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Nicotine receptor partial agonists for smoking cessation (Review)

Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T

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[Intervention Review]

Nicotine receptor partial agonists for smoking cessation

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ABSTRACT

Background

Nicotine receptor partial agonists may help people to stop smoking by a combination of maintaining moderate levels of dopamine to counteract withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist).

Objectives

To review the efficacy of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

Search methods

We searched the Cochrane Tobacco Addiction Group's specialised register for trials, using the terms ('cytisine' or 'Tabex' or 'dianicline' or 'varenicline' or 'nicotine receptor partial agonist') in the title or abstract, or as keywords. The register is compiled from searches of MEDLINE, EMBASE, and PsycINFO using MeSH terms and free text to identify controlled trials of interventions for smoking cessation and prevention. We contacted authors of trial reports for additional information where necessary. The latest update of the specialised register was in May 2015, although we have included a few key trials published after this date. We also searched online clinical trials registers.

Selection criteria

We included randomised controlled trials which compared the treatment drug with placebo. We also included comparisons with bupropion and nicotine patches where available. We excluded trials which did not report a minimum follow-up period of six months from start of treatment.

Data collection and analysis

We extracted data on the type of participants, the dose and duration of treatment, the outcome measures, the randomisation procedure, concealment of allocation, and completeness of follow-up.

The main outcome measured was abstinence from smoking at longest follow-up. We used the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Where appropriate we pooled risk ratios (RRs), using the Mantel-Haenszel fixed-effect model.

Main results

Two trials of cytisine (937 people) found that more participants taking cytisine stopped smoking compared with placebo at longest follow-up, with a pooled risk ratio (RR) of 3.98 (95% confidence interval (CI) 2.01 to 7.87; *low-quality evidence*). One recent trial comparing cytisine with NRT in 1310 people found a benefit for cytisine at six months (RR 1.43, 95% CI 1.13 to 1.80).

One trial of dianicline (602 people) failed to find evidence that it was effective (RR 1.20, 95% CI 0.82 to 1.75). This drug is no longer in development.

We identified 39 trials that tested varenicline, 27 of which contributed to the primary analysis (varenicline versus placebo). Five of these trials also included a bupropion treatment arm. Eight trials compared varenicline with nicotine replacement therapy (NRT). Nine studies tested variations in varenicline dosage, and 13 tested usage in disease-specific subgroups of patients. The included studies covered 25,290 participants, 11,801 of whom used varenicline.

The pooled RR for continuous or sustained abstinence at six months or longer for varenicline at standard dosage versus placebo was 2.24 (95% CI 2.06 to 2.43; 27 trials, 12,625 people; *high-quality evidence*). Varenicline at lower or variable doses was also shown to be effective, with an RR of 2.08 (95% CI 1.56 to 2.78; 4 trials, 1266 people). The pooled RR for varenicline versus bupropion at six months was 1.39 (95% CI 1.25 to 1.54; 5 trials, 5877 people; *high-quality evidence*). The RR for varenicline versus NRT for abstinence at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 8 trials, 6264 people; *moderate-quality evidence*). Four trials which tested the use of varenicline beyond the 12-week standard regimen found the drug to be well-tolerated during long-term use. The number needed to treat with varenicline for an additional beneficial outcome, based on the weighted mean control rate, is 11 (95% CI 9 to 13). The most commonly reported adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided over time. Our analysis of reported serious adverse events occurring during or after active treatment suggests there may be a 25% increase in the chance of SAEs among people using varenicline (RR 1.25; 95% CI 1.04 to 1.49; 29 trials, 15,370 people; *high-quality evidence*). These events include comorbidities such as infections, cancers and injuries, and most were considered by the trialists to be unrelated to the treatments. There is also evidence of higher losses to follow-up in the control groups compared with the intervention groups, leading to a likely underascertainment of the true rate of SAEs among the controls. Early concerns about a possible association between varenicline and depressed mood, agitation, and suicidal behaviour or ideation led to the addition of a boxed warning to the labelling in 2008. However, subsequent observational cohort studies and meta-analyses have not confirmed these fears, and the findings of the EAGLES trial do not support a causal link between varenicline and neuropsychiatric disorders, including suicidal ideation and suicidal behaviour. The evidence is not conclusive, however, in people with past or current psychiatric disorders. Concerns have also been raised that varenicline may slightly increase cardiovascular events in people already at increased risk of those illnesses. Current evidence neither supports nor refutes such an association, but we await the findings of the CATS trial, which should establish whether or not this is a valid concern.

Authors' conclusions

Cytisine increases the chances of quitting, although absolute quit rates were modest in two recent trials. Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and three-fold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion or with NRT. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The most frequently recorded adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time. Early reports of possible links to suicidal ideation and behaviour have not been confirmed by current research.

Future trials of cytisine may test extended regimens and more intensive behavioural support.

PLAIN LANGUAGE SUMMARY

Can nicotine receptor partial agonists, including cytisine and varenicline, help people to stop smoking?

Background

When people stop smoking they experience cravings to smoke and unpleasant mood changes. Nicotine receptor partial agonists aim to reduce these withdrawal symptoms and the pleasure people usually experience when they smoke. The most widely-available treatment in this drug type is varenicline, which is available world-wide as an aid for quitting smoking. Cytisine is a similar medication, but is only available in Central and Eastern European countries and through internet sales.

Study characteristics

We searched for randomised controlled trials testing varenicline, cytisine or dianicline. We found 39 studies of varenicline compared to placebo, bupropion or nicotine patches. We also found four trials of cytisine, one of which compared it to nicotine replacement therapy. We include one trial of dianicline, which is no longer in development, and so not available to use as a quitting aid. To be included, trials had to report quit rates at least six months from the start of treatment. We preferred the strictest available definition of quitting, and results which had been biochemically confirmed by testing blood or bodily fluids.We conducted full searches up to May 2015, although we have also included several key trials published after that date.

Key findings

From the information we found (27 trials, 12,625 people), varenicline at standard dose more than doubled the chances of quitting compared with placebo. Low-dose varenicline (four trials, 1266 people) roughly doubled the chances of quitting, and reduced the number and severity of side effects. The number of people stopping smoking with varenicline was higher than with bupropion (five trials, 5877 people) or with NRT (eight trials, 6264 people). Based on the evidence so far, we can calculate that varenicline delivers one extra successful quitter for every 11 people treated, compared with smokers trying to quit without varenicline.

The most common side effect of varenicline is nausea, but this is mostly at mild or moderate levels and usually clears over time. People taking varenicline appear to have about a 25% increased chance of a serious adverse event, although these include many which are unrelated to the treatment. We also note that more people were lost from the control groups than from the varenicline groups by the end of the trials, which may mean that the count of events in the control groups is lower than it should be. After varenicline became available to use, there were concerns that it could be linked with an increase in depressed mood, agitation, or suicidal thinking and behaviour in some smokers. However, the latest evidence does not support a link between varenicline and these disorders, although people with past or current psychiatric illness may be at slightly higher risk. There have also been concerns that varenicline may slightly increase heart and circulatory problems in people already at increased risk of these illnesses. The evidence is currently unclear whether or not they are caused or made worse by varenicline, but we should have clearer answers to these questions when a further study is published later this year.

Quality of the evidence

The varenicline studies were generally of high quality, providing evidence that we consider to be reliable and robust. We rate the quality of the evidence comparing varenicline with NRT as moderate quality (we are reasonably confident of the stability of the evidence), since in some of them the participants knew which treatment they were receiving (i.e. non-blinded open-label trials). We judge the evidence from the cytsine trials to be of low quality (we have limited confidence in the evidence), as there are only two trials, with relatively low numbers included.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Varenicline versus placebo or other first-line treatments for smoking cessation

Patient or population: Individuals who smoke tobacco
Setting: Varied
Intervention: Varenicline
Comparison: Varied controls

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Corresponding risk with varenicline				
Varenicline vs placebo: continuous/sustained abstinence at longest follow-up (24+ weeks)	Study population (where risk refers to quitters)		RR 2.24 (2.06 to 2.43)	12,625 (27 RCTs)	⊕⊕⊕⊕ HIGH [1,2]	
	111 per 1000	250 per 1000 (230 to 271)				
Varenicline vs bupropion: continuous/sustained abstinence (24 weeks)	Study population (where risk refers to quitters)		RR 1.39 (1.25 to 1.54)	5877 (5 RCTs)	⊕⊕⊕⊕ HIGH	
	171 per 1000	238 per 1000 (214 to 264)				
Varenicline vs NRT: point prevalence abstinence (24 weeks)	Study population (where risk refers to quitters)		RR 1.25 (1.14 to 1.37)	6264 (8 RCTs)	⊕⊕⊕◯ MODERATE [3]	
	189 per 1000	237 per 1000 (216 to 259)				

Varenicline vs placebo: number of participants reporting SAEs in duration of trials (trials reporting no events in either group excluded)	Study population (where risk refers to SAEs)		RR 1.25 (1.04 to 1.49)	15,370 (29 RCTs)	⊕⊕⊕⊕ HIGH
	30 per 1000	39 per 1000 (32 to 48)			
Varenicline vs placebo: number of participants reporting cardiac SAEs, including deaths, in duration of trials	Study population (where risk refers to SAEs)		RR 1.36 (0.91 to 2.04)	8587 (21 studies)	⊕⊕⊕◯ MODERATE [4]
	9 per 1,000	12 per 1,000 (8 to 17)			
Varenicline vs placebo: number of participants reporting nausea in duration of trials	Study population (where risk refers to SAEs)		RR 3.27 (3.00 to 3.55)	14963 (32 studies)	⊕⊕⊕⊕ HIGH
	85 per 1,000	277 per 1,000 (254 to 301)			

*__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).The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: Confidence interval; **RR:** Risk ratio; **SAEs:** Serious adverse events

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Moderate heterogeneity detected, however all but two studies showed positive effect of varenicline, so did not downgrade on this basis.
[2]Lack of smaller trials with negative findings suggests possible publication bias. However, earliest studies reported 2006. We are reasonably confident that licensing and subsequent trials have been registered online in clinical trials registries. Thus absence of negative studies may be marker of sustained efficacy rather than suppression or selective management of data.
[3]Downgraded once as three of the eight studies were rated at high risk of bias due to using an open-label design.

[4]Downgraded once due to imprecision; CIs do not rule out an increase in risk

BACKGROUND

Smoking is the main preventable cause worldwide of morbidity and premature death. Based on data from 2004, 12% of all deaths globally among adults aged 30 years and over were attributable to tobacco, with 5 million adults dying due directly to tobacco use (WHO 2012). The list of illnesses known to be linked to smoking includes cancers of the cervix, pancreas, kidneys and stomach, aortic aneurysms, acute myeloid leukaemia, cataracts, pneumonia, and gum disease. These are in addition to the long-established links between tobacco use and such illnesses as lung cancer, cardiovascular diseases, and emphysema, and with prematurity, sudden infant death syndrome and low birth weight in the babies of maternal smokers (Surgeon General 2004).

There is a growing understanding of the neurochemical basis of nicotine addiction (Fagerström 2006). There is strong evidence that dependence upon nicotine reflects the effects of the drug at neuronal nicotinic receptors in the brain (Benowitz 1999; Hogg 2007; Picciotto 1999). More recent studies have explored the potential of neuronal nicotinic acetylcholine receptors (nAChRs) as targets for a variety of therapeutic interventions (Hogg 2007). It is thought that the addictive properties of nicotine are mediated mainly through its action as an agonist at $\alpha 4\beta 2$nAChRs, which stimulates the release of dopamine (Coe 2005). Pharmacotherapies to aid smoking cessation have been developed which exploit this mechanism, by acting as nicotine receptor partial agonists.

Cytisine

Cytisine was developed as a treatment for tobacco dependence in Bulgaria in the 1960s, and is available in some eastern and central European countries and through internet sales, under the trade name of Tabex (Foulds 2004; Tutka 2005; Tutka 2006). Its manufacturers, Sopharma Pharmaceuticals, developed their phytoproduct from the plant Cytisus Laburnum L. (Golden Rain). Although cytisine (Tabex) is not licensed for use as a smoking cessation aid across most countries outside Eastern Europe (Walker 2014), studies by Vinnikov 2008 and West 2011 have highlighted the potential of this drug, especially in countries with lower average incomes and where smoking cessation programmes are not supported by insurance plans or by a national health service. In many regions, it may be considerably cheaper to continue smoking than to embark upon a course of pharmacotherapy for smoking cessation. West 2011 reports that a pack of cigarettes in China costs between 15¢ and 73¢, compared with a course of nicotine replacement therapy (NRT) (USD 230), bupropion (USD 123), or varenicline (USD 327). Similarly, a pack of 20 cigarettes in India costs around USD 1.10, or 5¢ for a pack of bidis, compared with USD 150 for a course of NRT, USD 100 for bupropion and USD 200 for varenicline. Tabex is currently available in Poland for the equivalent of USD 15 for a course of treatment, and in Russia for the equivalent of USD 6 as an over-the-counter medication. There is also heightened interest and activity in cytisine in New Zealand, where it is found in the seeds of the native Kowhai tree, widely used in traditional Mā ori healing (Thompson-Evans 2011). The current update adds a large single-blind randomised non-inferiority trial comparing cytisine with NRT, conducted in New Zealand between 2011 and 2013 (Walker 2014).

Dianicline

In 2006, Sanofi-Aventis registered two trials of dianicline, their version of a nicotine receptor partial agonist (Tonstad 2011; Ameridian 2007). However, unfavourable results have led to the withdrawal of this drug from further development (Kirchhoff 2009). We have been unable to locate results for the AMERIDIAN trial, and present only the EURODIAN trial report in this review.

Varenicline

Varenicline was developed by Pfizer Inc to counteract the effects of nicotine on the nAChRs. The drug was based on the naturally-occurring alkaloid compound cytisine described above, which had been shown to be an effective partial agonist for $\alpha 4\beta 2$ receptors (Papke 1994; Slater 2003).

Varenicline was developed in 1997 (Coe 2005), and is described as a selective nicotinic receptor partial agonist. It was designed to selectively activate the $\alpha 4\beta 2$nAChR, mimicking the action of nicotine and causing a moderate and sustained release of mesolimbic dopamine (Sands 2005). This, it was suggested, should counteract withdrawal symptoms consequent upon low dopamine release during smoking cessation attempts. However, because it is a partial agonist at these receptors, it elicits some dopamine overflow, but not the substantial increases evoked by nicotine. Perhaps more importantly, it blocks the effects of a subsequent nicotine challenge on dopamine release from the mesolimbic neurones thought pivotal to the development of nicotine dependence (Coe 2005). Although varenicline has been shown to be a partial agonist at heteromeric neuronal nicotine receptors, there is now evidence that it may also be a full agonist at the homomeric $\alpha 7$ receptor (Mihalak 2006).

Multicentre trials of varenicline have been conducted or are currently underway in the USA, Canada, Latin America, Europe, Australia, the Middle East and the Far East. There have also been studies in specific patient groups, including the following conditions: cardiovascular disease, chronic obstructive pulmonary disease, diabetes, drug or alcohol dependence, head and neck cancers, HIV infection, bipolar disorders, depression, schizophrenia or schizoaffective disorders.

Varenicline was approved as a prescription-only aid to smoking cessation in 2006 by the American Food and Drug Administration under the trade name Chantix, and by the European Medicines

Evaluation Agency under the trade name Champix. In July 2007 it was approved by the National Institute for Health and Clinical Excellence (NICE) for prescribing by the UK National Heath Service (ASH 2006; NICE 2007). Post-marketing surveillance has raised subsequent concerns about possible links between varenicline and major health risks, including suicidal ideation and behaviour, depression, and serious adverse cardiovascular events (FDA 2008). We consider these findings in the Discussion section of this review, and in our meta-analyses.

OBJECTIVES

To review the efficacy of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Adult smokers. Trials which target users of smokeless tobacco are not included in this review, but are listed among the Excluded Studies. Interventions for smokeless tobacco use cessation are covered in a companion review (Ebbert 2011).

Types of interventions

Selective nicotine receptor partial agonists, including cytisine, dianicline and varenicline, or any other in this class of drug as they reach Phase 3 trial stage. The efficacy of lobeline is covered in an earlier Cochrane review (Stead 2003).

For this update, and in anticipation of current ongoing trials reaching publication, we have extended the range of analyses to cover the following intervention types and subgroups:

I. Varenicline versus other pharmacotherapies:

1. Varenicline versus placebo
2. Varenicline versus bupropion
3. Varenicline versus NRT
4. Varenicline versus mecamylamine
5. Combination treatments (e.g. varenicline + NRT) versus single-therapy treatment, where the addition of varenicline is the intervention being tested
6. Varenicline tablets versus other formulations (e.g. patch, in solution)

II. Variations in usage:

1. Flexible quit dates
2. Variable dosages
3. Preloading (before TQD)
4. Reducing to quit
5. Maintenance therapy (relapse prevention)
6. Harm reduction

III. Specific patient groups:

1. Cardiovascular disease (CVD)
2. Chronic obstructive pulmonary disease (COPD)
3. Asthma
4. Schizophrenia/bipolar/psychiatric disorder
5. Depression
6. Substance use disorder/methadone-maintained
7. Alcohol-dependent smokers
8. HIV
9. Diabetes
10. Head and neck cancer
11. Varenicline in pregnancy
12. Long-term use of NRT

IV. Settings/subgroups:

1. Hospital inpatients/perioperative patients
2. Smokers who have previously failed to quit on varenicline or NRT or bupropion
3. Light or heavy smokers
4. Varenicline by gender
5. Varenicline in ethnic groups

We have not considered for inclusion any trials of varenicline used for conditions other than smoking cessation, such as alcoholism, cocaine dependence, Parkinson's disease, spinocerebellar degeneration, etc.

Types of outcome measures

A minimum of six months abstinence is the primary outcome measure. We have used sustained cessation rates in preference to point prevalence, and we have preferred biochemically verified rates to rates based on self report of quitting. In analysis, we treat participants lost to follow-up as continuing smokers. We have recorded any adverse effects of treatment.

