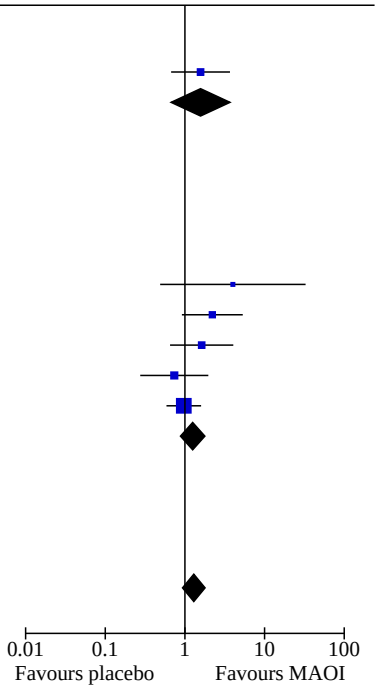
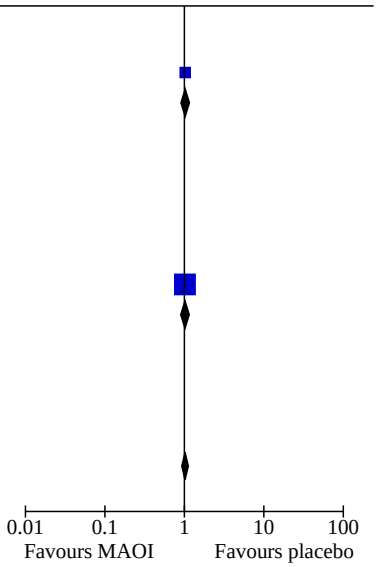
Analysis 12.1. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 1: Smoking cessation

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 Moclobemide						
Berlin 1995	11	44	7	44	13.0%	1.57 [0.67 , 3.68]
Subtotal (95% CI)		**44**		**44**	**13.0%**	**1.57 [0.67 , 3.68]**
Total events:	11		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
12.1.2 Selegiline						
George 2003	4	20	1	20	1.9%	4.00 [0.49 , 32.72]
Biberman 2003	14	56	6	53	11.4%	2.21 [0.92 , 5.32]
Kahn 2012	11	121	7	125	12.7%	1.62 [0.65 , 4.05]
Weinberger 2010	6	51	8	50	15.0%	0.74 [0.27 , 1.97]
Killen 2010	24	121	25	122	46.1%	0.97 [0.59 , 1.60]
Subtotal (95% CI)		**369**		**370**	**87.0%**	**1.25 [0.88 , 1.78]**
Total events:	59		47			
Heterogeneity: Chi² = 5.22, df = 4 (P = 0.27); I² = 23%						
Test for overall effect: Z = 1.25 (P = 0.21)						
Total (95% CI)		**413**		**414**	**100.0%**	**1.29 [0.93 , 1.79]**
Total events:	70		54			
Heterogeneity: Chi² = 5.52, df = 5 (P = 0.36); I² = 9%						
Test for overall effect: Z = 1.55 (P = 0.12)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.63), I² = 0%						



Analysis 12.2. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 2: Adverse events

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.2.1 Selegeline						
Weinberger 2010	47	51	45	50	28.9%	1.02 [0.91 , 1.16]
Subtotal (95% CI)		**51**		**50**	**28.9%**	**1.02 [0.91 , 1.16]**
Total events:	47		45			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.38 (P = 0.70)						
12.2.2 EVT302						
Berlin 2012	114	145	112	145	71.1%	1.02 [0.90 , 1.15]
Subtotal (95% CI)		**145**		**145**	**71.1%**	**1.02 [0.90 , 1.15]**
Total events:	114		112			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**196**		**195**	**100.0%**	**1.02 [0.93 , 1.12]**
Total events:	161		157			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.41 (P = 0.69)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



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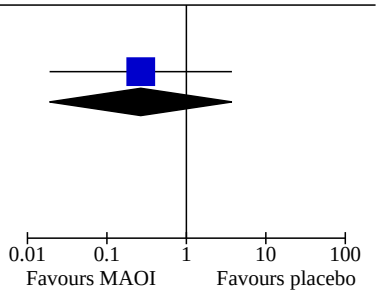
Analysis 12.3. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 3: Psychiatric adverse events

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.3.1 Selegeline						
Weinberger 2010	0	2	2	3	100.0%	0.27 [0.02 , 3.74]
Subtotal (95% CI)		**2**		**3**	**100.0%**	**0.27 [0.02 , 3.74]**
Total events:	0		2			

Heterogeneity: Not applicable

Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Not applicable



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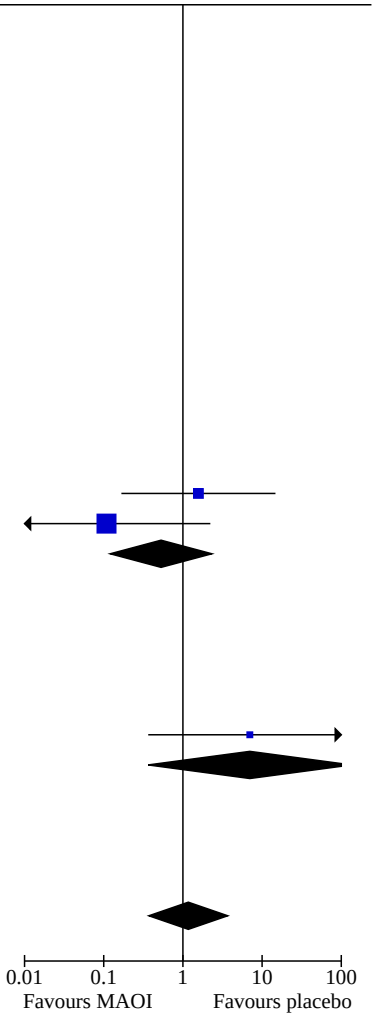
Analysis 12.4. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 4: Serious adverse events

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.4.1 Moclobemide						
Berlin 1995	0	44	0	43		Not estimable
Subtotal (95% CI)		**44**		**43**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.4.2 Selegeline						
Weinberger 2010	0	51	0	50		Not estimable
Subtotal (95% CI)		**51**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.4.3 Lazabemide						
Berlin 2002 (1)	3	107	1	56	26.0%	1.57 [0.17 , 14.75]
Berlin 2002 (2)	0	106	2	57	64.1%	0.11 [0.01 , 2.22]
Subtotal (95% CI)		**213**		**113**	**90.1%**	**0.53 [0.12 , 2.32]**
Total events:	3		3			
Heterogeneity: Chi² = 1.96, df = 1 (P = 0.16); I² = 49%						
Test for overall effect: Z = 0.84 (P = 0.40)						
12.4.4 EVT302						
Berlin 2012	3	145	0	145	9.9%	7.00 [0.36 , 134.32]
Subtotal (95% CI)		**145**		**145**	**9.9%**	**7.00 [0.36 , 134.32]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						
Total (95% CI)		**453**		**351**	**100.0%**	**1.17 [0.37 , 3.68]**
Total events:	6		3			
Heterogeneity: Chi² = 3.86, df = 2 (P = 0.15); I² = 48%						
Test for overall effect: Z = 0.27 (P = 0.79)						
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%						



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 100 mg lazabemide with half the placebo control grou

(2) This study has been split into two comparisons for this analysis – this comparison compares 200 mg lazabemide with half the placebo control grou