Search methods for identification of studies

We searched the Tobacco Addiction Review Group specialised register for trials, using the terms ('cytisine' or 'Tabex' or 'dianicline' or 'varenicline' or 'nicotine receptor partial agonist') in the title or abstract, or as keywords. This register has been developed from electronic searching of MEDLINE, EMBASE, and PsycINFO, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. The most recent search of the Register was in May 2015, and included reports of trials indexed in the Cochrane Central Register of Controlled trials (CENTRAL), issue 5, 2015; MEDLINE (via OVID) to update 20150501; EMBASE (via OVID) to week 201519; PsycINFO (via OVID) to update 20150506. See the Tobacco Addiction Group Module for details of the search strategies for these databases.

We also searched UK and US online clinical trials registers for ongoing and recently completed trials. Trials which may be candidates for inclusion (i.e. RCTs of smoking cessation interventions using a nicotine receptor partial agonist with a minimum follow-up of six months), and for which results are not yet available, are listed in the Characteristics of ongoing studies table.

We contacted the authors of ongoing studies of varenicline and cytisine where necessary.

We made a strategic decision to delay publication of this update until we could access the findings of the Pfizer EAGLES 2016 trial (NCT014569360) in April 2016. Although we did not conduct full-scale top-up searches during this waiting period, we checked the status of all ongoing studies known to us, and identified published results for six of them: two were journal articles (Baker 2016; Eisenberg 2016), now included studies, and four had posted their results on the ClinicalTrials.gov database; we have added two of the trials (NCT00828113; NCT01347112) to the included studies, and the other two (NCT01308736; NCT01806779) to the excluded studies.

Data collection and analysis

We checked the abstracts of studies generated by the search strategy for relevance, and acquired full reports of any trials that might be suitable for the review. One author (KC) extracted the data, and a second author (NLH) checked them. We resolved any discrepancies by mutual consent, or by recourse to a third author (TL). Studies that did not meet the inclusion criteria are listed in the Characteristics of excluded studies table, with reasons for their exclusion.

Studies were evaluated on the basis of the quality of the randomisation procedure and allocation concealment, as described in the *Cochrane Handbook* (Higgins 2011). The following information about each trial, where it is available, is reported in the table Characteristics of included studies:

- Country and setting (e.g. primary care, community, hospital outpatient/inpatient)
- Method of selection of participants
- Definition of smoker used
- Methods of randomisation and allocation, and blinding of trialists, participants and assessors
- Demographic characteristics of participants (e.g. average age, sex, average cigarettes/day)
- Intervention and control description (dose, provider, duration, number of visits, etc.)
- Outcomes including definition of abstinence used, and biochemical validation of cessation
- Proportion of participants with follow-up data
- Any adverse events
- Sources of funding

Studies in the Characteristics of included studies table are grouped by the type of treatment being tested (cytisine, dianicline, varenicline).

Quit rates are calculated based on the numbers of people randomised to an intervention, and excluding any deaths or untraceable moves, in accordance with the Russell Standard (West 2005). We regard those who drop out or are lost to follow-up as continuing smokers. We have noted any deaths and adverse events in the results section. Effects are expressed as risk ratios ((number of events in intervention condition/intervention denominator)/(number of events in control condition/control denominator)). For cessation a risk ratio greater than 1 indicates that more people are quitting in the intervention condition. For adverse events, a risk ratio greater than 1 indicates that more people experience adverse events in the intervention condition.

Where appropriate, we have conducted meta-analyses of the included studies, using the Mantel-Haenszel fixed-effect model, provided that there was no significant heterogeneity. We assessed statistical heterogeneity between trials using the I^2 statistic which describes the percentage of total variation between studies that is due to heterogeneity rather than chance (Higgins 2003). Values over 50% suggest moderate heterogeneity, and values over 75% substantial heterogeneity.

For studies of disease-specific patients (section III) and for patients in different settings (section IV), we have conducted and reported sensitivity analyses, treating them as subgroups of the main analyses and testing for subgroup differences.

For this update, we have produced 'Summary of findings' tables covering the main outcomes of smoking abstinence for varenicline versus placebo, varenicline versus bupropion, varenicline versus NRT (all in Summary of findings for the main comparison), and cytisine versus placebo (Summary of findings 2); and incidence of serious adverse events for the comparison of varenicline versus placebo. Our grading decisions are based on the five GRADE considerations: study limitations in design or execution (risks of bias), inconsistency of results, indirectness of evidence, imprecision of results, and publication bias. Evidence from studies is rated

as high quality (i.e. we are very confident of the findings), through moderate, low, and very low quality (i.e. the true effect is likely to be substantially different from the estimate of effect).
We include in this review the Tobacco Addiction Group glossary of tobacco-specific terms (Appendix 1).

RESULTS

Description of studies

Included studies

Full details of the included studies are given in the Characteristics of included studies tables.
For this update, we now have 44 trials (previously 24) which met our inclusion criteria. Four trials (Scharfenberg 1971; Vinnikov 2008; Walker 2014; West 2011) evaluated cytisine (Tabex) for smoking cessation, covering 3461 participants, 2102 of whom took cytisine. One trial of 602 smokers, 300 of whom took the active treatment, tested the Sanofi-Aventis drug dianicline for smoking cessation (Tonstad 2011). The remaining 39 trials tested varenicline in a variety of populations and settings, and against various comparators. Two trials, formerly classified as 'Ongoing studies' have now posted their findings on the www.ClinicalTrials.gov website, and we now treat them as included studies (NCT00828113; NCT01347112), albeit with limited information on design and findings. The trials cover more than 25,200 participants, 11,801 of whom took varenicline (see Appendix 2).
Nine studies which we originally treated as excluded are now classified as included studies, so that they can contribute data to the meta-analyses for neuropsychiatric adverse events. These studies are flagged with an asterisk in the study ID, indicating that they do not contribute to the efficacy findings (Brandon 2011*; Ebbert 2011*; Faessel 2009*; Fagerström 2010*; Garza 2011*; Hughes 2011*; McClure 2013* NCT00944554; Meszaros 2013*; Mitchell 2012*). We have not completed Characteristics of included studies tables or 'Risk of bias' assessments for these nine studies, but have recorded our judgements on why they are not eligible to be included in the efficacy findings.

Cytisine

Cytisine versus placebo was tested as a cessation aid in Germany (Scharfenberg 1971), in Kyrgyzstan (Vinnikov 2008), and in Poland (West 2011). Scharfenberg 1971 was set in a smoking cessation clinic in what was then East Germany, Vinnikov 2008 was set in a Kyrgyz mining company, and West 2011 in a Warsaw smoking cessation clinic. A recent New Zealand non-inferiority trial (Walker 2014) compared cytisine to NRT in a population of smokers contacting a national smoking quitline. The trials used 1.5 mg Tabex tablets over a 20-day (Scharfenberg 1971) or 25-day (Vinnikov 2008; Walker 2014; West 2011) treatment period, with behavioural support kept to a minimum in order to reduce programme costs. Vinnikov 2008 and Walker 2014 assessed their participants to six months, West 2011 to 12 months, and Scharfenberg 1971 to two years. Both Vinnikov 2008 and West 2011 verified claims of abstinence by testing expired carbon monoxide (CO) levels, while the remaining two trials relied upon self report without biochemical validation.

Dianicline

The dianicline trial (Tonstad 2011) was set in 22 sites across six European countries. Dianicline was administered as a 40 mg tablet twice a day for seven weeks, with brief counselling at each contact. Final follow-up of the participants was at 26 weeks, with claims of abstinence verified by expired CO and by plasma cotinine samples.

Varenicline

Study design

Thirty-four studies were double-blinded randomised trials; the remaining five were open-label. Three of the open-label trials compared varenicline with NRT (Aubin 2008; Baker 2016; Tsukahara 2010), one compared varenicline with NRT and with placebo (Heydari 2012), and one compared varenicline plus counselling with counselling alone (Carson 2014 (formerly Smith 2012)).

Setting

Seventeen studies were set in the USA, two in Japan, two in Denmark, one each in Australia, Canada, Iran and the UK, one in both Taiwan and Korea, one in both China and Singapore, two in North America (USA and Canada), and ten in multiple countries. The trials were conducted in smoking cessation clinics, hospitals, universities and other research centres.

Participants

Participants in the majority of the trials were adult smokers, willing to make a quit attempt (Aubin 2008; Baker 2016; Bolliger 2011; Cinciripini 2013; EAGLES 2016; Eisenberg 2016; Gonzales 2006; Gonzales 2014; Heydari 2012; Jorenby 2006; Nakamura 2007; NCT01347112; Niaura 2008; Niaura 2008; Nides 2006; Oncken 2006; Rennard 2012; Tsai 2007; Tsukahara 2010; Wang

2009; Williams 2007). Several trials were conducted in clinical subgroups, including hospital inpatients (Carson 2014; Steinberg 2011; Wong 2012), and disease-specific patient groups (CVD: Rigotti 2010; acute coronary syndrome Eisenberg 2016; COPD: Tashkin 2011; asthma: Westergaard 2015; substance use disorder: Nahvi 2014a; Stein 2013; alcohol abuse: NCT01347112; depression: Anthenelli 2013; bipolar/schizophrenia; schizoaffective disorder: Chengappa 2014; Evins 2014; Williams 2012). EAGLES 2016 enrolled two cohorts of adult smokers with and without histories of psychiatric disorders, including primary affective disorders (70%), anxiety disorders (19%), psychotic disorders (9.5%) and personality disorders (0.6%). Two trials targeted subgroups of smokers who were failing to respond to smoking cessation pharmacotherapies, either by increasing the dosage (Hajek 2015) or by switching to different medications (Rose 2013). Three studies focused on relapse prevention in successful quitters (NCT00828113; Tonstad 2006), or in people with schizophrenia who had successfully quit (Evins 2014). De Dios 2012 tested varenicline in Latino light smokers, and Ebbert 2015 in adult smokers unwilling to quit abruptly but prepared to reduce their smoking as a run-up to quitting completely. Tønnesen 2013 tested varenicline as an aid to weaning ex-smokers off extended use of NRT.

Interventions

Thirty-three of the 39 trials used the standard 12-week regimen of varenicline, routinely titrating the first week up to the recommended daily dose of 1 mg twice a day. Three trials (Nakamura 2007; Nides 2006; Oncken 2006) compared different dosage arms of varenicline against a placebo arm. One trial in non-responders regulated dosage up to the target quit date (day 21) to a maximum of 5 mg a day (Hajek 2015), and another allowed participants to regulate their own dosage throughout the treatment phase (Niaura 2008). NCT00828113 is a randomised trial comparing extended (52-week) and standard (12-week) courses of varenicline.

Of the eight trials that used NRT as a comparator condition, five (Aubin 2008; Baker 2016; De Dios 2012; EAGLES 2016; Rose 2013) provided a 12-week course, reducing the dosage as a weaning process, while two trials (Heydari 2012; Tsukahara 2010) provided an eight-week course, with only the Tsukahara 2010 trial progressively reducing the dosage to the end of treatment. Stein 2013 gave a 24-week course of NRT, tailored to the level of nicotine dependency, and matched to the duration of the placebo and varenicline arms of the trial.

The five trials which used bupropion all supplied the standard regimen of 150 mg twice a day, four of them for 12 weeks (Cinciripini 2013; EAGLES 2016; Gonzales 2006; Jorenby 2006) and Nides 2006 for seven weeks.

Comparisons

Twenty-six RCTs compared varenicline to an identical placebo regimen (Anthenelli 2013; Bolliger 2011; Chengappa 2014; EAGLES 2016; Ebbert 2015; Eisenberg 2016; Evins 2014; Gonzales 2014; Hajek 2015; Nahvi 2014a; Nakamura 2007; NCT01347112; Niaura 2008; Oncken 2006; Rennard 2012; Rigotti 2010; Steinberg 2011; Tashkin 2011; Tonstad 2006; Tonstad 2011; Tsai 2007; Wang 2009; Westergaard 2015; Williams 2007; Williams 2012; Wong 2012); all these trials used the standard 12-week course of treatment, apart from Ebbert 2015 (24 weeks, 'reduce to quit'), Evins 2014 (40 weeks, relapse prevention) and Williams 2007 (52 weeks, a safety trial). Four trials (Aubin 2008; Baker 2016; Rose 2013; Tsukahara 2010) used NRT as the comparator rather than a placebo, while three more trials (De Dios 2012; Heydari 2012; Stein 2013) used both NRT and placebo as comparator conditions, in a three-arm study design. EAGLES 2016 was a four-arm triple-dummy trial, comparing varenicline, bupropion and NRT with a placebo. Four trials (Cinciripini 2013; Gonzales 2006; Jorenby 2006; Nides 2006) compared varenicline with bupropion and with placebo. One trial (Carson 2014) compared varenicline plus quitline counselling to quitline counselling alone.

Outcomes

As a condition of inclusion, all the trials reported cessation at least six months from the start of the intervention. Seventeen of 39 studies reported longest follow-up at six months (point prevalence or continuous abstinence) (Bolliger 2011; Chengappa 2014; Cinciripini 2013; De Dios 2012; EAGLES 2016; Eisenberg 2016; Nahvi 2014a; NCT01347112; Rennard 2012; Rose 2013; Stein 2013; Steinberg 2011; Tsai 2007; Tsukahara 2010; Wang 2009; Westergaard 2015; Williams 2012), and 20 studies to 12 months. Hajek 2015, relevant for the exploration of dose variability, reported abstinence only to 12 weeks, and is not included in the main efficacy findings. Evins 2014 followed its participants until week 64, as part of a relapse prevention initiative.

All the trials except one (NCT01347112) used biochemical verification of abstinence by expired CO, at cut-offs ranging from 5 to 10 ppm, at one or more time points. Baker 2016 validated outcomes at both 9 ppm and 5 ppm cut-off levels. Heydari 2012 and Wong 2012 did not report their cut-offs. Carson 2014 tested "a random sub-set of subjects" (51/103 quitters). Five trials (Cinciripini 2013; De Dios 2012; Stein 2013; Tønnesen 2013; Wong 2012) also used salivary or urinary cotinine testing to confirm abstinence claims.

Excluded studies

Eight of the excluded studies tested cytisine (Granatowicz 1976; Kempe 1967; Maliszewski 1972; Metelitsa 1987; Monova 2004; Ostrovskaia 1994; Paun 1968; Schmidt 1974), and the remaining

48 tested varenicline, but did not meet our eligibility criteria to be treated as an included study.

The excluded studies are briefly described, with reasons for exclusion, in the Characteristics of excluded studies tables. Seven of the excluded studies (Ebbert 2014; Hajek 2013; Hoogsteder 2014; Koegelenberg 2014; NCT01806779; Ramon 2014; Rose 2014) administered varenicline to all participants, and tested the addition of another pharmacotherapy (nicotine replacement therapy, bupropion, or nicotine vaccine). Since varenicline was not primarily the intervention being tested, the findings of these trials are covered in the reviews which address the relevant adjunctive treatments. Swan 2010, which we had classified as an included study in the 2012 update, is now an excluded study, as all the participants received varenicline, and the intervention being tested was the addition and relative merits of internet- and telephone-based counselling. Two trials (NCT01308736; NCT01806779), formerly treated as 'Ongoing studies', have now posted their findings on the www.ClinicalTrials.gov website, and we now report them as excluded studies.

Risk of bias in included studies

Among the cytisine trials, we rated Vinnikov 2008, Walker 2014 and West 2011 as being at low risk of bias in their randomisation and allocation procedures; Scharfenberg 1971 gave no details about these, and was therefore rated as unclear. We rated Walker 2014 at high risk of bias for a lack of blinding of participants and personnel. This study may also have been at risk of bias for providing cytisine free of charge but NRT at a cost of NZD 3 per item. Although Vinnikov 2008 invokes the Russell Standard criteria (West 2005) in support of the conduct of their trial, they excluded 26 participants who took no medication from the denominator; we have reinstated them for our meta-analyses, in order to present an intention-to-treat estimate, i.e. all people randomised, excluding only those who died or who moved away.

Of the 39 varenicline trials, 23 reported randomisation and allocation procedures in sufficient detail to be assessed as being at minimal risk in their attempts to control selection bias. Fifteen trials (Chengappa 2014; Cinciripini 2013; De Dios 2012; Heydari 2012; NCT00828113; NCT01347112; Oncken 2006; Rose 2013; Stein 2013; Tashkin 2011; Tsukahara 2010; Wang 2009; Westergaard 2015; Williams 2007; Williams 2012) gave insufficient information for this to be confirmed. A sensitivity analysis removing these trials made no difference to the findings. None of the trials reported any assessment of the integrity of the double-blinding procedure. For the relapse prevention trials (Evins 2014; NCT00828113; Tonstad 2006), the integrity of the double-blind phase may be questionable, since all randomised participants had successfully used varenicline during the open-label phase.

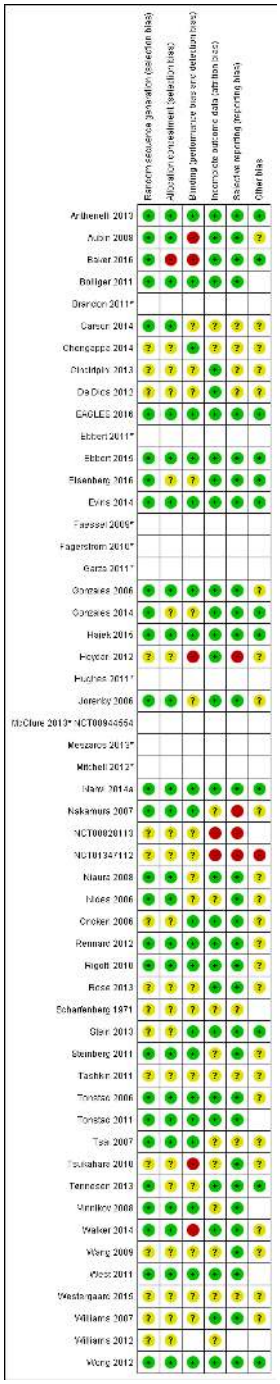
All except eight of the included studies reported prolonged, sustained or continuous abstinence as their most rigorous estimate of efficacy; De Dios 2012; Heydari 2012; Nahvi 2014a; NCT00828113; Westergaard 2015; Williams 2007; Williams 2012; and Wong 2012 all reported only point prevalence abstinence. Steinberg 2011 used repeated point prevalence at 4, 12 and 24 weeks, which we have treated as sustained abstinence for the purposes of our meta-analyses. 'Continuous abstinence' as defined in the remaining trials excluded the first eight weeks of treatment, and could more accurately be termed 'prolonged abstinence' (Hughes 2003).

Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomisation, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group. We rated four open-label trials of NRT versus varenicline (Aubin 2008; Baker 2016; Heydari 2012; Tsukahara 2010) at high risk of bias for being unblinded. Nakamura 2007 was assessed as being at high risk of selective reporting bias, since they reported continuous abstinence rates for all participants, but demographic information, craving and withdrawal measures for the highly nicotine-dependent smokers only. Cinciripini 2013 reported changing interventions (from nortriptyline to varenicline) three months into their study, but found no differences between the varenicline and nortriptyline cohorts and therefore combined them for analysis. Heydari 2012 used an eight-week course of varenicline (presumably to match the standard NRT regimen), which might be expected to have compromised its efficacy.

Two trials which posted their results on the www.ClinicalTrials.gov website are rated at high risk of bias for attrition and losses to follow-up. NCT00828113, comparing long-term and standard doses of varenicline, lost 60% from each of the groups by twelve-month follow-up, while NCT01347112, a small study of alcohol-dependent smokers using varenicline to quit, lost 25% from the varenicline group and 71% from the placebo group at 24 weeks. This study also relied upon self report, rather than biochemical validation of abstinence.

Our judgements on the risks of bias of all the included studies are summarised in Figure 1.

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Nicotine receptor partial agonists for smoking cessation; **Summary of findings 2** Nicotine receptor partial agonists for smoking cessation

1. Cessation

Cytisine

We pooled the findings of two cytisine trials, covering 937 participants, 470 of whom took the active drug. Both trials reported continuous abstinence rates at longest follow-up (24 weeks in Vinnikov 2008 and 52 weeks in West 2011), delivering an RR of 3.98 (95% CI 2.01 to 7.87; low-quality evidence; Analysis 1.1). We have not combined these recent trials with Scharfenberg 1971, as the design and conduct of the latter is of indeterminate quality, using self-reported point prevalence abstinence and without biochemical verification of its results. A sensitivity analysis combining the three trials increased the I^2 statistic from 0% to 68%, indicating substantial heterogeneity between the older study and the recent ones. The RR for Scharfenberg 1971 at two-year follow-up was 1.61 (95% CI 1.24 to 2.08; Analysis 1.2), and at six months 1.91 (95% CI 1.53 to 2.37; *analysis not shown*).

The largest cytisine trial (Walker 2014) compared it with NRT, and reported non-verified continuous abstinence at six months. Although this study (in 1360 participants) was designed as a test of non-inferiority, it demonstrated a significant benefit for cytisine over NRT, with a RR of 1.43 (95% CI 1.13 to 1.80; Analysis 2.1). The primary endpoint finding (at one month) also favoured cytisine: RR 1.30 (95% CI 1.12 to 1.51; *analysis not shown*).

The cytisine trials did not for the most part identify more adverse events in the intervention than the control arm; Scharfenberg 1971 reported similar rates of mild adverse events (nausea, restlessness, insomnia, irritability) in the cytisine and placebo groups at four weeks (23.4% and 20% respectively in abstinent participants), but did not report long-term rates for the full study population. Vinnikov 2008 reported 10 events in eight participants (four from each group), including dyspepsia, nausea and headache. West 2011 reported gastrointestinal disorders at higher rates in the cytisine than in the placebo group (13.8% vs 8.1%, P = 0.02). Walker 2014 reported significantly more adverse events (nausea, vomiting, sleep disorders) in the cytisine group compared with the NRT group (4.6% versus 0.03%; P = 0.0002), but similar rates of serious adverse events in the cytisine (6.9%) and the NRT (6.0%) groups.

Dianicline

The one trial of dianicline that has published its findings (Tonstad 2011) reported continuous abstinence at 26 weeks. The quit rate among 300 dianicline users was 16.7%, compared with a placebo quit rate of 13.9% in 302 participants; this yields an RR of 1.20 (95% CI 0.82 to 1.75; Analysis 3.1). Results from the companion trial (Ameridian 2007) have not been made available to us by the manufacturers. Development of the drug has now been abandoned by Sanofi-Aventis.

Varenicline

The evidence base includes 39 methodologically sound clinical trials, involving more than 25,290 participants, 11,801 of whom received varenicline (see Appendix 2). Where point prevalence measures were the only ones reported, we have noted this in footnotes for each analysis.

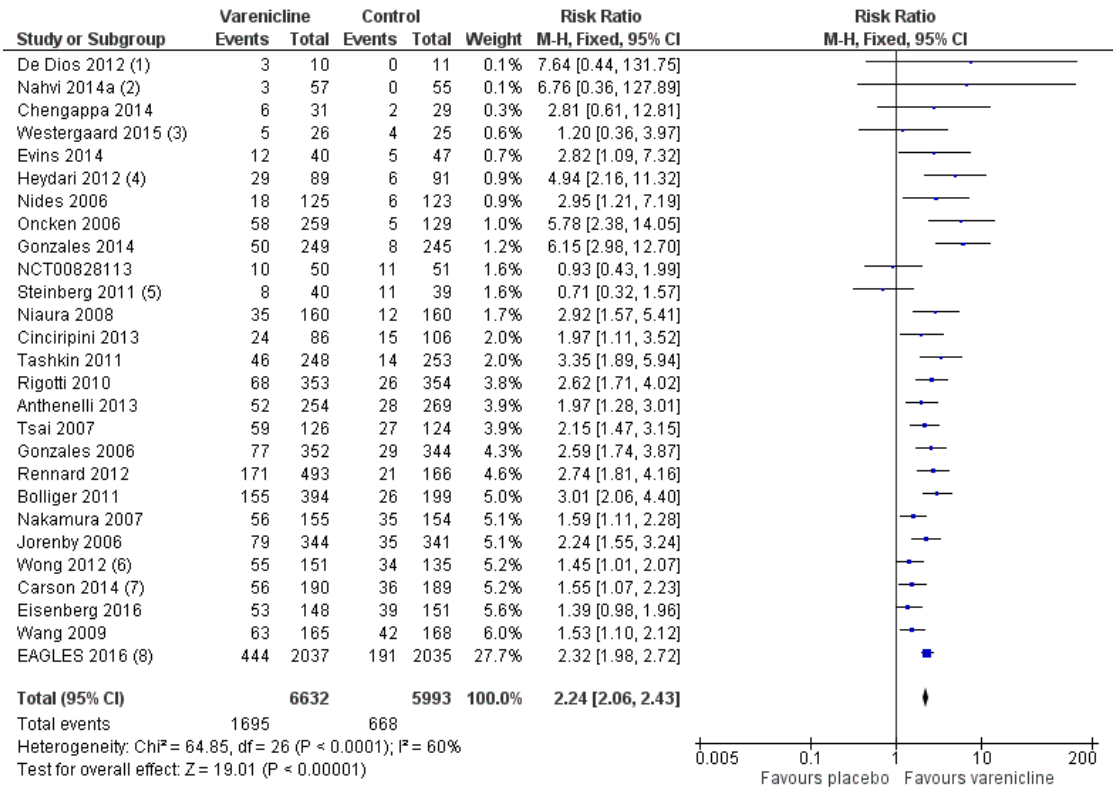
The Nides 2006 and Nakamura 2007 comparisons chosen for our primary meta-analysis were between the 1.0 mg twice a day group and the placebo group, since this matched the regimen now recommended for clinical practice. For the Oncken 2006 trial we combined the 1.0 mg twice a day titrated and non-titrated groups for the meta-analysis, since titration did not affect cessation rates.

1 Varenicline versus other pharmacotherapies

1.1. Varenicline versus placebo

The pooled risk ratio (RR) for validated continuous abstinence six months or more from the start of the intervention (longest follow-up) is 2.24 (95% CI 2.06 to 2.43; 27 trials, 12,625 participants, I^2 = 60%; high-quality evidence; Analysis 4.1; Figure 2). This finding is consistent with that reported in the previous version of this review, which included 14 trials and 6166 participants. The current RR is based on 27 cessation trials of varenicline (26 versus placebo, and one (Carson 2014) versus counselling only). Although the control group did not receive placebo medication, we have included Carson 2014 in the main meta-analysis; a sensitivity analysis excluding it made no appreciable difference to the estimate. All the trials in this analysis delivered varenicline at the standard dosage (1 mg twice a day) for 12 weeks, apart from Heydari 2012 and Nides 2006 (eight weeks). Limiting the analysis to the 15 studies with 12-month follow-up made little difference to the result (RR 2.29, 95% CI 2.02 to 2.60; 5904 participants). Six-month abstinence rates for all 25 studies reporting this measure yielded a virtually identical RR of 2.25 (95% CI 2.08 to 2.44; 12,304 participants, I^2 = 66%; Analysis 4.2).

Figure 2. Varenicline (1.0 mg 2/d) vs placebo, outcome: 3.1 Continuous abstinence at longest follow-up (24+ weeks)



Footnotes
(1) 7-day PPA at 6m
(2) 7-day PPA at 24 wks
(3) PPA at 24 wks
(4) PPA at 12m
(5) 7-day PPA at 24 weeks
(6) 7-day PPA at 12m
(7) 24-month follow-up
(8) Extrapolated from % reported quit

The EAGLES 2016 trial presents results separately for the two constituent cohorts, with and without a history of psychiatric disorders. The groups without a psychiatric history in all cases and at both time points (12 and 24 weeks) achieved higher quit rates than the groups in the psychiatric cohort. The RR in the non-psychiatric cohort for varenicline versus placebo was 2.42 (95% CI 1.97 to 2.99), with quit rates of 25.5% and 10.5% respectively; the corresponding measures in the psychiatric cohort were RR 2.20 (95% CI 1.73 to 2.80), and quit rates of 18.3% and 8.3% respectively. Treating the psychiatric cohort as a subgroup of the main analysis and testing for subgroup differences found no significant difference between the psychiatric cohort and the remaining trials (Chi^2 = 0.02, P = 0.88, I^2 = 0%; analysis not shown).

We have excluded from the main analysis four trials which tested extended varenicline treatment. Ebbert 2015 ('Reduce to quit') and Stein 2013 (substance-abusing smokers on methadone maintenance) both tested 24 weeks of varenicline, and NCT00828113 and Williams 2007 (a safety trial) both prescribed 12 months of treatment. Pooling these data demonstrated a clear benefit for varenicline, with a RR of 3.64 (95% CI 2.81 to 4.72; 2170 participants, I^2 = 78%; Analysis 4.3). A sensitivity analysis removing NCT00828113, which is at high risk of attrition bias, increased the RR to 4.15 (95% CI 3.14 to 5.49) and dropped the I^2 to 0%.

1.2. Varenicline versus bupropion

Five trials (Cinciripini 2013; EAGLES 2016; Gonzales 2006;

Jorenby 2006; Nides 2006) compared varenicline to bupropion. Although the Nides 2006 trial tested three dosing variants of varenicline, we have used the '1 mg twice a day' arm for our analysis, since this matches the regimen now recommended for clinical practice. The pooled RR for the five trials at six months was RR 1.39 (95% CI 1.25 to 1.54; 5877 participants, I^2 = 0%; moderate-quality evidence; Analysis 5.1), in favour of varenicline. We conducted a sensitivity analysis to test the effect of excluding Nides 2006, which had included previous users of bupropion, but the RR remained steady, at 1.37 (95% CI 1.23 to 1.52). The three-month and 12-month results were in line with the main finding (Analysis 5.2; Analysis 5.3).

The EAGLES 2016 trial demonstrated higher quit rates for this comparison in the non-psychiatric than in the psychiatric cohort, with a RR of 1.36 (95% CI 1.15 to 1.60; non-psychiatric), compared with RR 1.28 (95% CI 1.05 to 1.57; psychiatric). Quit rates were 25.5% for varenicline and 18.8% for bupropion in the non-psychiatric cohort, and 18.3% for varenicline and 13.7% for bupropion in the psychiatric cohort.

1.3 Varenicline versus NRT

Eight trials tested varenicline against nicotine replacement therapy. Three trials were open-label (Aubin 2008; Baker 2016; Tsukahara 2010), and one trial was an open-label comparison of varenicline, NRT and no pharmacotherapy. Baker 2016 compared nicotine patch (the reference treatment) against varenicline and against combination NRT (patch plus lozenge). Three trials were placebo-controlled three-arm studies, with De Dios 2012 and Stein 2013 testing varenicline against a placebo tablet and against NRT, and Rose 2013 comparing varenicline, bupropion and NRT, with all participants receiving an active treatment plus two dummy treatments. EAGLES 2016 was a double-blind four-arm trial, comparing varenicline, bupropion and NRT against placebo. The pooled analysis indicates a benefit for varenicline over NRT. The RR at 24 weeks was 1.25 (95% CI 1.14 to 1.37; 6264 participants, I^2 = 39%; moderate-quality evidence; Analysis 6.1). Removing the three open-label trials (all at high risk of bias for blinding) from the analysis slightly strengthened the effect estimate (RR 1.34, 95% CI 1.19 to 1.50), and increased the I^2 value to 47%. Stein 2013 treated its participants for 24 weeks rather than the standard 12; removing it from the analysis made little difference to the result or to the I^2 value. For Baker 2016, Analysis 6.1 uses the varenicline/patch comparison; substituting the combination NRT arm for the nicotine patch arm made minimal difference to the study or meta-analysis findings.

The EAGLES 2016 trial again demonstrated higher quit rates for this comparison in the non-psychiatric than in the psychiatric cohort, with a RR of 1.38 (95% CI 1.17 to 1.63; non-psychiatric), compared with RR 1.41 (95% CI 1.15 to 1.74; psychiatric). Quit rates were 25.5% for varenicline and 18.5% for NRT in the non-psychiatric cohort, and 18.3% for varenicline and 13.0% for NRT in the psychiatric cohort.

1.4 Varenicline versus mecamylamine

No trials currently report on this comparison.

1.5 Combination varenicline treatment versus single-therapy treatment

No trials currently report on this comparison.

1.6 Varenicline tablets versus other formulations

No trials currently report on this comparison.

II Variations in usage

2.1 Flexible quit date

One large multicentre study (Rennard 2012) allowed participants to select their own quit date anywhere between 8 and 35 days after joining the study. The trial found a clear benefit for varenicline over placebo, with an RR of 2.74 (95% CI 1.81 to 4.16; 659 participants; Analysis 7.1). By the end of the four-week 'quit window' (day 35), 80.5% of the varenicline group had made a quit attempt, compared with 73.3% of the placebo group. Varenicline participants were also found to have made an earlier quit attempt (median day 17) than the placebo participants (median day 24) (P = 0.0074).

2.2 Variable dosages

Low-dose varenicline versus placebo

Four trials investigated this comparison (Nakamura 2007; Niaura 2008; Nides 2006; Oncken 2006). For this review, we have combined the titrated and non-titrated arms of the Oncken 2006 trial, as there were no detectable differences between the arms for any outcomes. Three of the trials prescribed half the recommended daily dosage, either as a single 1 mg tablet or as two 0.5 mg doses, while Niaura 2008 allowed participants to regulate their own dosage at anywhere between 0.5 mg and 2.0 mg a day. The regimen favoured varenicline over placebo, with a RR at 52 weeks of 2.08 (95% CI 1.56 to 2.78; 1266 participants; Analysis 7.2). The Niaura 2008 trial found that those on varenicline settled on a mean modal dose of 1.35 mg a day, compared with 1.63 mg a day for the placebo group.

Variable dosing at the participant's or physician's discretion

Six studies (Anthenelli 2013; Chengappa 2014; Cinciripini 2013; Gonzales 2014; Hajek 2015; Niaura 2008) explored the option of

reducing the dosage to moderate side effects, either at the physician's behest or within the participant's own control. While this may have made the treatment more tolerable, it appeared not to have compromised efficacy, yielding a RR against placebo of 2.29 (95% CI 1.81 to 2.89; 1789 participants; I^2 = 70%; Analysis 7.2), which is very close to the point estimate for the main analysis, but with a wider confidence interval.

Standard-dose versus low-dose varenicline

Three trials (Nakamura 2007; Nides 2006; Oncken 2006) tested the standard regimen (1 mg twice a day) against half the recommended daily dose, either as a single 1 mg tablet or as two 0.5 mg doses, and found a modest advantage for the standard dosage: RR 1.25 (95% CI 1.00 to 1.55; 1079 participants; Analysis 7.3).

Standard dose versus high-dose varenicline

In one recent trial (Hajek 2015; not included in the main analyses), 200 smokers who were judged not to be responding to the standard dose of varenicline (no strong nausea, no clear reduction in smoking enjoyment, and less than 50% smoking reduction after 10 days) were allocated to additional treatment (varenicline or placebo) up to the target quit date (day 21). Participants maintained that dosage for three weeks, but could reduce it if side effects became intolerable. Participants could take up to 3 mg a day in addition to the standard daily dose of 2 mg. The trial found a marginal but non-significant benefit for quit rates with the higher dosing schedule, with an RR at 12 weeks of 0.88 (95% CI 0.54 to 1.44; Analysis 7.4), but noted a trend in the varenicline group for more fatigue and decreased appetite, and significantly higher levels of nausea and vomiting.

2.3 Preloading (before the TQD)

No trials currently report on this comparison.