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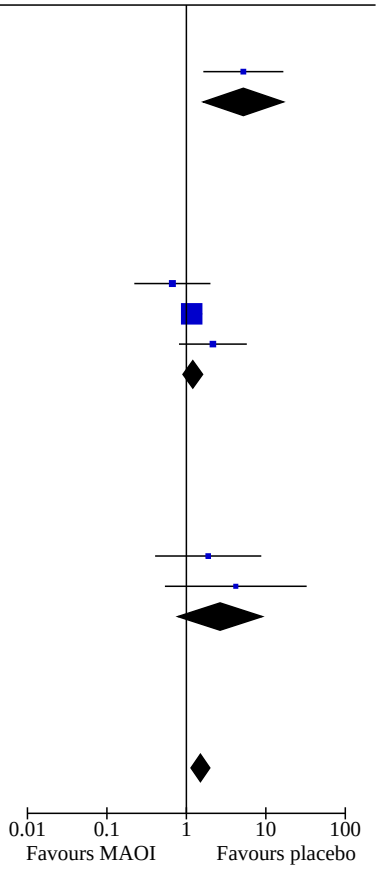
Analysis 12.5. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 5: Insomnia

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.5.1 Moclobemide						
Berlin 1995	16	44	3	43	5.1%	5.21 [1.64 , 16.61]
Subtotal (95% CI)		**44**		**43**	**5.1%**	**5.21 [1.64 , 16.61]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.79 (P = 0.005)						
12.5.2 Selegeline						
George 2003	4	20	6	20	10.0%	0.67 [0.22 , 2.01]
Killen 2010	49	99	42	99	70.0%	1.17 [0.86 , 1.58]
Weinberger 2010	11	51	5	50	8.4%	2.16 [0.81 , 5.76]
Subtotal (95% CI)		**170**		**169**	**88.4%**	**1.20 [0.91 , 1.60]**
Total events:	64		53			
Heterogeneity: Chi² = 2.50, df = 2 (P = 0.29); I² = 20%						
Test for overall effect: Z = 1.29 (P = 0.20)						
12.5.3 Lazabemide						
Berlin 2002 (1)	7	106	2	57	4.3%	1.88 [0.40 , 8.76]
Berlin 2002 (2)	8	107	1	56	2.2%	4.19 [0.54 , 32.64]
Subtotal (95% CI)		**213**		**113**	**6.5%**	**2.66 [0.78 , 9.00]**
Total events:	15		3			
Heterogeneity: Chi² = 0.38, df = 1 (P = 0.54); I² = 0%						
Test for overall effect: Z = 1.57 (P = 0.12)						
Total (95% CI)		**427**		**325**	**100.0%**	**1.50 [1.15 , 1.97]**
Total events:	95		59			
Heterogeneity: Chi² = 10.72, df = 5 (P = 0.06); I² = 53%						
Test for overall effect: Z = 2.94 (P = 0.003)						
Test for subgroup differences: Chi² = 7.02, df = 2 (P = 0.03), I² = 71.5%						



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 200 mg lazabemide with half the placebo control grou

(2) This study has been split into two comparisons for this analysis – this comparison compares 100 mg lazabemide with half the placebo control grou

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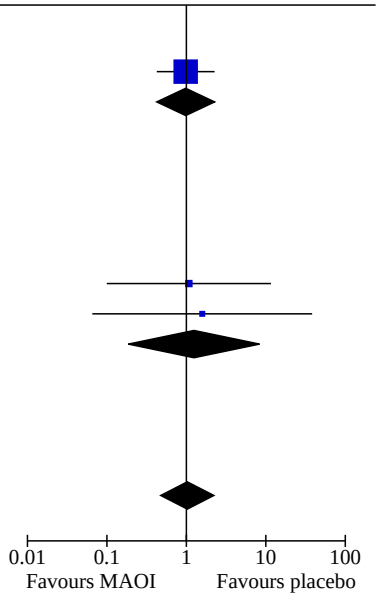
Analysis 12.6. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 6: Anxiety

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.6.1 Selegeline						
Weinberger 2010	9	51	9	50	82.3%	0.98 [0.42 , 2.27]
Subtotal (95% CI)		**51**		**50**	**82.3%**	**0.98 [0.42 , 2.27]**
Total events:	9		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
12.6.2 Lazabemide						
Berlin 2002 (1)	2	106	1	57	11.8%	1.08 [0.10 , 11.61]
Berlin 2002 (2)	1	107	0	56	5.9%	1.58 [0.07 , 38.25]
Subtotal (95% CI)		**213**		**113**	**17.7%**	**1.25 [0.19 , 8.32]**
Total events:	3		1			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
Total (95% CI)		**264**		**163**	**100.0%**	**1.03 [0.48 , 2.22]**
Total events:	12		10			
Heterogeneity: Chi² = 0.08, df = 2 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.82), I² = 0%						



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 200 mg lazabemide with half the placebo control grou

(2) This study has been split into two comparisons for this analysis – this comparison compares 100 mg lazabemide with half the placebo control grou

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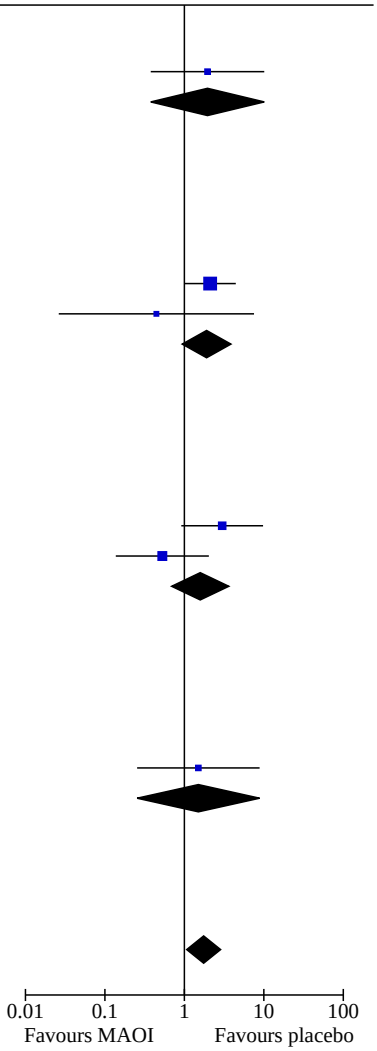
Analysis 12.7. Comparison 12: Monoamine oxidase inhibitor (MAOI) versus placebo, Outcome 7: Dropouts due to drug

Study or Subgroup	MAOI Events	MAOI Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.7.1 Moclobemide						
Berlin 1995	4	44	2	43	8.6%	1.95 [0.38 , 10.12]
Subtotal (95% CI)		**44**		**43**	**8.6%**	**1.95 [0.38 , 10.12]**
Total events:	4		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
12.7.2 Selegeline						
Killen 2010	19	99	9	99	38.3%	2.11 [1.00 , 4.44]
Weinberger 2010	0	2	1	3	5.5%	0.44 [0.03 , 7.52]
Subtotal (95% CI)		**101**		**102**	**43.8%**	**1.90 [0.94 , 3.85]**
Total events:	19		10			
Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 1.79 (P = 0.07)						
12.7.3 Lazabemide						
Berlin 2002 (1)	17	108	3	57	16.7%	2.99 [0.91 , 9.78]
Berlin 2002 (2)	4	108	4	57	22.3%	0.53 [0.14 , 2.03]
Subtotal (95% CI)		**216**		**114**	**39.0%**	**1.58 [0.69 , 3.62]**
Total events:	21		7			
Heterogeneity: Chi² = 3.66, df = 1 (P = 0.06); I² = 73%						
Test for overall effect: Z = 1.09 (P = 0.28)						
12.7.4 EVT302						
Berlin 2012	3	145	2	145	8.5%	1.50 [0.25 , 8.84]
Subtotal (95% CI)		**145**		**145**	**8.5%**	**1.50 [0.25 , 8.84]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**506**		**404**	**100.0%**	**1.75 [1.07 , 2.86]**
Total events:	47		21			
Heterogeneity: Chi² = 5.01, df = 5 (P = 0.41); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 0.16, df = 3 (P = 0.98), I² = 0%						



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 100 mg lazabemide with half the placebo control grou

(2) This study has been split into two comparisons for this analysis – this comparison compares 200 mg lazabemide with half the placebo control grou

Comparison 13. Venlafaxine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.2 Dropouts due to drug	1	152	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.33, 28.95]

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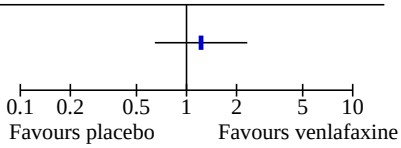
Analysis 13.1. Comparison 13: Venlafaxine versus placebo, Outcome 1: Smoking cessation

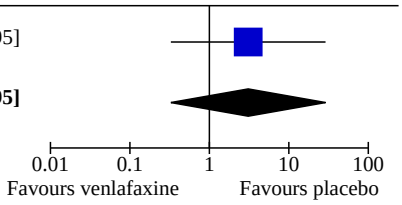
Study or Subgroup	Venlaxafine Events	Venlaxafine Total	Control Events	Control Total	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2005	16	71	14	76	1.22 [0.64 , 2.32]



Analysis 13.2. Comparison 13: Venlafaxine versus placebo, Outcome 2: Dropouts due to drug

Study or Subgroup	Venlaxafine Events	Venlaxafine Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cinciripini 2005	3	75	1	77	100.0%	3.08 [0.33 , 28.95]
Total (95% CI)		**75**		**77**	**100.0%**	**3.08 [0.33 , 28.95]**
Total events:	3		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)
Test for subgroup differences: Not applicable



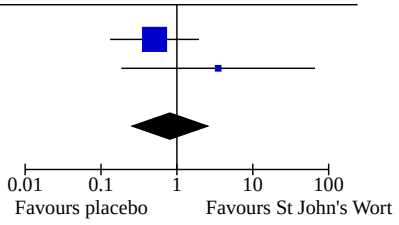
Comparison 14. Hypericum (St John's wort) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Smoking cessation	2	261	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.26, 2.53]
14.2 Serious adverse events	1	143	Risk Ratio (M-H, Fixed, 95% CI)	2.37 [0.36, 15.57]
14.3 All-cause mortality	1	143	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.13, 73.24]
14.4 Dropouts due to drug	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.36, 3.96]

Analysis 14.1. Comparison 14: Hypericum (St John's wort) versus placebo, Outcome 1: Smoking cessation

Study or Subgroup	St John's Wort Events	St John's Wort Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parsons 2009	3	71	6	72	89.9%	0.51 [0.13 , 1.95]
Sood 2010	3	79	0	39	10.1%	3.50 [0.19 , 66.12]
Total (95% CI)		**150**		**111**	**100.0%**	**0.81 [0.26 , 2.53]**
Total events:	6		6			

Heterogeneity: Chi² = 1.42, df = 1 (P = 0.23); I² = 29%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



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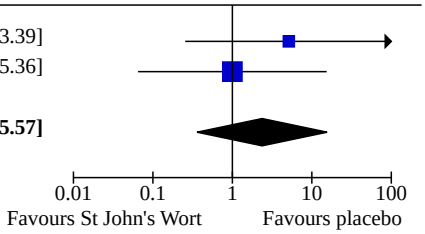
Analysis 14.2. Comparison 14: Hypericum (St John's wort) versus placebo, Outcome 2: Serious adverse events

Study or Subgroup	St John's Wort Events	St John's Wort Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parsons 2009 (1)	2	36	0	37	33.0%	5.14 [0.26 , 103.39]
Parsons 2009 (2)	1	35	1	35	67.0%	1.00 [0.07 , 15.36]
Total (95% CI)		**71**		**72**	**100.0%**	**2.37 [0.36 , 15.57]**
Total events:	3		1			

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

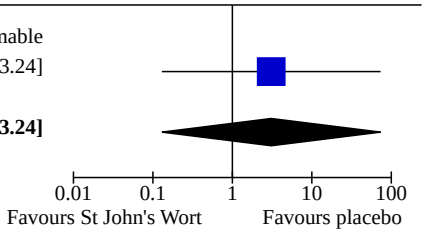


Footnotes
(1) SJW active + Cr active versus SJW placebo + Cr active
(2) SJW active + Cr placebo versus SJW placebo + Cr placebo

Analysis 14.3. Comparison 14: Hypericum (St John's wort) versus placebo, Outcome 3: All-cause mortality

Study or Subgroup	St John's Wort Events	St John's Wort Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parsons 2009 (1)	0	35	0	35		Not estimable
Parsons 2009 (2)	1	36	0	37	100.0%	3.08 [0.13 , 73.24]
Total (95% CI)		**71**		**72**	**100.0%**	**3.08 [0.13 , 73.24]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.70 (P = 0.49)
Test for subgroup differences: Not applicable

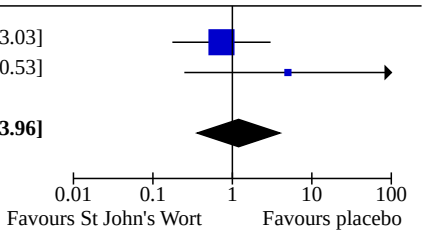


Footnotes
(1) SJW active + Cr placebo versus SJW placebo + Cr placebo
(2) SJW active + Cr active versus SJW placebo + Cr active

Analysis 14.4. Comparison 14: Hypericum (St John's wort) versus placebo, Outcome 4: Dropouts due to drug

Study or Subgroup	St John's Wort Events	St John's Wort Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Parsons 2009 (1)	3	36	4	35	89.0%	0.73 [0.18 , 3.03]
Parsons 2009 (2)	2	35	0	35	11.0%	5.00 [0.25 , 100.53]
Total (95% CI)		**71**		**70**	**100.0%**	**1.20 [0.36 , 3.96]**
Total events:	5		4			

Heterogeneity: Chi² = 1.34, df = 1 (P = 0.25); I² = 25%
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Footnotes
(1) SJW active + Cr active versus SJW placebo + Cr active
(2) SJW active + Cr placebo versus SJW placebo + Cr placebo

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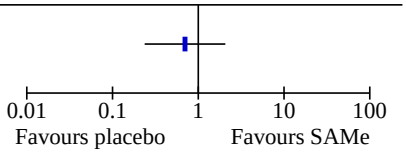
Comparison 15. S-Adenosyl-L-Methionine (SAMe) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.2 Adverse events	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.69, 3.65]
15.3 Insomnia	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.07, 36.11]
15.4 Dropouts due to drug	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.24, 17.76]