2.4 Reducing to quit

One recent trial (Ebbert 2015) tested varenicline against placebo in 1510 smokers disinclined to quit abruptly, but willing to reduce their smoking gradually as a gateway to quitting. Treatment was given in this trial for 24 weeks rather than the standard regimen of 12 weeks, with participants asked to reduce their smoking rate by 50% by week 4, by at least 75% by week 8, and by 100% by week 12. After 12 months, the RR for quitting was 3.99 (95% CI 2.93 to 5.44; Analysis 7.5) in favour of varenicline.

2.5 Maintenance therapy (relapse prevention)

Two trials have tested varenicline as an aid to relapse prevention in smokers who had successfully quit on varenicline. Tonstad 2006 randomised 1208 quitters to a further 12 weeks of either varenicline or placebo, while Evins 2014 randomised 87 quitters with schizophrenia, schizoaffective or bipolar disorder to a further 40 weeks of either varenicline or placebo treatment. We note that the integrity of the blinding in these trials may be questionable, as all the participants had already used open-label varenicline to achieve abstinence. At 12 months, the RR in favour of varenicline was 1.24 (95% CI 1.08 to 1.42; Analysis 7.6). Heterogenity was high, at 82%, possibly reflecting the relatively extended treatment period in the smaller trial. A random-effects analysis eliminated the significant difference (RR 1.75, 95% CI 0.71 to 4.33).

2.6 Harm reduction

No trials currently report on this comparison.

III Specific patient groups

3.1 Cardiovascular disease (CVD)

Rigotti 2010 compared varenicline to placebo in a trial of 714 people with stable cardiovascular disease. Eisenberg 2016 randomised 302 smokers admitted for acute coronary syndrome to 12 weeks of treatment plus 12 weeks follow-up. At longest follow-up (52 weeks and 24 weeks respectively), the RR was 1.88 (95% CI 1.4 to 2.47; 1006 participants; I^2 = 81%; Analysis 8.1) in favour of varenicline. Treating the trials as a subgroup of the main analysis (Analysis 4.1) and testing for subgroup differences demonstrated no significant difference between them (Chi^2 = 1.70, P = 0.19, I^2 = 41.1%; analysis not shown).

3.2 COPD

Tashkin 2011 compared varenicline to placebo in 504 adult smokers with mild to moderate COPD. At 52 weeks, the RR was 3.35 (95% CI 1.89 to 5.94; Analysis 8.2) in favour of varenicline.

3.3 Asthma

Westergaard 2015 compared varenicline to placebo in 52 young adults (aged 19 to 40) with asthma. At six months, there was no difference in quit rates between the intervention and control arms (RR 1.25, 95% CI 0.38 to 4.14; Analysis 8.3).

3.4 Schizophrenia/bipolar/psychiatric disorder

Four trials tested varenicline against placebo in smokers diagnosed with bipolar disorder (Chengappa 2014), with a history of various psychiatric disorders (and at least one-third of the cohort stably taking psychotropic medications (EAGLES 2016), with schizophrenia, schizoaffective or bipolar disorders (Evins 2014), and with schizophrenia or schizoaffective disorder (Williams 2012). The pooled analysis found a benefit for varenicline at six months, with a RR of 2.28 (95% CI 1.82 to 2.87; 2332 participants, I^2 = 0%; Analysis 8.4). Treating the trials as a subgroup of

the main analysis (Analysis 4.1) and testing for subgroup differences demonstrated no significant difference between them (Chi^2 = 0.10, P = 0.76, I^2 = 0%; analysis not shown).

3.5 Depression

Anthenelli 2013 compared varenicline to placebo in 523 adult smokers with current or past depression. At 52 weeks, the RR was 1.97 (95% CI 1.28 to 3.01; Analysis 8.5) in favour of varenicline.

3.6 Substance use disorder/methadone-maintained

Two trials tested varenicline against placebo in smokers on methadone treatment for substance use disorder. Nahvi 2014a covered 112 outpatients in New York, and Stein 2013 315 outpatients in New England. The latter study included a combination NRT arm (patch + ad lib nicotine gum), which is included in Analysis 6.1. The pooled analysis did not find an effect of varenicline: RR 3.72 (95% CI 0.50 to 27.59; I^2 = 0%: Analysis 8.6). Treating the trials as a subgroup of the main analysis (Analysis 4.1) and testing for subgroup differences demonstrated no significant difference between them (Chi^2 = 0.25, P = 0.62, I^2 = 0%; analysis not shown).

3.7 Alcohol-dependent smokers

NCT01347112, which posted its results on the www.ClinicalTrials.gov website, reported cessation rates of 25% (4/16) for the varenicline group, and 0% (0/17) for the placebo group. These findings were not biochemically verified, and the study sustained high losses, putting it at high risk of bias.

3.8 HIV

No trials currently report on this comparison, although NCT00918307 includes a conference abstract giving preliminary findings. No results have been posted on the www.ClinicalTrials.gov trials registry database.

3.9 Diabetes

No trials currently report on this comparison.

3.10 Head and neck cancer

No trials currently report on this comparison.

3.11 Varenicline in pregnancy

No trials currently report on this comparison.

3.12 Varenicline for long-term use of NRT

Tønnesen 2013 aimed to wean 139 ex-smokers off long-term use of NRT. All had been consuming an average of 16 NRT units a day for approximately six years. Participants were randomly allocated to varenicline or placebo for the standard 12-week treatment phase, and were followed up to 52 weeks. The trial did not find a difference between the varenicline and placebo arms for participants, either for having smoked (10% in the varenicline group and 11.6% in the placebo group between weeks 36 and 52) or for not using NRT, with a RR of 1.31 (95% CI 0.83 to 2.08; Analysis 8.8).

IV Different settings and subgroups

4.1 Hospital inpatients/perioperative patients

Three trials currently address this population of smokers. Carson 2014 targeted adult smokers admitted to hospital for smoking-related acute illnesses, Steinberg 2011 adult smokers admitted with any diagnosis, and Wong 2012 adult smokers admitted for non-cardiac elective surgery. The pooled analysis at longest follow-up favoured varenicline treatment, with a RR of 1.39 (95% CI 1.09 to 1.77; 744 participants, I^2 = 36%; Analysis 9.1). Treating the trials as a subgroup of the main analysis (Analysis 4.1) and testing for subgroup differences demonstrated a significant difference between the hospital group and the remaining trials (Chi^2 = 15.87, P < 0.0001, I^2 = 93.7%; analysis not shown). This may be linked to the negative findings of the Steinberg 2011 trial.

4.2 Smokers who have previously failed to quit on varenicline or NRT or bupropion

Gonzales 2014 tested varenicline versus placebo in a group of smokers who had previously used varenicline for two weeks or more, at least three months prior to admission to the study, and had failed to quit but were motivated to try again. The trial found a clear benefit for varenicline, with a RR at 52 weeks of 6.15 (95% CI 2.98 to 12.70; 494 participants; Analysis 9.2).

4.3 Light or heavy smokers

De Dios 2012 is a small pilot study conducted in 32 Latino light smokers (smoking 10 or fewer cigarettes a day), randomising to varenicline, NRT or placebo tablets. The six-month result, although favouring the varenicline arm, did not achieve statistical significance: RR 7.64 (95% CI 0.44 to 131.75; Analysis 9.3)

4.4 Varenicline by gender

No trials currently address this comparison, although a recent meta-analysis (McKee 2015) presents abstinence data stratified

by gender from 16 RCTs (supplied by Pfizer). Their meta-analysis demonstrates, compared with other smoking cessation treatments, greater efficacy for short- and immediate-term outcomes in women smokers versus men, and equal efficacy for abstinence at one year.

4.5 Varenicline in ethnic groups

No trials currently report on this comparison.

2. Craving and withdrawal

The results of the trials included in our review lend support to the theoretical basis for the development of varenicline. Its properties as a partial agonist, causing moderate activation of the $\alpha 4\beta 2$nAChR, may be expected to mitigate craving and withdrawal symptoms, while its antagonist properties in blocking nicotine binding may lead to reduced smoking satisfaction and reduced psychological reward in those who continue to smoke while taking the drug. The varenicline trials which tested withdrawal and craving all reported its superiority over placebo in reducing withdrawal symptoms, as measured on the Minnesota Nicotine Withdrawal Scale or the Wisconsin Smoking Withdrawal Scale; craving, as measured on the Brief Questionnaire of Smoking urges; and enjoyment of concurrent smoking, as measured on the modified Cigarette Evaluation Questionnaire.Those trials (Nides 2006; Oncken 2006; Nakamura 2007; Niaura 2008) which measured the effects of varying dosage detected greater reductions in craving and withdrawal symptoms in the standard dose groups (1.0 mg twice a day) than in the reduced dose groups. Hajek 2015 noted similar disparities in enjoyment of smoking when participants moderated their own dosage up to the TQD. Full details of the comparative incidence of craving and withdrawal symptoms are shown in Appendix 3.

3. Adverse events (AEs)

The predominant adverse event for varenicline was mild to moderate nausea, subsiding over time, at rates between 6% (Stein 2013) and 51% (Nahvi 2014a), but with almost half the studies reporting levels between 24% and 29%. The trials testing non-standard regimens found a dose-response relationship for the incidence of nausea: rates ranged from 17.5% (0.3 mg daily) to 52% (1.0 mg twice daily) in Nides 2006, and from 7.2% (0.25 mg twice daily) to 24.4% (1.0 mg twice daily) in Nakamura 2007. Self regulation of treatment in Niaura 2008 appeared to reduce rates of nausea, with 13.4% of varenicline users reporting it compared with 5.2% of the placebo group. Both titration and dosage levels affected the incidence and severity of nausea in Oncken 2006, with the lower dose resulting in rates of 16.3% (titrated) and 22.6% (non-titrated), compared with 34.9% (titrated) and 41.9% (non-titrated) in the standard dosage groups. Hajek 2015 allowed participants to increase their dosage up to 5 mg a day by the TQD, and reported nausea rates of 80% in the varenicline group compared with 18% among the placebo participants. In Gonzales 2006 and Jorenby 2006, an average of 9.5% in the varenicline groups discontinued treatment but remained in the trial for follow-up, compared with an average of 14% in the bupropion groups and 8% in the placebo groups. Discontinuation rates for any adverse event were highest in Williams 2007, where participants took the trial medication for a year, at 28.3% in the varenicline group and 10.3% in the control group. In the 12-week open-label phase of Evins 2014, 31.8% of participants taking varenicline discontinued the study because of adverse events, or for non-adherence to the protocol, or because they no longer wished to stop smoking. In Phase 1 of Rose 2013, 62 of 112 (55%) non-responders to NRT assigned to varenicline withdrew or were lost to follow-up, but this was a comparable attrition rate to those lost from the NRT group (60%) and from the bupropion group (58%), and appeared not to be associated with adverse events. The study also noted that 25% of participants across all three conditions reduced their dosage at some point during treatment.

Adverse events were monitored weekly during treatment from weeks one to seven (Gonzales 2006; Jorenby 2006; Nides 2006; Oncken 2006), weekly throughout 12 weeks of treatment (Anthenelli 2013; Aubin 2008; Bolliger 2011; Carson 2014; Cinciripini 2013; EAGLES 2016; Ebbert 2015; Evins 2014; Gonzales 2014; Nakamura 2007; Niaura 2008; Rennard 2012; Rigotti 2010; Tashkin 2011; Tsai 2007; Wang 2009), or fortnightly throughout 12 weeks of treatment (Rose 2013; Tønnesen 2013). Stein 2013 monitored participants at weeks two and four, for adherence and adverse events. Tonstad 2006 monitored at week 13 (end of open-label phase) and at week 25 (end of double-blind phase), and Williams 2007 monitored weekly from weeks one to eight and then monthly to week 52. Baker 2016 monitored adverse events and delivered counselling at weeks 1, 4, 8 and 12. Steinberg 2011 collected adverse event data through self report at weeks 2, 4, 12 and 24, and Nahvi 2014a in four visits over 12 weeks of treatment. Hajek 2015 followed the UK's NHS Stop Smoking Service protocol and monitored weekly for the first month post-TQD, and again at 12-week end of treatment. The trials reported only those adverse events occurring in at least 5% of the varenicline groups, and at higher rates than in the placebo groups, with the exception of Bolliger 2011, Nahvi 2014a, Nakamura 2007, Stein 2013, Steinberg 2011, and Tønnesen 2013 (any occurrence), Anthenelli 2013 (occurring in 1% of either group), Ebbert 2015 (occurring in at least 2% of either group), Chengappa 2014, Cinciripini 2013, Gonzales 2014, and Hajek 2015 (at least 5% in either group), Evins 2014 (occurring in 10% of either group), and Rennard 2012 (any event occurring in at least 5% of either group, and psychiatric events in at least 1% of either group).

Meta-analyses of the four main adverse events in the varenicline versus placebo groups yielded RRs of 3.27 (95% CI 3.00 to 3.55; 32 studies; 14,963 participants; I^2 = 22%) for nausea (Analysis 10.1); 1.49 (95% CI 1.35 to 1.65; 29 studies; 14,447 participants;

I^2 = 0%) for insomnia (Analysis 10.2); 2.12 (95% CI 1.88 to 2.38; 26 studies; 13,682 participants; I^2 = 62%) for abnormal dreams (Analysis 10.3); and 1.17 (95% CI 1.07 to 1.29; 25 studies; 13,835 participants; I^2 = 27%) for headache (Analysis 10.4). All differences were statistically significant.

4. Serious Adverse Events (SAEs)

A serious adverse event (SAE) may be defined as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalisation or prolongation of existing hospitalisation; resulted in persistent or significant disability or incapacity; or resulted in a congenital anomaly or birth defect (Nakamura 2007).

Vinnikov 2008 reported no SAEs in their cytisine trial, while West 2011 reported seven, none of which was deemed to be related to the medication, and Scharfenberg 1971 gave no information about the incidence of SAEs in either group. Walker 2014, comparing cytisine with NRT (no placebo group), reported 56 SAEs in 45 participants taking cytisine (eight of the SAEs occurring in one person), and 45 SAEs in 39 participants taking NRT. One person died in each group, but neither death (one alcohol-related asphyxiation and one heart attack) was deemed to be treatment-related.

Among the varenicline studies, there were no treatment-related deaths in any of the intervention groups during treatment or follow-up phases. However, Carson 2014 reported 13 fatalities during the first 12 months of the study period, in a population of inpatients admitted for acute episodes of smoking-related illnesses. All the deaths (six in the varenicline + counselling group and seven in the counselling-only group) were in people with known underlying comorbidities, including COPD, bradycardia, arrhythmia, lung cancer, stroke and non-ST-elevation myocardial infarction. The authors do not attribute any of the deaths to study medication (Carson 2011).

Non-fatal SAEs occurred in 29 of the varenicline trials. We discounted from this analysis four trials which did not report any SAEs (De Dios 2012; Heydari 2012; Westergaard 2015; Wong 2012) and a further four which had no placebo group (Aubin 2008; Baker 2016; Rose 2013; Tsukahara 2010). Event counts for Analysis 11.1 and Analysis 11.2 are of individuals reporting one or more SAEs. Analysis 11.1 demonstrates an RR of 1.25 (95% CI 1.04 to 1.49; 15,370 participants, I^2 = 0%; high-quality evidence), indicating an increased risk of SAEs in the varenicline groups compared with the placebo groups. A secondary analysis restricted to SAEs occurring within or immediately after the treatment phase demonstrated a similar effect (RR 1.25, 95% CI 1.02 to 1.52; 15,000 participants, I^2 = 0%). A sensitivity analysis using a Peto odds ratio (appropriate for the analysis of rare events) made no difference to the findings. Details of the SAEs among 32 of the included studies are given in Appendix 4.

We also include a meta-analysis of cardiac SAEs including deaths (Analysis 11.4). There were 92 events in 8587 participants from 21 studies. There were more events in the varenicline groups and the confidence intervals are wide and do not rule out an increase (RR 1.36, 95% CI 0.91 to 2.04; I^2 = 0%; moderate-quality evidence).

For this update. we have conducted new meta-analyses of neuropsychiatric adverse events, using any study included in the efficacy findings which reported the incidence of these events, plus nine studies (flagged with an asterisk in the study ID) excluded from the efficacy analyses, but offering data on safety. The RR for depression is 0.94 (95% CI 0.77 to 1.14; 36 studies; 16,189 participants, I^2 = 0%; Analysis 10.5), with non-significantly lower rates in the varenicline groups. The RR for suicidal ideation is 0.68 (95% CI 0.43 to 1.07; 24 studies; 11,193 participants, I^2 = 0; Analysis 10.6), with border-line non-significantly lower rates in the varenicline groups. It should be noted that all five events in the varenicline group for suicidal ideation occurred in the psychiatric cohort, with none reported in the non-psychiatric group.

The EAGLES Study

EAGLES 2016, a double-blind triple-dummy RCT, is the largest trial to have been conducted with varenicline, and was stratified by the presence (n = 4074) or absence (n = 3984) of a history of psychiatric disorders. The authors estimate that at least one-third of the psychiatric cohort participants were stably taking psychotropic medications throughout the course of the study. The primary safety endpoint was a composite measure of 16 neuropsychiatric adverse events, including anxiety, depression, feeling abnormal, and hostility (all rated as severe), and agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour, and completed suicide (all rated as moderate or severe). Outcomes were assessed using the Columbia Suicide Severity Rating Scale (C-SSRS), the Suicide Behavior Questionnaire - Revised (SBQ-R), and the Hospital Anxiety and Depression Scale (HADS) at visits throughout the treatment and follow-up phases of the study.

Rates of neuropsychiatric AEs were similar across all four treatment groups, with more AEs in the psychiatric than in the non-psychiatric cohort. Event rates in the psychiatric cohort during treatment and up to 30 days after were varenicline 6.5%, bupropion 6.7%, NRT 5.2% and placebo 4.9%; the corresponding rates in the non-psychiatric cohort were 1.3%, 2.2%, 2.5% and 2.4% respectively. The risk difference between groups was significantly lower for the varenicline group compared with placebo in the non-psychiatric cohort (RD -1.28, 95% CI -2.40 to -0.15); all other differences in the remaining comparisons (varenicline, bupropion, NRT, all versus placebo) in both cohorts were statistically non-significant. The study authors interpret this as indicating that none of the first-line smoking cessation treatments compared with placebo significantly increases the risk of neuropsychiatric adverse events in smokers with or without psychiatric disorders.