Analysis 15.1. Comparison 15: S-Adenosyl-L-Methionine (SAMe) versus placebo, Outcome 1: Smoking cessation

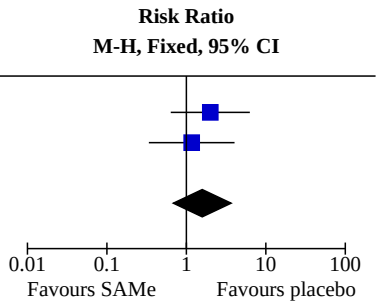
Study or Subgroup	SAMe Events	SAMe Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Sood 2012	7	80	5	40	0.70 [0.24 , 2.07]



Analysis 15.2. Comparison 15: S-Adenosyl-L-Methionine (SAMe) versus placebo, Outcome 2: Adverse events

Study or Subgroup	SAMe Events	SAMe Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sood 2012 (1)	12	40	3	20	50.0%	2.00 [0.64 , 6.29]
Sood 2012 (2)	7	40	3	20	50.0%	1.17 [0.34 , 4.04]
Total (95% CI)		**80**		**40**	**100.0%**	**1.58 [0.69 , 3.65]**
Total events:	19		6			

Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.08 (P = 0.28)
Test for subgroup differences: Not applicable



Footnotes

(1) This study has been split into two comparisons for this analysis – this comparison compares 1600 mg SAMe with half the placebo control group
(2) This study has been split into two comparisons for this analysis – this comparison compares 800 mg SAMe with half the placebo control group

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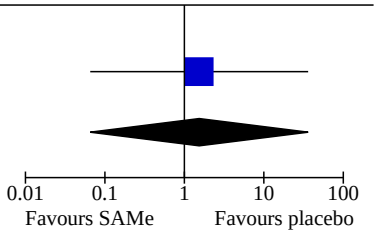
Analysis 15.3. Comparison 15: S-Adenosyl-L-Methionine (SAMe) versus placebo, Outcome 3: Insomnia

Study or Subgroup	SAMe Events	SAMe Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sood 2012 (1)	0	40	0	20		Not estimable
Sood 2012 (2)	1	40	0	20	100.0%	1.54 [0.07 , 36.11]
Total (95% CI)		**80**		**40**	**100.0%**	**1.54 [0.07 , 36.11]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.27 (P = 0.79)
Test for subgroup differences: Not applicable

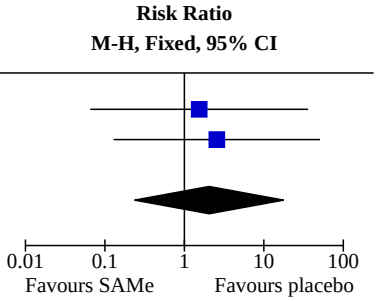


Footnotes
(1) This study has been split into two comparisons for this analysis – this comparison compares 800 mg SAMe with half the placebo control group
(2) This study has been split into two comparisons for this analysis – this comparison compares 1600 mg SAMe with half the placebo control group

Analysis 15.4. Comparison 15: S-Adenosyl-L-Methionine (SAMe) versus placebo, Outcome 4: Dropouts due to drug

Study or Subgroup	SAMe Events	SAMe Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sood 2012 (1)	1	40	0	20	50.0%	1.54 [0.07 , 36.11]
Sood 2012 (2)	2	40	0	20	50.0%	2.56 [0.13 , 50.95]
Total (95% CI)		**80**		**40**	**100.0%**	**2.05 [0.24 , 17.76]**
Total events:	3		0			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Footnotes
(1) This study has been split into two comparisons for this analysis – this comparison compares 1600 mg SAMe with half the placebo control group
(2) This study has been split into two comparisons for this analysis – this comparison compares 800 mg SAMe with half the placebo control group

Comparison 16. Nortriptyline plus nicotine replacement therapy (NRT) versus NRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16.1 Smoking cessation	4	1644	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.94, 1.55]
16.2 Insomnia	1	158	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.30, 3.32]
16.3 Dropouts due to drug	1	158	Risk Ratio (M-H, Fixed, 95% CI)	10.00 [1.31, 76.28]

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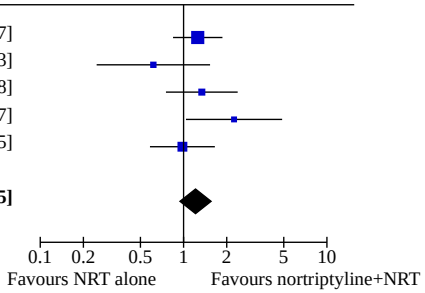
Analysis 16.1. Comparison 16: Nortriptyline plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 1: Smoking cessation

Study or Subgroup	Nortriptyline & NRT Events	Nortriptyline & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Aveyard 2008	49	445	40	456	41.4%	1.26 [0.84 , 1.87]
Hall 2004 (1)	6	39	10	40	10.3%	0.62 [0.25 , 1.53]
Hall 2004 (2)	17	40	13	41	13.5%	1.34 [0.75 , 2.38]
Prochazka 2004	18	79	8	79	8.4%	2.25 [1.04 , 4.87]
Richmond 2013	24	206	26	219	26.4%	0.98 [0.58 , 1.65]
Total (95% CI)		**809**		**835**	**100.0%**	**1.21 [0.94 , 1.55]**
Total events:	114		97			

Heterogeneity: Chi² = 5.37, df = 4 (P = 0.25); I² = 26%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

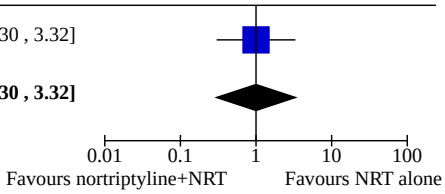


Footnotes
(1) With brief behavioural support
(2) With extended behavioural support

Analysis 16.2. Comparison 16: Nortriptyline plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 2: Insomnia

Study or Subgroup	Nortriptyline & NRT Events	Nortriptyline & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Prochazka 2004	5	79	5	79	100.0%	1.00 [0.30 , 3.32]
Total (95% CI)		**79**		**79**	**100.0%**	**1.00 [0.30 , 3.32]**
Total events:	5		5			

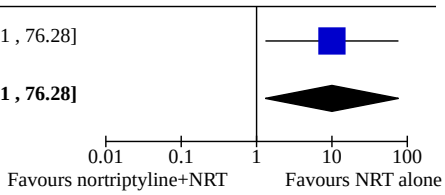
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 16.3. Comparison 16: Nortriptyline plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 3: Dropouts due to drug

Study or Subgroup	Nortriptyline & NRT Events	Nortriptyline & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Prochazka 2004	10	79	1	79	100.0%	10.00 [1.31 , 76.28]
Total (95% CI)		**79**		**79**	**100.0%**	**10.00 [1.31 , 76.28]**
Total events:	10		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable



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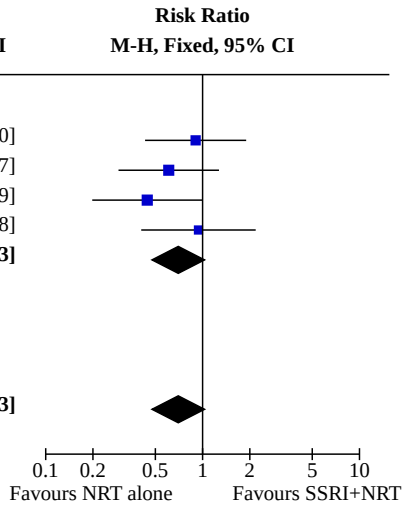
Comparison 17. Selective serotonin reuptake inhibitor (SSRI) plus NRT versus NRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Smoking cessation	3	466	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.03]
17.1.1 Fluoxetine	3	466	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.48, 1.03]

Analysis 17.1. Comparison 17: Selective serotonin reuptake inhibitor (SSRI) plus NRT versus NRT alone, Outcome 1: Smoking cessation

Study or Subgroup	SSRI & NRT Events	SSRI & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
17.1.1 Fluoxetine						
Blondal 1999	10	48	12	52	24.1%	0.90 [0.43 , 1.90]
Brown 2014 (1)	12	71	10	36	27.8%	0.61 [0.29 , 1.27]
Brown 2014 (2)	9	73	10	36	28.1%	0.44 [0.20 , 0.99]
Saules 2004	14	102	7	48	20.0%	0.94 [0.41 , 2.18]
Subtotal (95% CI)		**294**		**172**	**100.0%**	**0.70 [0.48 , 1.03]**
Total events:	45		39			
Heterogeneity: Chi² = 2.29, df = 3 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Total (95% CI)		**294**		**172**	**100.0%**	**0.70 [0.48 , 1.03]**
Total events:	45		39			
Heterogeneity: Chi² = 2.29, df = 3 (P = 0.51); I² = 0%						
Test for overall effect: Z = 1.82 (P = 0.07)						
Test for subgroup differences: Not applicable						



Footnotes

(1) This intervention arm received 16 weeks of treatment

(2) This intervention arm received 10 weeks of treatment

Comparison 18. Selegeline plus nicotine replacement therapy (NRT) versus NRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.1 Serious adverse events	1	109	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
18.2 Dropouts due to drug	1	109	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.42, 4.75]

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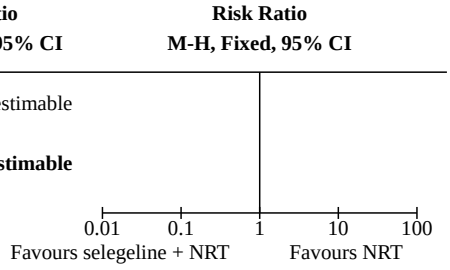
Analysis 18.1. Comparison 18: Selegeline plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 1: Serious adverse events

Study or Subgroup	Selegeline & NRT Events	Selegeline & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Biberman 2003	0	56	0	53		Not estimable
Total (95% CI)		**56**		**53**		**Not estimable**
Total events:	0		0			

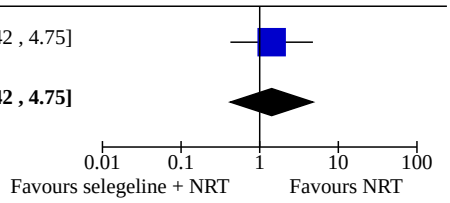
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 18.2. Comparison 18: Selegeline plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 2: Dropouts due to drug

Study or Subgroup	Selegeline & NRT Events	Selegeline & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Biberman 2003	6	56	4	53	100.0%	1.42 [0.42 , 4.75]
Total (95% CI)		**56**		**53**	**100.0%**	**1.42 [0.42 , 4.75]**
Total events:	6		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.57 (P = 0.57)
Test for subgroup differences: Not applicable



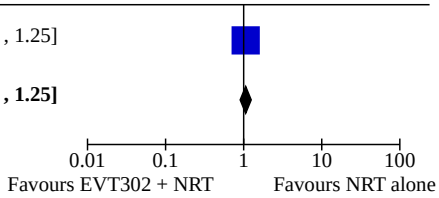
Comparison 19. EVT302 plus nicotine replacement therapy (NRT) versus NRT alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Adverse events	1	122	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.90, 1.25]
19.2 Serious adverse events	1	122	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.23]
19.3 Dropouts due to drug	1	122	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.12, 72.23]

Analysis 19.1. Comparison 19: EVT302 plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 1: Adverse events

Study or Subgroup	EVT302 & NRT Events	EVT302 & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2012	52	61	49	61	100.0%	1.06 [0.90 , 1.25]
Total (95% CI)		**61**		**61**	**100.0%**	**1.06 [0.90 , 1.25]**
Total events:	52		49			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



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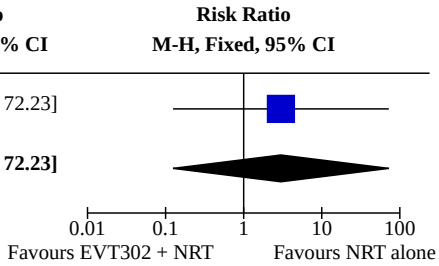
Analysis 19.2. Comparison 19: EVT302 plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 2: Serious adverse events

Study or Subgroup	EVT302 & NRT Events	EVT302 & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2012	1	61	0	61	100.0%	3.00 [0.12 , 72.23]
Total (95% CI)		**61**		**61**	**100.0%**	**3.00 [0.12 , 72.23]**
Total events:	1		0			

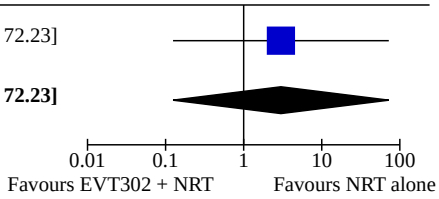
Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



Analysis 19.3. Comparison 19: EVT302 plus nicotine replacement therapy (NRT) versus NRT alone, Outcome 3: Dropouts due to drug

Study or Subgroup	EVT302 & NRT Events	EVT302 & NRT Total	NRT alone Events	NRT alone Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2012	1	61	0	61	100.0%	3.00 [0.12 , 72.23]
Total (95% CI)		**61**		**61**	**100.0%**	**3.00 [0.12 , 72.23]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.50)
Test for subgroup differences: Not applicable



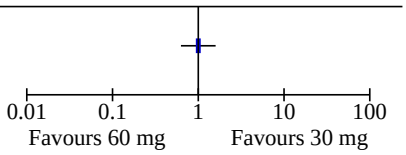
Comparison 20. Fluoxetine (30 mg versus 60 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.2 Dropouts due to drug	1	656	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.87]

Analysis 20.1. Comparison 20: Fluoxetine (30 mg versus 60 mg), Outcome 1: Smoking cessation

Study or Subgroup	30 mg Events	30 mg Total	60 mg Events	60 mg Total	Risk Ratio M-H, Fixed, 95% CI
Niaura 2002	32	328	32	328	1.00 [0.63 , 1.59]

Test for subgroup differences: Not applicable



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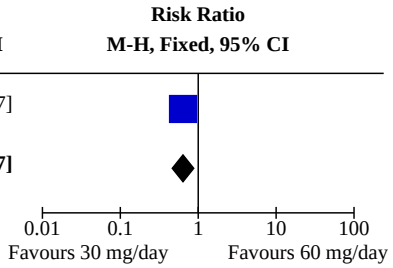
Analysis 20.2. Comparison 20: Fluoxetine (30 mg versus 60 mg), Outcome 2: Dropouts due to drug