An analysis by treatment group in the psychiatric cohort, assessing the incidence of AEs categorised by severity (severe or serious), discontinuation and corrective intervention (including medication, psychotherapy, counselling and hospitalisation), found few differences between the groups: counts of severe AEs were identical across the active treatment groups (14 in each), with the placebo group reporting 13. Serious AEs were similar: varenicline six, bupropion five, NRT and placebo three each. AEs leading to permanent treatment discontinuation were varenicline 16, bupropion and placebo 15 each, and NRT 12, while AEs requiring intervention were varenicline and NRT seven each, bupropion 12, and placebo 11. Based on the upper limits of the confidence intervals, the authors conclude that it is highly unlikely that varenicline and buporpion contribute to neuropsychiatric adverse events of moderate to severe intensity at a rate above 1.5% in smokers without a psychiatric disorder, and above 4% in smokers with such disorders. These estimates are also consistent with no increase in neuropsychiatric event rates in either population of smokers.

The authors report the limitations of their findings, confirming that the results may not be generalisable to smokers with untreated or unstable psychiatric disorders. For the psychiatric cohort, they confined recruitment to smokers with any of four major disease categories (mood, anxiety, psychosis and borderline personality disorder), and did not include smokers with current substance use disorders or imminent risk of suicide. They also point out that light smokers (fewer than 10 cigarettes a day) were excluded from the study population, and that the trial has low power to detect rare neuropsychiatric events.

The evidence currently presented demonstrates an inconsistent pattern between the two cohorts in AE event rates, with the psychiatric cohort reporting higher rates in the active treatment groups compared with placebo, and the reverse pattern in the non-psychiatric cohort. This difference is in line with current SPC warnings that care should be taken in people with a history of psychiatric illness, and with the FDA 2015 Drug Safety Communication advising that they were unable to draw reliable conclusions on these issues. The reliance in this study on a composite safety endpoint, covering a mix of adverse and serious adverse events, also precludes firm conclusions about the risk levels for individual disorders, which may be elevated for some components and reduced for others. We await further details of the findings to explore the robustness of the risk profile.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Cytisine versus placebo for smoking cessation

Patient or population: Individuals who smoke tobacco
Setting: Varied
Intervention: Cytisine
Comparison: Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Corresponding risk with Cytisine				
Cytisine vs placebo: continuous abstinence at longest follow-up (24+ weeks)	Study population (where risk refers to quitters)		RR 3.98 (2.01 to 7.87)	937 (2 RCTs)	⊕⊕◯◯ LOW [1]	
	21 per 1000	85 per 1000 (43 to 169)				

***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).The assumed risk in the comparison group is calculated as the median risk in control groups.

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Imprecision rated 'very serious' (downgraded two levels on this basis) as only two studies, and fewer than 300 events in each arm.

DISCUSSION

This update now covers four trials of cytisine, and 39 trials of varenicline. Full searches were conducted to May 2015, although we have included key trials which we obtained after this date.

Summary of main results

Cytisine

Two studies (Vinnikov 2008; West 2011) have demonstrated a benefit for cytisine over placebo. However, absolute quit rates were relatively low, with Vinnikov 2008 reporting 9% for cytisine and 1% for placebo at 24 weeks, and West 2011 8.4% and 2.4% respectively at 52 weeks. The authors note that their deliberately parsimonious intervention for the Polish trial, with a 25-day regimen (in accordance with the manufacturer's guidelines; Tabex 2011) and minimal behavioural support, may have limited the achievable cessation rates. Further trials with modified regimens may need to be conducted to explore the balance between the positives of affordability and availability within lower- and middle-income economies and the modest efficacy demonstrated to date. A recent non-inferiority trial comparing cytisine with NRT (Walker 2014) demonstrated a benefit for cytisine at six months, with continuous abstinence rates of 21.8% and 15.3% respectively.

Varenicline

The evidence from 27 trials in 12,625 participants indicates that varenicline increases the chances of successful smoking cessation between two- and three-fold compared with placebo. This estimate has remained stable, despite the growing inclusion of pragmatic trials in real-world settings and in particular groups of smokers normally excluded from clinical trials, e.g. in lower- and middle-income countries, and in disease-specific populations. Long-term use of varenicline (two trials of 24 weeks, two trials of 52 weeks) delivered an unequivocal advantage for varenicline over placebo, without a concomitant increase in adverse or serious adverse events.

In five trials (5877 participants), varenicline was shown to increase the probability of quitting more than bupropion. Eight trials (three of them open-label) in 6264 people compared varenicline with nicotine patches, and found a modest but clear benefit for varenicline. One trial found no differences between any of the three tested treatments (varenicline, nicotine patch, and nicotine patch plus lozenge).

More smokers quit successfully with varenicline than with a placebo or an alternative intervention in all the populations and subgroups that we reviewed, including variations in usage (flexible versus fixed quit dates, different dosages, reducing to quit, relapse prevention therapy), in disease-specific groups of patients (cardiovascular, COPD, schizophrenia and psychiatric disorders, depression), and in various subgroups or settings (hospital inpatients, smokers who failed to quit on other therapies). The exceptions to these findings were standard versus high-dose varenicline, and varenicline versus placebo in young adults with asthma, in Latino light smokers, in methadone-maintained substance abusers, and in long-term users of NRT. In these instances the results favoured varenicline, but did not reach statistical significance.

The number needed to treat for an additional beneficial outcome (NNTB) can be derived from the pooled difference between placebo and treatment quit rates. However, absolute quit rates vary considerably between trials, according to the definition of cessation, length of follow-up, the population treated and the extent of the counselling and follow-up support given. The risk ratio should be independent of these factors and can be used to derive NNTBs for the assumed placebo rates that will apply in each local setting. We estimated a control quit rate with behavioural support at six months of 7.5%, derived from the weighted mean of the control event rates in the first few varenicline trials conducted in the USA. Based on this rate, the NNTB for varenicline is 11 (95% CI 9 to 13). For comparison we can estimate NNTBs from recent meta-analyses of nicotine replacement therapy (NRT) (RR 1.60, 95% CI 1.53 to 1.68, Stead 2012) and bupropion (RR 1.62, 95% CI 1.49 to 1.76, Hughes 2014). Assuming the same 7.5% rate in the behavioural support-only conditions, the NNTB for all types of NRT is 23 (95% CI 20 to 25), and the NNTB for bupropion is 22 (95% CI 18 to 28).

Adverse events

The main adverse effect of varenicline was nausea, which was generally mild to moderate, diminished over time, and was associated with low discontinuation rates. Those trials which tested levels of dosage and the presence or absence of titration found an increase in adverse events (apart from headache) with increasing dosage, and also found that titration appeared to reduce the incidence of nausea. The transitory nature of this adverse event may find further support in the relapse prevention study (Tonstad 2006), which reported nausea in 33.5% of varenicline users in the open-label phase; once the successful quitters were randomised to varenicline or placebo, rates of nausea fell to 1.2% in the varenicline group and 0.7% in the placebo group. This virtual elimination of nausea as an adverse event may suggest that habituation over 12 weeks of treatment had resolved the condition. However, it is also plausible that those who suffered most with adverse events during the open-label phase may not have successfully completed treatment or, having quit, would be less likely to accept the invitation to take part during the double-blind phase. It would therefore be unwise to draw too strong an inference from the difference in rates between the two phases of the study.

New for this update are analyses of neuropsychiatric events (depression and suicidal ideation). In both cases, the event rates were higher in the placebo groups than in the varenicline groups, although neither point estimate reached statistical significance.

Serious adverse events

Our meta-analysis of serious adverse event (SAE) data from 29 trials suggests there may be a 25% increased risk of such events among the varenicline groups compared with the controls. While this finding (RR 1.25, 95% CI 1.04 to 1.49; 15,370 participants; I^2 = 0%) reaches statistical significance, it must be noted that it is based on simple counts across the trials of participants reporting one or more such events, and does not distinguish between events attributed and those unrelated to treatment. A sensitivity analysis removing events known to have occurred after the treatment phase made a negligible difference to the point estimate (see Analysis 11.2). This finding should also be considered in the light of the higher losses to follow-up in the control arm (mean of 28.4%) of most of the studies (25/29) compared with the varenicline arm (mean of 23.8%) (see Analysis 12.1), making it likely that the event rate in the intervention groups was consistently underestimated. A calculation of the number needed to treat for an additional harmful outcome (NNTH), based on a typical control rate of 2%, returned a figure of 143 (95% CI 74 to 556), i.e. one additional SAE for every 143 people treated with varenicline.

Neuropsychiatric SAEs

Post-marketing surveillance has raised continuing safety issues concerning varenicline. In February 2008 the US Food and Drug Administration (FDA 2008) issued a public health advisory, reporting that an association between varenicline and an increased risk of behaviour change, agitation, depressed mood, suicidal ideation and behaviour "appears increasingly likely". Three months later, the FDA approved changes to the product labelling, including a boxed warning, and a Medication Guide produced by Pfizer Inc.

Tonstad 2010a points out the complexities of separating treatment-related events during the cessation process from those associated with nicotine withdrawal, with normalisation of monoamine oxidase levels, and possibly with increased caffeine levels. Any causal relationship between varenicline and serious neuropsychiatric events must be convincingly disentangled from possible confounding factors. A review of the ten trials completed up to the end of 2008 (Tonstad 2010b) found no significant excess incidence of disorders in varenicline users compared with control groups (RR 1.02, 95% CI 0.86 to 1.22), apart from sleep disorders (RR 1.70, 95% CI 1.50 to 1.92). However, although the absolute risk of depressed mood disorders and disturbances appears to be low in these study populations (varenicline 2.8% vs placebo 1.9%), the RR of 1.42 (95% CI 0.96 to 2.08), while not statistically significant, suggests an increased likelihood of such disorders for varenicline users. It must also be noted that these trials excluded participants with current or recent depression, panic disorder, psychosis, bipolar disorder or alcohol/drug abuse or dependence, and represent an atypically 'healthy' population of smokers. The findings may not be readily generalisable to a mixed real-world population of smokers.

Recent studies have explored possible links between varenicline use and suicidal ideation and behaviour. Any such evaluation is complicated by the fact that people who smoke have a two- to three-fold increased risk of suicide (Hemmingsson 2003; Miller 2000). A UK cohort study (Gunnell 2009) evaluating rates of fatal and non-fatal self harm, suicidal thoughts and depression in users of varenicline compared with NRT and bupropion found no clear evidence of an association. The hazard ratio for self harm among people using varenicline compared with NRT was 1.12 (95% CI 0.67 to 1.88), and compared with bupropion was 1.17 (95% CI 0.59 to 2.32). Similarly, current evidence did not detect an effect for an increase in risks of depression or suicidal thoughts associated with varenicline compared with the other two medications. Although the upper level of the confidence interval for the self-harm estimate does not preclude the possibility of a two-fold increase for varenicline users, the data broadly confirm that the absolute incidence was low. The Gunnell 2009 analysis has subsequently been updated by Thomas 2013, using validated outcomes, and deploying instrumental variable analysis to counter residual confounding. The updated analyses confirmed that people taking varenicline were no more likely than those taking NRT to suffer fatal or non-fatal self harm (HR 0.88, 95% CI 0.52 to 1.49) or treated depression (HR 0.75, 95% CI 0.65 to 0.87). The interim report by the UK-based Drug Safety Research Unit of their cohort study of prescription event monitoring (Kasliwal 2009) has found no evidence of an excess of suicidal thoughts or behaviours; both of the reported suicide attempts in the cohort of 2682 patients occurred in people with a previous history of psychiatric illness and with precipitating factors for the event. A similar study conducted in New Zealand by the Intensive Medicines Monitoring Programme identified one suicide (0.03%, 95% CI 0.007% to 0.16%) in a cohort of 3415 recipients of dispensed varenicline prescriptions (Harrison-Woolrych 2011).

Thomas 2014 used MHRA yellow card data to review the incidence of depression and suicidal behaviour spontaneously reported for 110 different drugs, including varenicline. Varenicline was ranked first for the number of reports per million prescriptions for depression (248, 95% CI 233 to 264), second behind paroxetine for non-fatal suicidal behaviour (172 per million, 95% CI 159 to 185), and sixth for completed suicide behind clozapine, citalopram, fluoxetine, paroxetine and venlafaxine (10 per million, 95% CI 8 to 14).

Three recent retrospective cohort studies have reported on the incidence of psychiatric events, criminal offending and traffic accidents and offences (Molero 2015), on cardiovascular and neuropsychiatric events in users of varenicline (Kotz 2015), and on neuropsychiatric events in varenicline compared with NRT users in the Military Health System (Meyer 2013). The Swedish study (Molero 2015) reviewed a cohort of 7,917,436 adults, of whom 69,757 had been treated with varenicline between 2006 and 2009. They found that varenicline use was not associated with suicidal behaviour, with criminal offending, with traffic accidents or offences, or with psychoses. There were, however, marginally in-

creased risks of anxiety (hazard ratio (HR) 1.23, 95% CI 1.01 to 1.51) and of mood conditions (HR 1.31, 95% CI 1.06 to 1.63) in people with a pre-existing psychiatric disorder. In those without an existing psychiatric disorder, the risks were elevated but not statistically significantly different. In the English study (Kotz 2015), data from 753 NHS general practices were reviewed to compare recipients of NRT (106,759; the reference group) with users of varenicline (51,450) and bupropion (6557), for the incidence of neuropsychiatric and cardiovascular events. Varenicline was not associated with an increased risk for any neuropsychiatric conditions, compared with NRT users. The hazard ratio for depression was 0.66 (95% CI 0.63 to 0.69), and for self harm 0.56 (95% CI 0.46 to 0.68), compared with rates in NRT users. However, note comments below on this study and the Thomas 2013 data. Meyer 2013 compared propensity-matched cohorts of people prescribed varenicline or NRT (10,814 in each group) within the American military system for rates of hospitalisation for neuropsychiatric events within 30 days of prescription. The adjusted HR at 30 days was 1.14 (95% CI 0.56 to 2.34), and at 60 days 1.11 (0.59 to 2.10), indicating no evidence for an elevated risk of hospitalisation among varenicline users compared with those taking NRT (reference group).

In contrast with these broadly reassuring findings, Moore 2011 used the FDA's Adverse Events Reporting System (AERS) to assess the occurence of suicidal behaviour or depression in 9575 case reports of varenicline use, and in 1751 case reports of bupropion use for smoking cessation. They concluded that varenicline was linked to a steep increase in depression or self-injurious behaviours (OR 8.4, 95% CI 6.8 to 10.4) compared with NRT. While this report highlights continuing concerns about safety, it must be noted that inferences drawn from spontaneous reporting systems should be treated with caution. Because of heightened media coverage and FDA warnings, suicidal ideation or behaviour during varenicline use may be more likely to be reported to the AERS than if the patient exhibited the same features while on NRT, for example. The FDA caution against ascribing a causal connection between a drug and the event, pointing out that there is often insufficient information on the report forms to evaluate the event, and that not all adverse events will be reported to them: "Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population" (FDA 2012). The limitations of this class of data include potential confounding by indication (i.e. the patient's condition may predispose to higher rates of adverse event); underreporting; double-counting from multiple sources; the use of concomitant medications; and lack of representativeness which limits generalisability (Gibbons 2011). The Institute for Safe Medication Practice (ISMP) has questioned whether a spike in routine reports of serious adverse events for varenicline submitted to the AERS in the third quarter of 2010 is associated with a delay in passing the information from Pfizer to the FDA, and with classifying such events as "expected" rather than fast-tracking them (ISMP 2011). In light of the constraints of spontaneous reporting systems, Moore and colleagues compared reports submitted for NRT use (to estimate baseline risks for smokers) with those submitted for antibiotic use (as a proxy for population-based risks), which indicated that smokers may already be at a fourfold-increased risk of suicidal behaviour or depression, regardless of which cessation aids they use. The authors recommended that varenicline should not be offered as a first-line treatment for smoking cessation, and noted that the Veterans Affairs Center for Medication Safety shared this precautionary approach (VA 2011). It is notable, however, that a matched observational study of more than 28,000 participants commissioned by the FDA and conducted by the VA Center found no difference in rates of hospitalisation for psychiatric events between users of NRT and users of varenicline; the hazard ratio for varenicline versus NRT was 0.76; 95% CI 0.40 to 1.46 (FDA 2011a). A recent FDA Drug Safety Communication (FDA 2011a, October 2011) concludes that "Based on FDA's assessment of currently available data, the Agency continues to believe that the drug's benefits outweigh the risks and the current warnings in the Chantix drug label are appropriate".

Cardiovascular SAEs

Following the publication of Rigotti 2010 (testing varenicline in people with stable cardiovascular disease (CVD)), the FDA issued a Drug Safety Communication (FDA 2011b) advising that varenicline may be associated with a small increased risk of certain cardiovascular adverse events in people with CVD. A systematic review of 14 trials (Singh 2011) claims that varenicline may increase the risk of serious cardiovascular events among tobacco users, with a meta-analysis yielding a Peto odds ratio of 1.72 (95% CI 1.09 to 2.71). While the authors describe this as "a 72% increased risk", it should be noted that the incidence of such events was low, at 1.06% in varenicline users and 0.82% in the placebo group, returning an absolute difference of 0.24%, i.e. about 1 in 400. The review has some acknowledged limitations, including the validity of the classification of the cardiac events (unadjudicated, other than those derived from the Rigotti trial); higher losses to follow-up in the placebo groups, which may underestimate the true rate of control events; and the choice of a Peto rather than a Mantel-Haenszel odds ratio (the latter just missing statistical significance [M-H OR 1.56, 95% CI 0.99 to 2.44]). The choice of a random-effects rather than a fixed-effect model would also lower the point estimate (OR 1.47, 95% CI 0.92 to 2.34). The assumption of a baseline risk rate of 5.57% for cardiac adverse events in their calculation of a number needed to treat for an additional harmful outcome (NNTH) may also be questionable, since it is based on the Rigotti study population of smokers with established cardiac disease, while the event counts used to derive the odds ratio come from trials which were mostly in unusually 'healthy' trial participants.