Study or Subgroup	30 mg/day Events	30 mg/day Total	60 mg/day Events	60 mg/day Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Niaura 2002	51	328	80	328	100.0%	0.64 [0.46 , 0.87]
Total (95% CI)		**328**		**328**	**100.0%**	**0.64 [0.46 , 0.87]**
Total events:	51		80			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.79 (P = 0.005)
Test for subgroup differences: Not applicable



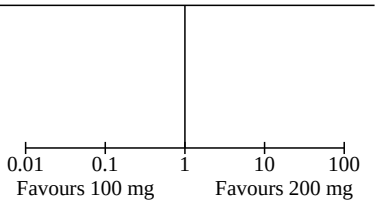
Comparison 21. Lazabemide (100 mg versus 200 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Serious adverse events	1	213	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
21.2 Insomnia	1	213	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.43, 3.01]
21.3 Anxiety	1	213	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.38]
21.4 Dropouts due to drug	1	216	Risk Ratio (M-H, Fixed, 95% CI)	4.25 [1.48, 12.22]

Analysis 21.1. Comparison 21: Lazabemide (100 mg versus 200 mg), Outcome 1: Serious adverse events

Study or Subgroup	100 mg Events	100 mg Total	200 mg Events	200 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2002	0	107	0	106		Not estimable
Total (95% CI)		**107**		**106**		**Not estimable**
Total events:	0		0			

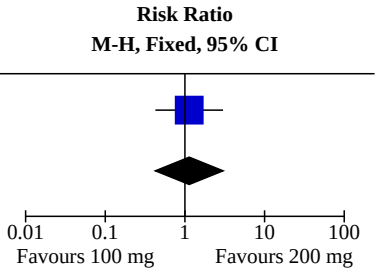
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 21.2. Comparison 21: Lazabemide (100 mg versus 200 mg), Outcome 2: Insomnia

Study or Subgroup	100mg Events	100mg Total	200mg Events	200mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2002	8	107	7	106	100.0%	1.13 [0.43 , 3.01]
Total (95% CI)		**107**		**106**	**100.0%**	**1.13 [0.43 , 3.01]**
Total events:	8		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



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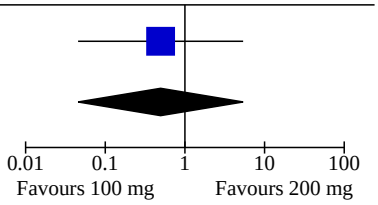
Analysis 21.3. Comparison 21: Lazabemide (100 mg versus 200 mg), Outcome 3: Anxiety

Study or Subgroup	100mg Events	100mg Total	200mg Events	200mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2002	1	107	2	106	100.0%	0.50 [0.05 , 5.38]
Total (95% CI)		**107**		**106**	**100.0%**	**0.50 [0.05 , 5.38]**
Total events:	1		2			

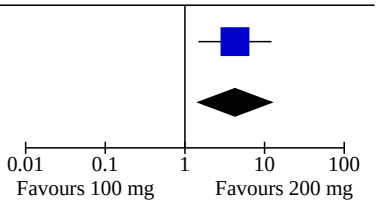
Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 21.4. Comparison 21: Lazabemide (100 mg versus 200 mg), Outcome 4: Dropouts due to drug

Study or Subgroup	100 mg Events	100 mg Total	200 mg Events	200 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Berlin 2002	17	108	4	108	100.0%	4.25 [1.48 , 12.22]
Total (95% CI)		**108**		**108**	**100.0%**	**4.25 [1.48 , 12.22]**
Total events:	17		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.69 (P = 0.007)
Test for subgroup differences: Not applicable



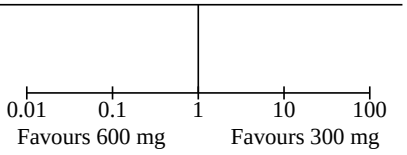
Comparison 22. Hypericum (St John's wort) (300 mg versus 600 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
22.2 Adverse events	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.63, 2.67]

Analysis 22.1. Comparison 22: Hypericum (St John's wort) (300 mg versus 600 mg), Outcome 1: Smoking cessation

Study or Subgroup	SJW 300 mg Events	SJW 300 mg Total	SJW 600 mg Events	SJW 600 mg Total	Risk Ratio M-H, Fixed, 95% CI
Barnes 2006	0	15	0	13	Not estimable

Test for subgroup differences: Not applicable



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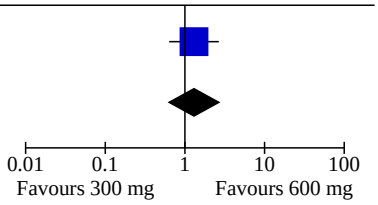
Analysis 22.2. Comparison 22: Hypericum (St John's wort) (300 mg versus 600 mg), Outcome 2: Adverse events

Study or Subgroup	SJW 300mg Events	SJW 300mg Total	SJW 600mg Events	SJW 600mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barnes 2006	9	15	6	13	100.0%	1.30 [0.63 , 2.67]
Total (95% CI)		**15**		**13**	**100.0%**	**1.30 [0.63 , 2.67]**
Total events:	9		6			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



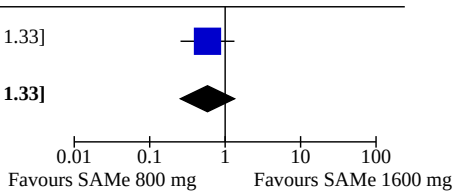
Comparison 23. S-Adenosyl-L-Methionine (SAMe) (800 mg versus 1600 mg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.1 Adverse events	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.26, 1.33]
23.2 Dropouts due to drug	1	80	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.19, 21.18]

Analysis 23.1. Comparison 23: S-Adenosyl-L-Methionine (SAMe) (800 mg versus 1600 mg), Outcome 1: Adverse events

Study or Subgroup	SAMe 800 mg Events	SAMe 800 mg Total	SAMe 1600 mg Events	SAMe 1600 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sood 2012	7	40	12	40	100.0%	0.58 [0.26 , 1.33]
Total (95% CI)		**40**		**40**	**100.0%**	**0.58 [0.26 , 1.33]**
Total events:	7		12			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



Analysis 23.2. Comparison 23: S-Adenosyl-L-Methionine (SAMe) (800 mg versus 1600 mg), Outcome 2: Dropouts due to drug

Study or Subgroup	SAMe 800 mg Events	SAMe 800 mg Total	SAMe 1600 mg Events	SAMe 1600 mg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sood 2012	2	40	1	40	100.0%	2.00 [0.19 , 21.18]
Total (95% CI)		**40**		**40**	**100.0%**	**2.00 [0.19 , 21.18]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable

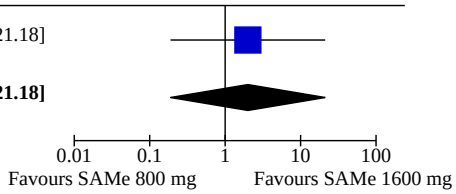


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Table 1. Sensitivity analyses excluding industry-supported studies