These concerns were echoed by an observational prospective cohort study of dispensed prescriptions for varenicline in New Zealand between April 2007 and November 2010 (Harrison-Woolrych 2012). The study, conducted by the Intensive Medicines

Monitoring Programme, covered all patients who received varenicline, and has so far identified 172 cardiovascular adverse events within that cohort. Forty-eight of these were classified as myocardial ischaemia (including 12 reports of myocardial infarction and eight of angina), and 50 were classified as hypotensive events. Within each of these two subgroups, the investigators considered that two key cases may have been triggered by the use of varenicline. Twenty-seven episodes of dysrythmia were also reported, two of which culminated in sudden death; one was attributed to pre-existing heart disease, while the other displayed no definitive underlying cause. Although this cohort was subject to raised baseline risks because of their smoking and to multiple confounding factors, the authors speculate on possible mechanisms of dysregulation of blood pressure, which could have contributed to the events.

A Danish cohort study (Svanström 2012) compared propensity-matched cohorts of people prescribed varenicline or bupropion (17,926 in each group) from 2007 to 2010 for rates of acute coronary syndrome, ischaemic stroke, and cardiovascular death six months from the start of treatment. The study found no excess of events in the varenicline group (6.9 cases per 1000 person-years) compared with the bupropion group (7.1 cases per 1000 person-years). The hazard ratio (varenicline versus bupropion) for acute coronary syndrome was 1.20 (95% CI 0.75 to 1.91), for ischaemic stroke 0.77 (95% CI 0.40 to 1.48), and for cardiovascular death 0.51 (95% CI 0.13 to 2.02). The presence or absence of a history of cardiovascular disease did not affect the overall findings.

The Kotz 2015 cohort study, briefly reported above, found significantly reduced risks of ischaemic heart disease (HR 0.80, 95% CI 0.72 to 0.87), of cerebral infarction (HR 0.62, 95% CI 0.52 to 0.73), of heart failure (HR 0.61, 95% CI 0.45 to 0.83) and of arrhythmia (HR 0.73, 95% CI 0.60 to 0.88) in varenicline users compared to NRT users.

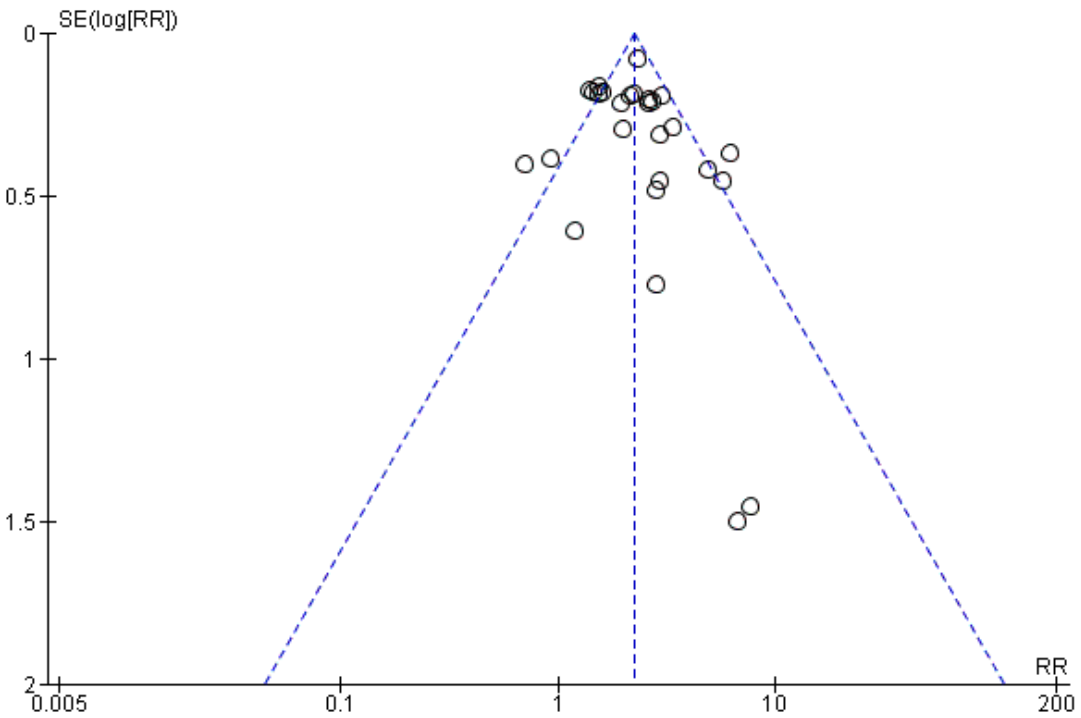
A recent systematic review and meta-analysis (Sterling 2016) of varenicline and cardiovascular serious adverse events included 38 RCTs (12,706 participants) published up to 2015, and found no evidence of an association, in people with (RR 1.04, 95% CI 0.57 to 1.89) or without (RR 1.03, 95% CI 0.64 to 1.64) cardiovascular illness. This study also analysed all-cause mortality, and found no difference between the varenicline and placebo groups (RR 0.88, 95% CI 0.50 to 1.52).

We await results from the CATS study (NCT01574703), conducted among participants in the EAGLES 2016 study, and designed to monitor the incidence of major cardiovascular events (MACEs) for 28 weeks after the completion of the EAGLES 2016 trial. The CATS study was completed in July 2015, and is expected to report later this year.

Overall completeness and applicability of evidence

We have followed standard Cochrane methodology to perform this update. Figure 3 (a funnel plot of the main analysis) appears to identify a lack of smaller trials with negative findings. However, the earliest studies in this review were reported in 2006, and we are reasonably confident that the licensing and subsequent trials have been routinely registered online in clinical trials registries. The absence of negative studies may be more a marker of sustained efficacy than of the suppression or selective management of data.

Figure 3. Funnel plot of comparison: 4 Varenicline (1.0 mg 2/d) vs placebo, outcome: 4.1 Continuous or sustained abstinence at longest follow-up (24+ weeks).



Varenicline's efficacy for smoking cessation is now well established, with the point estimate remaining unchanged as more studies (including non-Pfizer trials) accumulate. Trials are now being conducted and reported in patient groups originally excluded from the earlier studies, and more flexible regimens appear not to compromise levels of efficacy. However, concerns about possible adverse events in vulnerable individuals mean that varenicline is unlikely to be made available as an over-the-counter option, or outside the supervision of a health professional. The costs of treatment have hitherto restricted usage to high-income countries, although trials are increasingly being conducted in low- and middle-income countries. Cytisine, an unlicensed treatment in the European Union and the USA, is an affordable alternative available in parts of Eastern Europe and Russia, and for online purchase worldwide, and may have the potential to meet the needs of smokers wishing to quit in areas of economic constraint.

Quality of the evidence

We judge the current evidence from the cytsine trials to be of low quality, meaning that we have limited confidence in the evidence; only two trials contribute to the meta-analysis, with relatively small numbers taking part. We rated the evidence from studies comparing varenicline with placebo and bupropion as comparators as being of high quality, i.e. reliable and robust. We rate the evidence from studies that compared varenicline with NRT as moderate quality (i.e. we are reasonably confident of the stability of the evidence), since three of them were non-blinded open-label trials.

Potential biases in the review process

We have delayed publication of this update in order to be able to report on the EAGLES 2016 trial. Our information on that trial has been drawn from the trial registry summary (NCT01456936) with results posted on May 3rd 2016, from Society for Research on Nicotine and Tobacco (SRNT) conference abstracts, from a presentation made at the SRNT conference in Chicago (March 3rd 2016), from correspondence with the Pfizer Medical Information Department, and from the in-press release of the initial findings in *The Lancet*. Further results as they become available may moderate our findings in this update.

The comprehensive searches for this update are current to May 2015. Since May 2015 we have checked the status of all ongoing studies, and have generated monthly routine searches of PubMed (keywords 'varenicline' and 'cytisine') to identify any additional relevant research. Studies collected in this way include

Baker 2016; EAGLES 2016; Ebbert 2015; Eisenberg 2016; Hajek 2015; Westergaard 2015. However, we cannot vouch for the completeness of the evidence base beyond the May 2015 search date, and may have missed some relevant reports or developments.

All the varenicline trials reported in this review apart from seven (Carson 2014; De Dios 2012; Heydari 2012; Nahvi 2014a; Rose 2013; Stein 2013; Tsukahara 2010) were funded and/or supported by Pfizer Inc, the manufacturers of varenicline. Evidence from systematic reviews suggests that industry-funded trials, although conducted to a high standard, are more likely to have outcomes favourable to the product sponsor than studies with other sponsors (Etter 2007; Walsh 2011). However, a sensitivity analysis removing them from the main analysis made no difference to the result. Future updates of this review are increasingly likely to cover findings from community-based independently-conducted trials.

Although we have reported information from studies other than RCTs for the incidence and likelihood of adverse events and serious adverse events, it is important to acknowledge the risks of relying upon evidence from cohort studies, surveys, and prescription event-monitoring data. There is, for example, evidence from observational studies (Kotz 2015; Thomas 2013) of residual confounding contributing to the observed reductions in the hazard ratios for depression and death. The lower rates in the varenicline users are attributable not to a protective effect conferred by the treatment but to baseline differences between the varenicline and NRT cohorts; the former were healthier, wealthier and younger (Davies 2015). The Thomas 2015 study (see below), based on 39 RCTs, found no significant reductions in depression, self harm or death rates, compared with placebo.

Agreements and disagreements with other studies or reviews

Reviews of controlled studies of cytisine (Etter 2006; Etter 2008; Tutka 2005; Tutka 2006; Tutka 2008) have focused upon its potential as an established and affordable aid to smoking cessation. Many of the early cytisine studies excluded from this review are discussed and evaluated in Etter 2006. A recent systematic review and network meta-analysis (Leaviss 2014) has compared the efficacy and cost effectiveness of cytisine (two trials: Vinnikov 2008; West 2011) versus varenicline (21 trials). While the analysis found both treatments to be effective for smoking cessation, cytisine delivered more quality-adjusted life-years at a lower cost than varenicline. Cytisine was also associated with lower rates of headache and nausea than varenicline.

A Cochrane overview and network meta-analysis of a number of pharmacological interventions for smoking cessation (Cahill 2013) assessed 12 Cochrane reviews published to November 2012, and therefore drew on the previous version of this review. Comparisons between varenicline, bupropion and single-treatment NRT found varenicline to be superior to both treatments (OR 1.59; 95% credible interval 1.29 to 1.96, and OR 1.57, 95% credible interval 1.29 to 1.91 respectively). Varenicline demonstrated comparable efficacy to combination NRT (OR 1.06, 95% credible interval 0.75 to 1.48), but the number of NRT trials informing this comparison was low (nine trials). The direct comparisons between varenicline and placebo, varenicline and bupropion and varenicline and NRT reported in the EAGLES 2016 trial confirmed in all cases the network results of the same comparisons in Cahill 2013. A 2012 network meta-analysis (Mills 2012), comparing high-dose and combination NRT versus varenicline and versus bupropion across 146 RCTs, found varenicline (11 trials) to be superior to placebo and to bupropion at all time points, and similar in efficacy to standard and to high-dose NRT.

Attention in recent years has tended to shift from efficacy (now clearly established) to adverse and serious adverse events. A meta-analysis of gastrointestinal adverse events associated with varenicline use in 12 RCTs (Leung 2011) found that the drug produced higher rates of nausea (NNTH of 5), constipation (NNTH of 24), and flatulence (NNTH of 35). Another meta-analysis in 12 RCTs of adverse effects during varenicline use (Drovandi 2015) found elevated rates of discontinuation attributable to adverse effects (OR 1.47, 95% CI 1.19 to 1.81) among the varenicline users compared to placebo, and higher rates of nausea, insomnia and headache. Since publication of the Singh 2011 systematic review, a number of other meta-analyses and commentaries have addressed the risks of cardiovascular adverse events associated with varenicline usage. Two reviews which covered largely the same research as the Singh review did not demonstrate a statistically significantly raised event rate for cardiovascular disorders (Prochaska 2012, 22 studies; Ware 2013, 15 studies); the discrepancies were attributed by the Singh team to differences in interpretation of the outcomes and to modifications to the statistical computations. Mills 2013, a network meta-analysis of 63 RCTs of NRT, bupropion and varenicline, found no elevated risk of serious cardiovascular events associated with any of the treatments, although trials of NRT demonstrated an increased risk for less serious events. The RR for major adverse cardiovascular events (MACEs) in varenicline compared with placebo was 1.34 (95% credible interval 0.66 to 2.66; 18 trials).

Thomas 2015 is a systematic review and meta-analysis of 39 RCTs (10,761 participants), assessing the risk of neuropsychiatric adverse events among users of varenicline. The authors found no evidence of an increased risk of suicide or attempted suicide (Peto odds ratio (OR) 1.67, 95% CI 0.33 to 8.57), suicidal ideation (Peto OR 0.58, 95% CI 0.28 to 1.20), depression (Peto OR 0.96, 95% CI 0.75 to 1.22) or death (Peto OR 1.05, 95% CI 0.47 to 2.38) associated with varenicline. There was no evidence that the risk of depression and suicidal ideation differed by age, sex, ethnicity, smoking status, the presence or absence of psychiatric illness, or study sponsorship. This analysis included varenicline prescribed for any indication; our own analyses of depression (Analysis 10.5) and suicidal ideation (Analysis 10.6) use most of the same studies (including nine trials which did not contribute to our efficacy anal-

yses), but we have dropped six trials which did not target smoking cessation, and have included four studies not then available to the Thomas team (Carson 2014; Ebbert 2015; Hajek 2015; Nahvi 2014a).

Because they are relatively rare, the incidence of serious neuropsychiatric events associated with varenicline has tended to be examined through retrospective cohort studies and prescription event monitoring studies, rather than through randomised trials, and has been considered in the Discussion section above. Gibbons 2013 is a re-analysis of SAE neuropsychiatric data from 17 RCTs of varenicline, stratifying by the presence or absence of psychiatric disorders. The analysis found no excess of suicidal thoughts or behaviour in the varenicline group without psychiatric disorders (0.47 events per 1000, compared with 1.46 per 1000 in the placebo group), nor in the varenicline group with a history of psychiatric disorders (14.57 events per 1000, compared with 15.39 per 1000 in the placebo group). No suicides were reported in any of the groups. The same study also analysed a Department of Defence data set comparing events in a varenicline cohort (19,933 people) versus a cohort of NRT users (15,867 people) between August 2006 and August 2007 (i.e. before the FDA issued a black-box warning). Rates of neuropsychiatric events in this cohort were 2.28% for varenicline and 3.1% for nicotine patch.

AUTHORS' CONCLUSIONS

Implications for practice

- Varenicline at standard dosage (1.0 mg twice a day) increased the chances of successful long-term smoking cessation by more than two-fold compared with pharmacologically unassisted quit attempts.

- Varenicline at reduced dosage remained an effective aid to smoking cessation, delivering success rates similar to those achieved with nicotine replacement and bupropion, and appearing to reduce the impact of adverse events in the early weeks of treatment.

- More people quit successfully with varenicline than with bupropion.

- Eight trials of varenicline versus nicotine replacement therapy indicate a modest but unequivocal benefit for varenicline.

- Limited evidence suggests that varenicline may have a role to play in relapse prevention.

- The most commonly reported adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time.

- Users of varenicline may have an elevated risk of any serious adverse event, with rates about 25% higher than in those not using the drug.

- Evidence from randomised controlled studies does not confirm a causal link between varenicline and psychiatric adverse events in people without a history of psychiatric disorders.

- The evidence is less clearcut for the relationship between varenicline and neuropsychiatric events in people with past or current psychiatric disorders. The largest RCT suggests there may be up to a 4% increased risk of moderate-to-severe neuropsychiatric events in smokers with psychiatric disorders taking varenicline, compared with a 1.5% increased risk in smokers without these disorders. These estimates are also consistent with no increased risk in either cohort.

- The imminent publication of data from a large recent trial should provide more definitive data on how varenicline may impact on major cardiovascular events.

- Cytisine was shown to be effective and affordable, although absolute quit rates were modest.

- Dianicline was no more effective than placebo in helping smokers to quit. Development of the drug has been suspended by the manufacturers.

Implications for research

- Further varenicline trials may be useful in disorder-specific groups of patients, excluded from the earlier trials.

- Future trials should continue to investigate the long-term success of extended treatment compared with standard 12-week treatment.

- The incidence of serious adverse events should continue to be monitored through controlled trials, and described with greater precision than is currently reported.

- Further exploration of safety issues in people with past or current psychiatric disorders may still be warranted.