Comparison and outcome	RR and CI excluding industry funded studies	RR and CI excluding studies with funding or medication provided by industry
Analysis 1.1	1.49 (1.33 to 1.66); studies = 26	1.48 (1.26 to 1.74); studies = 14
Analysis 1.4	1.24 (1.14 to 1.35); studies = 9	1.24 (1.09 to 1.41); studies = 7
Analysis 1.5	0.85 (0.60 to 1.21); studies = 11	0.88 (0.61 to 1.26); studies = 10
Analysis 1.6	1.19 (0.72 to 1.94); studies = 4	1.19 (0.72 to 1.94); studies = 4
Analysis 1.7	2.04 (0.23 to 17.84); studies = 7	2.61 (0.11 to 60.51); studies = 6
Analysis 1.8	Not estimable	Not estimable
Analysis 1.9	Not estimable	Not estimable
Analysis 1.10	Not estimable	Not estimable
Analysis 1.11	1.51 (0.44 to 5.27); studies = 6	1.51 (0.44 to 5.27); studies = 6
Analysis 1.12	2.08 (0.93 to 4.64); studies = 4	2.27 (0.46 to 11.17); studies = 2
Analysis 1.13	1.85 (1.55 to 2.20); studies = 11	1.85 (1.55 to 2.20); studies = 7
Analysis 1.14	1.32 (0.98 to 1.77); studies = 11	1.11 (0.77 to 1.58); studies = 8
Analysis 2.1	1.09 (0.91 to 1.32); studies = 11	0.78 (0.46 to 1.32); studies = 4
Analysis 2.2	1.21 (1.02 to 1.43); studies = 2	1.24 (0.98 to 1.56); studies = 1
Analysis 2.3	2.06 (0.20 to 21.67); studies = 2	Not estimable
Analysis 2.4	2.93 (0.12 to 72.31); studies = 1	2.93 (0.12 to 72.31); studies = 1
Analysis 2.5	Not estimable	Not estimable
Analysis 2.6	Not estimable	Not estimable
Analysis 2.7	0.68 (0.12 to 3.98); studies = 1	0.68 (0.12 to 3.98); studies = 1
Analysis 2.10	1.04 (0.16 to 6.83); studies = 1	Not estimable
Analysis 2.8	1.26 (0.60 to 2.65); studies = 1	Not estimable
Analysis 2.9	1.62 (0.72 to 3.65); studies = 2	Not estimable
Analysis 3.1	1.14 (0.85 to 1.51); studies = 2	Not estimable
Analysis 3.2	1.05 (0.98 to 1.12); studies = 3	1.80 (0.53 to 6.16); studies = 1
Analysis 3.3	1.31 (0.60 to 2.84); studies = 3	Not estimable
Analysis 3.4	1.15 (1.03 to 1.30); studies = 2	Not estimable

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Table 1. Sensitivity analyses excluding industry-supported studies *(Continued)*

Analysis 3.5	Not estimable	Not estimable
Analysis 3.6	0.34 (0.01 to 8.27); studies = 2	Not estimable
Analysis 3.7	0.34 (0.04 to 3.27); studies = 2	Not estimable
Analysis 3.8	Not estimable	Not estimable
Analysis 3.9	0.34 (0.01 to 8.40); studies = 1	Not estimable
Analysis 3.12	0.72 (0.37 to 1.40); studies = 4	Not estimable
Analysis 3.10	1.49 (0.95 to 2.33); studies = 1	Not estimable
Analysis 3.11	1.48 (1.15 to 1.89)	Not estimable

CI: confidence interval; RR: risk ratio

Table 2. Depression as a moderator of the relationship between antidepressants and smoking cessation

Study ID	Antidepressant	Direction of relationship	Evidence for interaction
Anthenelli 2016	Bupropion	None	"Varenicline, bupropion and NRT were all effective in smokers with mental health problems (assessed with a number of variables, e.g. diagnostic history, HADS, use of psychotropic medication), and their relative efficacy was similar to that in smokers without a psychiatric history."
Aubin 2004	Bupropion	None	"A similar subgroup analysis performed according to previous history of depression (evaluated by the MINI questionnaire) also failed to reveal an interaction with bupropion treatment."
Aveyard 2008	Nortriptyline	None	"Participants randomised to nortriptyline plus nicotine replacement therapy for smoking cessation experienced less depression (OR 0.15) and anxiety early in the quit attempt when the risk of return to smoking is at its highest than those randomised to placebo plus nicotine replacement therapy. Contrary to expectations, no evidence was found that this led to greater abstinence."
Cinciripini 2018	Bupropion	None	"Several measures failed to demonstrate significant effects as a function of time, treatment, or the interaction of treatment and time. For example, CES-D scales including Depressive Affect, Interpersonal Relations, Positive Affect, and Somatic Symptoms, failed to demonstrate any effects of treatment or any treatment by time interactions."
Da Costa 2002	Nortriptyline	Negative	"The best results were obtained with educational intervention, in those patients having no personal history of depression, who received the active drug. A negative history of depression was, however, the most important factor for the success of the treatment."
George 2003	Selegiline	None (history), negative (current)	“There was no significant influence of a past history of major depression on smoking cessation outcomes (B = -0.49, SE = 0.90, Wald Statistic = 0.29, df = 1, p = .59), and when past his-

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Table 2. Depression as a moderator of the relationship between antidepressants and smoking cessation *(Continued)*

			tory of major depression was entered into the logistic regression model as a covariate, it did not predict treatment failure with selegiline study medication (medication past history of depression status interaction: B = -0.02, SE = 1.03, Wald statistic = 0.00, df = 1, p = .98)." and "Furthermore, bivariate logistic regression analysis confirmed that having depressive symptoms at baseline negatively predicted smoking cessation outcomes with SEL on this continuous abstinence measure (B = 18.9, SE = 0.58, Wald statistic = 1048.9, df = 1, P < .01)."
Hall 2002	Bupropion, nortripyline	Positive (for bupropion)	“There were higher abstinence rates for bupropion than nortriptyline for participants with a history of depressive disorder"
Kahn 2012	Selegiline	None	"At the final HAM-D assessment, the selegiline group (n = 90) reported a mean increase of 0.41 points and the placebo group (n = 85) reported a mean increase of 0.21 points. The difference between treatment groups was not statistically significant (t test, p = .65)."
Kalman 2011	Bupropion	None	“Interaction effects between medication and tobacco dependence and medication and depressive symptoms were also nonsignificant.”
Killen 2000	Paroxetine	None	"A stepwise logistic regression analysis was used to examine the association of abstinence at Week 26 with the variables [including depression scores] listed in Table 1. None of these variables were prospectively associated with abstinence."
Saules 2004	Fluoxetine	None	“Examination of pre-specified subgroups (i.e., gender, race, and history of major depressive disorder) did not reveal significant differences in smoking cessation by group”
Spring 2007	Fluoxetine	None	Fluoxetine initially enhanced cessation for smokers with a history of major depression (P = .02) but subsequently impaired cessation regardless of depressive history.
Stapleton 2013	Bupropion	Positive	“There was some evidence that the relative effectiveness of bupropion and NRT differed according to depression ($\chi 2$ = 2.86, P = 0.091), with bupropion appearing more beneficial than NRT in those with a history of depression (29.8 versus 18.5%)."
Wagena 2005	Bupropion, nortriptyline	Positive (for bupropion)	“Results indicated that bupropion SR [sustained release] treatment was efficacious in helping smokers who were classified as depressed in achieving prolonged abstinence from smoking throughout the 26-week period. The number of depressed participants from the nortriptyline-treated group was considered too low to study this relationship."