- Additional trials of cytisine are needed to explore variations in the drug regimen and in the level of behavioural support needed to boost quit rates.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[author-defined order]*

Scharfenberg 1971

Methods	Country: East Germany Aim: To test the efficacy of cytisine for smoking cessation Setting: smoking cessation clinic, Magdeburg, July-December 1967 Study Design: double-blind placebo-controlled randomised trial Analysis: Chi squared test (P < 0.1)
Participants	1214 smokers recruited from 1452 applicants through smoking clinics and via initial press releases. 88.2% M. 2.5% of participants smoked < 10 CPD, 42.4% 10 - 20 CPD, 48.9% 21 - 30 CPD, 5.2% > 30 CPD 40.4% had smoked > 20yrs. 40.6% had tried to quit at least once before. Randomised to cytisine (607) or placebo (607) Exclusion criteria not stated (214 volunteers excluded at initial screening)
Interventions	1. 20-day course of cytisine. 1.5 mg tabs: Days 1 - 3 6/day; days 4 - 12 5/day; days 13 - 16 4/day; days 17 - 20 3/day. 2. Placebo tablets, same regimen Behavioural support: None
Outcomes	Self-reported abstinence at 4 wks, 6m and 2 yrs ITT analysis. Attrition rate 34% by longest follow-up
Treatment type	Medication: CYTISINE [TABEX]
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not stated
Allocation concealment (selection bias)	Unclear risk	"a numbered pouch"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	not stated
Selective reporting (reporting bias)	Unclear risk	not stated

Vinnikov 2008

Methods	Country: Kyrgyzstan Setting: Mining company (Kumtor Operating Company) Aim: To test the efficacy and safety of cytisine for smoking cessation in a workplace setting Study Design: Double-blind placebo-controlled parallel-group RCT Analysis: Logistic regression used to assess influence of cytisine use, age, weight, CPD, smoking duration, previous quit attempts, FTND score and exhaled CO levels
Participants	197 adult smokers, aged 20+, smoking at least 15 CPD, no prior use of cytisine, and motivated to quit Randomised to cytisine (100) or placebo (97). 26 (15 cytisine, 11 placebo) who took no medication were excluded from trial report 97% men, mean age 39, mean CPD 22, mean FTND 5.3, 86% had tried to quit previously; mean previous quit attempts 3.3 Exclusion criteria: Standard pharmacotherapy trial criteria
Interventions	Tabex tablets (1.5 mg cytisine): 1. First 3 days: 6 tabs per day; reduce smoking by half 2. Days 4 - 12: 5 tabs per day; stop smoking completely 3. Days 13 - 16: 4 tabs per day 4. Days 17 - 20: 3 tabs per day 5. Days 21 - 22: 2 tabs per day 6. Days 23 - 25: 1 tab per day Placebo tablets, same regimen Treatment period was 25 days, with TQD Day 5. All participants received "behavior counselling" (no further detail)
Outcomes	Primary outcome: CO-validated CAR from Day 5 to wk 8 Secondary outcome: CO-validated CAR from Day 5 to wk 26 Validation was by expired CO $\leq$ 8ppm Other outcomes: Change in health-related QoL measures, changes in body weight, adverse events, SAEs Attrition to 8 wks was 6 in cytisine group and 7 in placebo group; to 26 wks 10 in cytisine group and 16 in placebo group
Treatment type	Medication: CYTISINE [TABEX]
Notes	New for 2012 update Additional information supplied by the author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was done by independent statistician in an Excel programme and the randomization key was kept by an independent person"
Allocation concealment (selection bias)	Low risk	See above

Vinnikov 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Nor patients neither investigators did not know where Tabex and where placebo were"; "follow-up was blind"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26 participants who did not take a single treatment dose were excluded from denominators by authors (restored to our MAs)
Selective reporting (reporting bias)	Low risk	Expected and predicted outcomes reported

West 2011

Methods	Country: Poland Setting: Smoking cessation clinic in Warsaw Aim: To test the efficacy and safety of cytisine for smoking cessation with minimal counselling and support Dates conducted: December 2007 - September 2010 Study Design: Single-centre, double-blind placebo-controlled parallel-group RCT Analysis: Power calculation (80%, alpha = 0.05, to detect a between-group difference of 6 percentage points for primary outcome)
Participants	740 healthy adults, smoking 10+ CPD, motivated to quit. Randomised to cytisine (370) or placebo (370) 46.5% men, mean age 48, mean CPD 23, prior quit attempts 82%, mean FTND 6.2 Exclusions were current psychiatric disorder or any medical condition contraindicated on cytisine label
Interventions	Tabex tablets (1.5 mg cytisine): 1. First 3 days: 6 tabs per day 2. Days 4 - 12: 5 tabs per day 3. Days 13 - 16: 4 tabs per day 4. Days 17 - 20: 3 tabs per day 5. Days 21 - 22: 2 tabs per day 6. Days 23 - 25: 1 tab per day Placebo tablets, same regimen Treatment period was 25 days. Quitting advice, randomisation and drugs dispensed at baseline visit; phone calls at TQD + 1 wk later (+ optional clinic visit). Clinic visit 4 wks post-TQD, then phone calls at 6m and 12m, with visit to confirm abstinence if claimed. Behavioural support was minimal, to simulate likelihood of real-world conditions in countries where Tabex is available
Outcomes	Primary: CO-validated abstinence 12m after end of treatment. Abstinence defined as smoking < 5 cigs during preceding 6m, and none in week before visit Secondary outcomes: sustained CO-validated abstinence at 6m follow-up; 2-wk PPA at 4 wks; 7-day PPA at 12m Validation was expired CO < 10ppm Attrition: 79 (cytisine) and 89 (placebo) participants were lost to follow-up over 12m. Drug discontinuation or reduction rates similar in both groups: 6.2% for cytisine and

West 2011 (*Continued*)

	4.6% for placebo Other outcomes: Adverse events, SAEs
Treatment type	Medication: CYTISINE [TABEX]
Notes	New for 2012 update The trial was funded by the UK National Prevention Research Initiative, Cancer Research UK, and the National Institute for Health Research

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"performed by a statistician at Sopharma, who generated a list of study-group assignments for 740 participants with nQuery Advisor software. Assignments were made in variable block sizes of either 20 (10 cytisine, 10 placebo) or 10 (5 and 5)"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"Trial staff and participants were unaware of the group assignments and the randomization scheme"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and attrition fully reported
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes reported

Walker 2014

Methods	Country: New Zealand Setting: National Quitline Aim: "a non-inferiority trial to investigate whether cytisine was at least as effective as nicotine-replacement-therapy" Study Design: parallel-group non-inferiority RCT Dates conducted: March 2011 - February 2013 Analysis: Power calculation (90%, 1-tailed, alpha = 0.05) and assuming a 20% loss to follow-up, to detect a 5% difference in 1-month quit rates; cytisine 1-month quit rate was assumed to be 55%, with a non-inferiority margin of 5%
Participants	1310 daily smokers, callers to the NZ National Quitline, aged 18+, motivated to quit. Allocated to cytisine (655) or to open-label NRT (655). Mean age 38, 57% women, 33% NZ Maori, mean CPD 19, mean FTND 5.4

Interventions	All participants received standard Quitline support, i.e. average 3 x 10 - 15-minute calls over 8 wks 1. 25-day course of cytisine (Tabex) tablets, + NRT vouchers in case they needed them AFTER completing the cytisine course 2. Usual care, i.e. 8-week course of NRT (patch, gum or lozenge), tailored to dependence level, supplied by vouchers
Outcomes	Self-reported CAR (5 cigarettes or fewer) at 1m CAR and 7-day PPA (no smoking) at 1 wk, 1m, 2m and 6m. Adverse events Validation: None used
Treatment type	Medication: CYTISINE [TABEX] / NRT OPEN-LABEL
Notes	Funding by Health Research Council of New Zealand; cytisine supplied at no cost by Sopharma New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly allocated, by computer ... in a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	"Randomization was stratified with the use of minimization according to sex, ethnicity (Maori, Pacific Islander, or non-Maori and non-Pacific Islander), and cigarette dependence, which was determined by means of the Fagerström Test of Cigarette Dependence, in which smokers were assigned to one of two groups: those with scores of 5 or lower, indicating lower dependence, and those with scores greater than 5, indicating greater dependence"
Blinding (performance bias and detection bias) All outcomes	High risk	"Participants and researchers collecting outcome data were aware of treatment allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported. By 6m, 182 cytisine participants (28%) lost to follow-up, and 16 withdrawals; 173 NRT participants (26%) lost to follow-up, and 14 withdrawals. 19 cytisine users crossed over to NRT, and 1 NRT user crossed over to cytisine. ITT analyses conducted

Selective reporting (reporting bias)	Low risk	None noted
Other bias	Unclear risk	Cytisine was supplied free, while NRT users had to pay a nominal charge (NZD 3 for an 8-wk course of each NRT item); Duration of treatment differed (25 days vs 8 wks), but 1º outcome set to 1m to counteract this

Tonstad 2011

Methods	Countries: France, Spain, Belgium, Sweden, Denmark, Norway Setting: 22 research centres Aim: To test the efficacy and safety of dianicline for smoking cessation Dates conducted: June 2006 - June 2007 Study Design: Double-blind placebo-controlled parallel group RCT Study name: EURODIAN study Analysis: Power calculation (72% - 99%, alpha = 0.05, for an OR of 2 - 2.4, given a placebo quit rate of 7.5% - 15%); ITT denominators used
Participants	602 healthy adult volunteers, smoking 10+ CPD within previous 2m, aged 18+; allocated to dianicline (300), or placebo (302). 42% men, mean age 45, mean CPD 21, mean previous quit attempts 3.4, mean FTND score 5.75. Treatment groups were comparable at baseline Exclusion criteria: Standard pharmacotherapy trial criteria, plus any quit attempt in previous 3m, any use of bupropion, NRT, tobacco other than cigarettes 3+ times in previous 3m
Interventions	1. Dianicline 40 mg bid for 7 wks (not titrated). 2. Placebo inactive tablets, same regimen TQD was set for days 3 - 7 following baseline visit All participants received standardised brief counselling ($\leq$ 10 mins, based on *Smoke-Free and Living It*) at each visit Weekly visits throughout wks 1 - 7, then (for treatment completers) at wks 8, 10, 14, 18, 22 and 26 Smoking status and brief advice at each visit Participants completed smoking diaries
Outcomes	Primary outcome: CO-confirmed CAR for wks 4 - 7 Secondary outcomes: CO-confirmed CAR at 26 wks. PPA wks 4 - 7 Validation by expired CO < 10 ppm (all visits) and plasma cotinine $\leq 8\mu$g/L (wks 4 and 7) Other outcomes: adverse events, SAEs; craving and withdrawal symptoms Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) 25.2% dianicline and 23% placebo participants did not complete the study. AE-related dropouts were 4.3% dianicline and 7.6% placebo
Treatment type	Medication: DIANICLINE

Tonstad 2011 (*Continued*)

Notes	New for 2012 update The trial was funded by Sanofi-Aventis. "The sponsor did not play a role in writing of the manuscript"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"a predefined, central, and computer-generated randomization accessed through an Interactive Voice Response System assigned participants on a 1:1 ratio"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants and investigators were blinded to drug treatment assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts fully reported
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Anthenelli 2013

Methods	Country: USA (9 centres) and international (24 centres, across Bosnia & Herzogovina, Croatia, Germany, Hungary, Romania, Russian Federation, Spain) Setting: Academic clinical trial centres and smoking cessation clinics Aim: To assess the efficacy and safety of 12 weeks of varenicline treatment or placebo for smoking cessation, with 40 weeks of non-treatment follow-up, in adults with current or past depression (MDD) Study Design: Double-blind placebo-controlled RCT Dates conducted: March 2010 - June 2012 Analysis: Power calculation of 250 in each arm (80%, alpha = 0.05) to detect an OR of 2.35, assuming a placebo efficacy rate of 7%
Participants	525 adult smokers, aged 18 - 75, smoking at least 10 CPD, motivated to quit, diagnosed with unipolar MDD without psychotic features. 37% male, mean age 46, av CPD at baseline 22, mean FTND 5.9. Allocated to varenicline (256) or placebo (269) Exclusion criteria: Current or past diagnosis of dementia, schizophrenia, schizoaffective disorder, or other psychotic disorder, bipolar I disorder, bipolar II disorder. People with antisocial, schizotypal, or any other personality disorder severe enough to compromise their ability to comply with the study requirements Current use of either bupropion or nortryptiline

Interventions	1. Varenicline 1 mg x 2/day, titrated for first wk 2. Placebo inactive tablets, same regimen All participants received manual-guided SC support, telephone support and one-to-one 10-minute counselling by the same person where possible. Participants in both groups could reduce the dosage if they wished TQD was set for wk 1 visit Treatment period was 12 wks. Visits at screening, baseline, weekly for wks 1 - 12, and then at wks 13, 16, 24, 32, 40, 52 (or early termination); phone calls at wks 14, 20, 28, 36, 44 and 48. Weekly pill counts to assess adherence Safety data were reviewed regularly by an external independent data safety monitoring committee
Outcomes	Primary: CO-confirmed CAR for wks 9 - 12 Secondary: CO-confirmed CAR for wks 9 - 24, 9 - 52; 7-day PPA at wks 12, 24, 52; AEs and SAEs Verification: CO < 10 ppm
Treatment type	Medication: VARENICLINE
Notes	New for 2016 update Funding by Pfizer; Dept of VA merit review award; NIAAA grant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned to varenicline or placebo in a 1:1 ratio by using a computer generated, 4-block randomization scheme at each site."
Allocation concealment (selection bias)	Low risk	"Randomization was stratified by antidepressant medication use at baseline (any vs. none) and baseline Montgomery-Åsberg Depression Rating Scale (MADRS) score (11 vs. 11) (32). Investigators obtained participant identification numbers and randomized study drug assignments by using a Web-based or telephone call-in computerized drug management system."
Blinding (performance bias and detection bias) All outcomes	Low risk	"The study drug was supplied in blinded bottles by the sponsor to the study sites, where they were dispensed according to computerized instructions."
Incomplete outcome data (attrition bias) All outcomes	Low risk	68.4% of varenicline group completed study (lost 15.6% in treatment and 16% in

		follow-up); 66.6% of placebo group completed study (lost 21.9% in treatment and 11.5% in follow-up)
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Aubin 2008

Methods	Country: Belgium, France, Netherlands, UK, USA Setting: 24 research centres Aim: To compare the efficacy of varenicline with nicotine patch, both open-label Dates conducted: January 2005 - June 2006 Study design: Open-label randomised trial Analysis: Power calculation (90%, alpha = 0.05) based on expected OR of 1.75 at wk 12; logistic regression model including terms for treatment, centre and country
Participants	Healthy adults, recruited from smoking cessation clinics or by local advertising, aged 18 - 75, weight > 45.5 kg, BMI 15 - 38, smoking ≥ 15 CPD. Varenicline arm 378, NRT arm 379. Mean age 42.9, 49.2% men, 93% white. Mean CPD 22.7. Previous use of nicotine patch 47.4%, previous use of bupropion 20%. Mean FTND 5.5. Exclusion criteria: Standard pharmacotherapy trial criteria, + participants must not have been in a varenicline trial in previous year, or used NRT in previous 6m
Interventions	1. Varenicline 1mg x 2/day for 12 wks, titrated 1st wk 2. Nicotine patch (21 mg wks 2 - 6, 14 mg wks 7 - 9, 7 mg wks 10 - 11) No placebo control group All participants received *Clearing the Air* S-H booklet at baseline, and brief counselling (≤ 10 mins) at each clinic visit or by phone. TQD was at wk 1 visit. Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at wks 13, 16, 24, 32, 40, 48 and 52, plus brief phone calls at wks 14, 20, 28, 36 and 44
Outcomes	CO-confirmed CAR for last 4 wks treatment (varenicline wks 9 - 12, NRT wks 8 - 11) CO-confirmed CAR at wks 9 - 24 and 9 - 52 (varenicline) and 8 - 24 and 8 - 52 (NRT) 7-day PPA at EoT and at wks 24 and 52 Other outcomes: Weight change, withdrawal symptoms (using MNWS and mCEQ), adverse events Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 17.3% varenicline, 20.3% NRT. Losses to follow-up 17% in each group 65.7% of varenicline and 62.2% of NRT groups completed study
Treatment type	Medication: VARENICLINE / NRT OPEN-LABEL

Aubin 2008 (*Continued*)

Notes	The trial was funded by Pfizer Inc New for 2008 update Denominator used in trial report is all treated (V 376, Pl 370). We have used all randomised [378/379], which tips the RR into statistical significance Not included in main MA, as no placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a central computer-generated sequence"
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding (performance bias and detection bias) All outcomes	High risk	"Using an open-label design"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Missing CO data were assumed to be < 10 ppm provided other conditions were met", i.e. no NRT other than prescribed patches. Missing = negative assumption reduced successes by 1 in each group
Selective reporting (reporting bias)	Low risk	All predicted outcomes fully reported, + analysis by country and treatment centre
Other bias	Unclear risk	Different duration of regimens, but effect sizes similar in last 4 wks of each course

Baker 2016

Methods	Country: USA Setting: 2 University sites in Wisconsin (Madison, Milwaukee) Aim: To compare the efficacy of varenicline with nicotine patch, and with combination NRT (C-NRT) Dates conducted: May 2012 - November 2015 Study design: Open-label randomised trial (no placebo) Analysis: Logistic regression, comparing varenicline and C-NRT arms against nicotine patch (reference) arm. Power calculations based on detecting a 10% difference, with > 80% power; numbers required: patch 227, varenicline and C-NRT 387
Participants	Healthy adults, recruited from participants in the ongoing Wisconsin Smokers Health Study or by media and community outreach, aged 17+, smoking ≥ 5 CPD, motivated to quit. Varenicline arm 424, nicotine patch arm 241, combination NRT arm 421 Mean age 48.1, 47.9% men, 67% white. Mean CPD 17. Mean FTND 4.8