CES-D: Center for Epidemiologic Studies Depression; df: degrees of freedom; HADS: Hospital Anxiety and Depression scale; HAM-D: Hamilton Depression Rating Scale; MINI: Mini-International Neuropsychiatric Interview; NRT: nicotine replacement therapy; OR: odds ratio; SE: standard error

APPENDICES

Appendix 1. Specialized Register search strategy

Searched using CRS web

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#1 (bupropion or zyban):TI,AB,MH,EMT,KY,XKY

#2 nortriptyline:TI,AB,MH,EMT,KY,XKY

#3 (monoamine oxidase inhib*):TI,AB,MH,EMT,KY,XKY

#4 (moclobemide or selegiline or lazabemide):TI,AB,MH,EMT,KY,XKY

#5 (SSRI* or (selective serotonin re?uptake inhibitor*)):TI,AB,MH,EMT,KY,XKY

#6 (fluoxetine or sertraline or paroxetine or zimelidine):TI,AB,MH,EMT,KY,XKY

#7 (doxepin or imipramine or tryptophan or venlafaxine):TI,AB,MH,EMT,KY,XKY

#8 ((john?s wort) or hypericum):TI,AB,MH,EMT,KY,XKY

#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

(MH, EMT, KY and XKY are keyword fields)

WHAT'S NEW

Date	Event	Description
4 May 2021	Amended	Minor corrections to figures in Summary of Findings tables (no changes to interpretation)

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 3, 1997

Date	Event	Description
24 January 2020	New search has been performed	33 new included studies identified and study data added to existing comparators
24 January 2020	New citation required but conclusions have not changed	33 new included studies; additional safety analyses added. Main conclusions remain unchanged
14 June 2016	Amended	Corrected typographical error in Abstract results. Risk ratio for buproprion + NRT (12 trials) changed from 1.9 to 1.19. Now matches meta-analysis 1.5
8 October 2013	New search has been performed	Updated with 24 new included studies. Studies of S-Adenosyl-L-Methionine and St John's wort included for the first time. Meta-analyses of serious adverse events added
8 October 2013	New citation required but conclusions have not changed	Conclusions largely unchanged. Efficacy findings unchanged
22 June 2011	Amended	Additional table converted to appendix to correct pdf format
5 October 2009	Amended	Correction to excluded studies table, detail added to Carrão 2007

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Date	Event	Description
30 July 2009	New search has been performed	Updated with 13 new included trials including 3 of selegiline, not previously covered. No substantial change to effects; main conclusions not altered
17 June 2008	Amended	Converted to new review format
11 October 2006	New citation required but conclusions have not changed	Seventeen new trials were added to the review for Issue 1, 2007. There were no major changes to the reviewers' conclusions.
16 July 2004	New citation required but conclusions have not changed	New trials of bupropion, nortriptyline and fluoxetine were added for Issue 4, 2004, and additional information on adverse effects was included. There were no major changes to the reviewers' conclusions.
8 January 2003	New citation required but conclusions have not changed	New trials of bupropion and nortriptyline were added to the review in Issue 2, 2003. There were no major changes to the reviewers' conclusions.
19 September 2001	New citation required but conclusions have not changed	Four new studies on bupropion, and one each on nortriptyline and paroxetine were added to the review in Issue 1, 2002. In press data from a trial of fluoxetine are included which differ from unpublished data previously used. The reviewers' conclusions about the efficacy of bupropion and nortriptyline were not changed substantively.
28 August 2000	New citation required and conclusions have changed	Updates the earlier Cochrane Review 'Anxiolytics and antidepressants for smoking cessation'. Anxiolytics are evaluated in a separate review.

CONTRIBUTIONS OF AUTHORS

For the most recent update NL, JHB and SH decided on changes to analyses and the presentation of the review. SH updated the text of the review and all other authors commented. SH, NL, JHB, JLB screened and extracted study data, and BH also extracted study data.

DECLARATIONS OF INTEREST

SH: none reported

JHB: none reported

JLB: none reported

BH: none reported

NL: none reported

SOURCES OF SUPPORT

Internal sources

- Nuffiled Department of Primary Care Health Sciences, University of Oxford, UK

  Editorial base for Cochrane Tobacco Addiction

External sources

- National Institute for Health Research, UK

  Infrastructure funding for Cochrane Tobacco Addiction

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- Research England's Strategic Priorities Fund (SPF), UK

  Funding to carry out this particular Cochrane Tobacco Addiction Review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The changes below were made for the 2020 update.

- We no longer include harm reduction and relapse prevention studies as these are covered in other reviews (Lindson-Hawley 2016; Livingstone-Banks 2019).
- We changed the wording of the primary outcome from smoking abstinence to smoking cessation. These terms measure the same thing however we feel that the latter term makes it clearer that we are measuring the act of quitting smoking.
- We have specified exactly which safety and tolerability outcomes were assessed as follows: 1) adverse events (AEs), 2) serious adverse events (SAEs), and 3) dropouts due to AEs, and also collected information on the following specific SAEs: seizures; overdoses; suicide attempts; death by suicide; and all-cause mortality. We went back to all previously included studies to check that these were extracted uniformly across studies.
- We explicitly state that we investigated whether studies had investigated depression status as a modifier of efficacy. This has been extracted uniformly across studies and the information is now summarized in Table 2.
- Any observational studies are now excluded from this review. There were previously included to assess safety outcomes.
- We have explicitly stated that "We excluded trials where an additional, uncontrolled non-antidepressant intervention component was used in only one of the trial arms" and checked that included studies conform to this requirement.
- We no longer assess the outcome: reduction in smoking, as this is not deemed to be a clinically-relevant outcome - there is no evidence that it results in health benefits, and studies that aim specifically to reduce smoking are covered in our harm reduction review (Lindson-Hawley 2016).
- We restructured our 'Summary of findings' tables to include the most clinically-relevant comparators and to include safety outcomes as well as efficacy.
- We carry out sensitivity analyses, excluding studies from meta-analyses with industry funding, or where the medication was supplied by the pharmaceutical industry. We judged whether this exclusion notably altered the pooled risk ratios (RRs) (95% confidence interval (CI)) and summarized the results in Table 1.
- We carried out a post hoc, exploratory analysis merging the following safety and tolerability outcome data: AEs, psychiatric AEs, SAEs and dropouts due to drug, across three comparisons, that effectively all compared bupropion to no bupropion treatment (1) bupropion versus placebo/no pharmacotherapy control; 2) bupropion plus nicotine replacement therapy (NRT) versus NRT; 3) bupropion plus varenicline versus varenicline). We carried out a subgroup analysis to test for any interactions between comparisons.

NOTES

This review was first published as part of the review 'Anxiolytics and antidepressants for smoking cessation.' From Issue 4, 2000 the classes of drugs are reviewed separately.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Anxiety Agents [adverse effects] [*therapeutic use]; Antidepressive Agents [adverse effects] [*therapeutic use]; Bupropion [adverse effects] [therapeutic use]; Nortriptyline [therapeutic use]; Randomized Controlled Trials as Topic; Serotonin Uptake Inhibitors [therapeutic use]; Smoking [*drug therapy] [psychology]; Smoking Cessation [*methods] [psychology]; Tobacco Use Cessation Devices; Varenicline [adverse effects] [therapeutic use]

MeSH check words

Humans

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