	Exclusion criteria: Standard pharmacotherapy trial criteria, CO < 4 ppm, no suicide attempts in previous 5 years, or current suicidal ideation,diagnosis or treatment of psychoses in previous 10 years
Interventions	1. Varenicline 1mg x 2/day for 12 wks, titrated 1st wk 2. Nicotine patch: 11+ CPD on 21 mg wks 1 - 8, 14 mg wks 9 - 10, 7 mg wks 11 - 12; 5 - 10 CPD on 14 mg wks 1 - 10, 7 mg wks 11 - 12 3. Nicotine patch as for (2), plus nicotine lozenge (2 mg or 4 mg), at least 5 times a day for 12 wks No placebo control group. All participants received counselling (20 mins at visits 1, 2 and 3, and 10 mins by phone and at visits 4, 5) at 1 week pre-TQD and at TQD, wks 1, 4, 12 post-TQD, plus phone call at wk 8 In follow-up phase, participants were contacted at wks 26 and 52 by phone
Outcomes	All comparisons were based on varenicline and C-NRT versus patch (reference arm), and on varenicline versus C-NRT CO-confirmed PPA at wk 26 CO-confirmed PA from day 7 post-TQD to day 181 CO-confirmed PPA at wks 4, 12, 52 Other outcomes: Adherence, withdrawals, adverse events Validation was by expired CO $\leq$ 9 ppm and $\leq$ 5 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Withdrawal rates were 8.3% varenicline, 6.2% nicotine patch, 3.1% C-NRT
Treatment type	Medication: VARENICLINE / NRT OPEN-LABEL
Notes	The trial was funded by grant 5R01HL109031 from National Heart, Lung, and Blood Institute, and by grant K05CA139871 from the National Cancer Insitute New for 2016 update Not included in the main MA, as no placebo group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-based randomisation"
Allocation concealment (selection bias)	High risk	"Treatment assignment was unblinded" [open-label]
Blinding (performance bias and detection bias) All outcomes	High risk	"Treatment assignment was unblinded" [open-label]. "The follow-up telephone assessments were intended to be blinded, but a database search by interviewers could have revealed treatment assignment"

Baker 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low rates of attrition, ITT analysis used
Selective reporting (reporting bias)	Low risk	All predicted outcomes reported, protocol available
Other bias	Low risk	None noted

Bolliger 2011

Methods	Countries: Brazil, Colombia, Costa Rica, Egypt, Jordan, Lebanon, Mexico, Saudi Arabia, South Africa, United Arab Emirates, Venezuela Setting: 42 research centres (51.2% Latin America, 30.6% Africa, 18.2% Middle East) Aim: To test the efficacy and tolerability of varenicline in regions not previously exposed to smoking cessation RCTs of varenicline Dates conducted: April 2008 - August 2009 Study Design: Double-blind placebo-controlled RCT Analysis: Power calculation (90%, alpha = 0.05); ITT denominators and logistic regression analysis (step-down procedure)
Participants	593 adults, recruited from smoking cessation clinics, aged 18 - 75, weight > 45.5 kg, BMI 15 - 38, smoking ≥ 10 CPD, motivated to quit. Randomised to varenicline 394 (390 got medication), or placebo 199 (198 got medication). Mean age 43.5, 63.6% men, mean CPD 23.8, mean FTND 6.0. 55% had no prior quit attempt Exclusion criteria: Standard pharmacotherapy trial criteria, + participants must not have used NRT, bupropion, clonidine or nortriptyline in previous 6m
Interventions	1. Varenicline 1mg x 2/day, titrated during wk 1 2. Placebo inactive tablets, same regimen Treatment period was 12 wks. All participants received *You can quit smoking* self-help booklet (available in English, Spanish, Portugese and Arabic) at baseline, and brief counselling (≤ 10 mins) at each clinic or telephone contact. TQD set for wk 1. Clinic visits at wks 2, 3, 4, 6, 8, 10 and 12 throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at wks 13, 16, 20 and 24, plus brief phone calls at wks 14, 18 and 22
Outcomes	Primary outcome: CO-validated CAR at 9 -12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks; 7-day PPA at wks 12 and 24 Other outcomes: Adverse events, clinically significant changes in vital signs, SAEs. Abstinence was assessed using the Nicotine-Use Inventory (NUI); validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis). [4 (V) 1 (P) who did not receive allocated intervention reincluded in denominators in this analysis.] Attrition in treatment phase was 11.2% (V) and 20.6% (P); in follow-up phase 2.5% (V) and 0.5% (P)
Treatment type	Medication: VARENICLINE

Bolliger 2011 (*Continued*)

Notes	New for 2012 update The study was funded and managed by Pfizer Inc	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Using a block randomization within each site, eligible participants were randomly assigned in a 2:1 ratio to receive varenicline or placebo"
Allocation concealment (selection bias)	Low risk	"a web-based or telephone call-in drug management system directed by the sponsor"
Blinding (performance bias and detection bias) All outcomes	Low risk	"All of the study personnel and participants were blinded to treatment assignment until the end of the nontreatment follow-up phase"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and attrition fully reported
Selective reporting (reporting bias)	Low risk	All predicted and expected outcomes reported

Carson 2014

Methods	Country: Australia Setting: Respiratory, cardiology, neurology, vascular and general medicine wards of 3 Adelaide (South Australia) hospitals Aim: To evaluate efficacy and safety of varenicline + quitline counselling vs quitline counselling alone in people admitted with smoking-related acute illnesses Study Design: Phase II/III open-label single-blind RCT Dates conducted: August 2008 - December 2011 Power calculation: 196 participants per arm, based on a 15% difference (45% vs 30%) at 52 wks, giving 80% power, 0.05 2-sided significance Study name: Smoking Termination Opportunity for inPatients (STOP)
Participants	392 adult smokers, aged 18 - 75, smoking 10 CPD+, willing to quit, admitted with acute smoking-related illnesses; randomised to varenicline + counselling (196) or counselling alone (196) Mean age 53, 32% women, 96% white, mean CPD 25, mean FTND 5.6, mean baseline LoS 6.5 days Exclusion criteria: Standard pharmacotherapy criteria, acute or pre-existing psychiatric illness, history of psychosis or suicidal ideation, use of varenicline in past 12m

Carson 2014 (*Continued*)

Interventions	1. Varenicline 1.0 mg x 2/d for 12 wks, including wk 1 at titrated dose (described as standard MIMS dosing schedule), + counselling 2. Counselling only Both groups received Quit SA 5A behavioural counselling, i.e. maximum of 8 calls over 3m. Also booklet *Quit because you can,* + stickers and fridge magnets. Participants had to set a TQD within 1st 2 wks Contacts were attempted with all participants at days 3 and 5, wks 1, 2, 3, 4, 12 (EoT). Additional contacts at wks 26 and 52
Outcomes	Primary outcome: Self-reported CAR (< 5 cigs in total) (2 wks - 12m) Secondary outcomes: CAR at 4, 12 and 26 wks. 7-day PPA each week for 1st 4 wks; craving; prevalence of I/P smoking; Reduced hospital bed utilisation; Reduction in healthcare costs CO validation ≤ 10 ppm used only in "a random sub-set of subjects"
Treatment type	Medication: VARENICLINE
Notes	Partially funded by the Department of Respiratory Medicine, Queen Elizabeth Hospital, Adelaide, SA; information based on unpublished data supplied by authors, + published 2014 study report New for 2012 update (study ID was Smith 2012; changed for 2015 update)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A pre-defined, central, computer-generated randomization sequence was used to assign subjects in a 1:1 ratio to either 12 weeks of treatment with varenicline plus Quitline-counseling or 12 weeks of Quitline-counseling alone."
Allocation concealment (selection bias)	Low risk	"using opaque, sealed envelopes with consecutive numbers"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Open-label design. Attempt at single-blinding (statistical investigator). "Participants and investigators were not blinded to treatment assignment" "Randomization and allocation concealment were performed by respiratory staff independent of the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Missing data from questionnaire (e.g., a question missed when administering follow-up) were randomly imputed via a computer programme"

Carson 2014 (*Continued*)

		84% varenicline completed the study at 52 wks, vs 82% in the placebo group
Selective reporting (reporting bias)	Unclear risk	None noted
Other bias	Unclear risk	None noted

Chengappa 2014

Methods	Country: Pittsburgh, USA Setting: 2 outpatient clinics, Western Psychiatric Institute and Clinic; and Dubois Medical Regional Center, Pennsylvania Aim: To assess the efficacy and safety of varenicline to assist in smoking cessation among patients with bipolar disorder who were euthymic and motivated to quit smoking Study Design: Double-blind placebo-controlled RCT Dates conducted: February 2010 - March 2013 Analysis: Power calculation of 60 in each arm Randomised placebo-controlled quadruple-blind trial
Participants	60 outpatient smokers with DSMIV-diagnosed bipolar disorder, aged 18 - 65, stable state or on medication, willing to quit in the next 30 days, 10+ CPD; randomised to varenicline (31) or placebo (29) Mean age 46, 69% women, 66% white, mean CPD 18.1, mean FTND 6.2 Exclusions: Bupropion use (for SC); usual pharmacological criteria
Interventions	1. Varenicline 1 mg x 2/day, titrated for first wk 2. Placebo inactive tablets, same regimen All participants received 15-minute SC counselling at each visit. CO tested and pill counts at each visit. Participants in both groups could reduce the dosage if they wished. TQD was set for wk 2 onwards (i.e. full dosage reached) Treatment period was 12 wks. Weekly pill counts to assess adherence Safety data were reviewed blind monthly by an external independent data safety and monitoring board (DSMB)
Outcomes	Primary: 7-day PPA, CO-verified, at 12 wks Secondary outcomes: 7-day PPA at 24 wks; CA at 12, 24 wks Validation: CO < 10 ppm
Treatment type	Medication: VARENICLINE
Notes	New for 2016 update Funding from the National Insitute of Mental Health, and Pfizer

Risk of bias

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

Chengappa 2014 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method not stated, other than "stratified by gender"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"The treatment assignment was blinded to participating subjects, raters, investigators and statisticians"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	24 participants in each group completed treatment phase, and 24 (77%) and 20 (69%) completed full study in varenicline and placebo groups respectively Data were analysed using ITT with LOCF
Selective reporting (reporting bias)	Unclear risk	None noted
Other bias	Unclear risk	8 participants (4 in each arm) were on bupropion for depression; 3/15 varenicline quitters and 1/3 placebo quitters were on long-term bupropion

Cinciripini 2013

Methods	Country: Houston, TX, USA Setting: University of Texas MD Anderson Cancer Center Aim: To assess the relative efficacy of varenicline and bupropion SR plus intensive counselling on smoking cessation and emotional functioning Study Design: Double-blind placebo-controlled RCT Dates conducted: August 2006 - October 2007 Analysis: "our sample size provided adequate power for assessing our primary outcome of prolonged abstinence at EOT (ie, ß= 0.99 for differences relative to placebo for varenicline and ß = 0.84 for differences relative to placebo for bupropion SR) but modest power for detecting drug group differences (ß = 0.74)."
Participants	294 volunteer smokers, aged 18 - 65, 5+ CPD, fluent in English, no uncontrolled chronic illness, baseline CO > 6 ppm. Mean age 44, 39% women, 66% white, mean CPD 20, mean FTND 4.5, mean baseline CO 24.5 ppm. Allocated to varenicline (86), bupropion (102) or placebo (106) Exclusions: Usual pharma exclusions, current or history of psychotic disorder, moderate or high risk of suicidality, contra-indications to varenicline or bupropion
Interventions	1. Varenicline: 12-week course (1 mg x 2/day) + non-active bupropion course (placebo) 2. Bupropion: 12-week course (150 mg x 2/day) + non-active varenicline course (placebo) 3. Placebo: 12-week course (placebo pill x 2/day) Blinded study physician could adjust dosages to reduce side effects if required throughout study All participants got intensive counselling, i.e. 6 x in-person 30-minute individual coun-

	selling sessions and 4 x 15-minute phone calls during treatment phase, based on MI techniques. During follow-up, each participant got a 15-minute in-person visit at 3m and 6m, and a 15-minute phone call at 4m
Outcomes	Primary: PA at EoT Secondary: PA at 3m post-quit, 6m post-quit; CA at 3m post-quit, 6m post-quit; 7-day PPA at EoT, 3m post-quit, 6m post-quit Validation: CO < 10 ppm. Self-reported abstainers were asked to send a salivary cotinine sample (< 15 ng/mL) by post
Treatment type	Medication: VARENICLINE and BUPROPION
Notes	New for 2016 update Funding: NIDA grant DA017073, NCI grant P50CA70907; varenicline supplied by Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Adaptive randomization (minimization) was used to stratify the groups for sex, race/ethnicity, history of depression, and baseline smoking rate."
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Study physician was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to treatment and follow-up reported, and key variables with significant differences (FTND, years of education) identified between those who stayed in and those who left. ITT analysis conducted. By 6m, 21/86 for varenicline (24.4%), 29/102 for bupropion (28.4%) and 30/106 for placebo (28.3%) had been lost to follow-up
Selective reporting (reporting bias)	Unclear risk	None noted
Other bias	Unclear risk	Study began as nortriptyline vs bupropion; 3 months later, 19 people had been recruited to bupropion and 18 to placebo; nortriptyline was replaced as the target treatment by varenicline. The nortriptyline phase group (cohort 1) had 19 days of med-

		ication and 3 counselling sessions before TQD, whereas varenicline phase group (cohort 2) had 12 days of medication and 2 counselling sessions before TQD. No differences were found between the 2 cohorts, nor between overall findings and cohort 2 findings. Authors therefore combined both groups into a single study cohort for analysis

De Dios 2012

Methods	Country: Rhode Island and Massachussetts, USA Setting: Butler Hospital, RI Aim: To assess the relative efficacy of varenicline and NRT on smoking cessation in Latino light smokers (< 10 CPD) Study Design: Feasibility double-blind placebo-controlled 3-arm RCT Dates conducted: April 2010 - July 2010 Analysis: No power calculation, as this was a pilot study with small sample size
Participants	32 Latino volunteer light smokers (≤ 10 CPD), aged 18+, willing to set a quit date. Mean age 42, 53.1% women, mean CPD 7.6, mean FTND 2.9. Allocated to varenicline (10), NRT (11), placebo (11) Exclusions: Usual pharmacological conditions, on NRT or smokeless tobacco, history of suicide attempts, chronic or acute psychiatric disorder, employed as a pilot, driver or heavy machinery operator
Interventions	1. Varenicline 12-wk treatment course, titrated 1st wk 2. NRT 24-hour patch: 12 wks: 4 wks @ 14 mg, 8 wks @ 7 mg 3. Varenicline-placebo, i.e. identical tablet, same regimen All participants received a 30-minute face-to-face "culturally informed" smoking cessation behavioural intervention, + a non-tailored self-help brochure, all available in both English and Spanish. All participants were compensated for attendance, and could receive travel vouchers if necessary
Outcomes	Primary: 7-day PPA at 6m Secondary: 7-day PPA at wks 1, 2, 1m, 2m, 3m, 4m; adherence Validation: CO < 5 ppm; salivary cotinine (not for the NRT group) > 10 mg/nL Adverse events not reported in detail, although study reports that "There was no pattern that suggested a higher side-effect profile for those in the varenicline group"
Treatment type	Medication: VARENICLINE / NRT
Notes	New for 2016 update Funding: NCI grant R01CA0129226-S1 (De Dios); NIDA grant K24-DA000512 (Stein); NIDA grant R01-DA1234, NCI grant K07-CA95623 (Stanton)

Risk of bias

De Dios 2012 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Study personnel and participants in the two-pill groups (varenicline and varenicline-placebo) were blinded to treatment condition. The research pharmacy maintained the study blind." NRT group could not be blinded to treatment; outcome assessment blinding not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up were fully reported; per protocol and ITT analyses conducted
Selective reporting (reporting bias)	Unclear risk	None noted
Other bias	Unclear risk	None noted

EAGLES 2016

Methods	Countries: Argentina, Australia, Brazil, Bulgaria, Canada, Chile, Denmark, Finland, Germany, Mexico, New Zealand, Russian Federation, Slovakiam South Africa, Spain, USA Setting: multiple research centres Aim: To evaluate the efficacy of varenicline, bupropion SR, nicotine patch and placebo for smoking cessation, and to assess how far this is moderated by the presence of psychiatric disorders Dates conducted: November 2011 - January 2015 Study Design: Phase 4 triple-dummy, double-blind placebo-controlled parallel-group RCT Study name: EAGLES (Evaluating Global Events in a Global Smoking Cessation Study)
Participants	Treatment-seeking adult smokers, aged 18 - 75, smoking at least 10 CPD, with exhaled CO > 10 ppm at screening. Participants in the psychiatric disorder cohort had to have a current or lifetime stable psychiatric diagnosis, confirmed by Structured Clinical Interview for DSM IV disorders (SCID), i.e. no acute exacerbation in the previous 6 months, no changes to treatment for 3 months, not imminently likely to change treatment, and not at risk of self harm. Allocation for the pyshiatric cohort was balanced across four diagnostic group disorders, i.e. mood, anxiety, psychotic, personality 44% men, mean age 46, mean CPD 20.7, mean FTND 5.8 Exclusions: Past or current diagnosis of schizophreniform or delusional disorders, all delirium, dementia, and other cognitive disorders, and all substance-induced disorders (other than nicotine)

	In the psychiatric disorders group, 70% had primary affective disorders, 19% anxiety disorders, 9.5% psychotic disorders, 0.6% personality disorders, and at least ⅓ were taking psychotropic medications Participants were grouped by the presence (4116) or absence (4028) of a history of psychiatric disorders Psychiatric disorders: varenicline 1032; bupropion 1033, NRT patch 1025, placebo 1026 No psychiatric disorders: varenicline 1005; bupropion 1001, NRT patch 1013, placebo 1009 Safety analyses were conducted in cohorts of 4074 (psychiatric) and 3984 (non-psychiatric)
Interventions	1. Varenicline, 1 mg x 2/day (1 wk titrated, then 11 weeks full dose) 2. Bupropion SR, 150 mg x 2/day (titrated for 3 days, then full dose for 11 weeks) 3. Nicotine patch, 21 mg x 7 weeks, 14 mg x 2 wks, 7 mg x 2 weeks (11 weeks) 4. Triple-dummy placebo for each arm of the trial (12 weeks) All participants received counselling (up to 10 mins) at all contacts, and were encouraged to complete all visits even if treatment was discontinued Participants were monitored at weeks 1 - 6, 8, 12, 13, 16, 20, 24; contacts were up to 15 face-to-face visits and 11 telephone visits
Outcomes	At least 1 SAE of anxiety depression, feeling abnormal, or hostility, and/or moderate or severe AE of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic paranoia, psychosis, suicidal ideation/behaviour/completed 4-week abstinence confirmed by CO < 10 ppm at wks 9 - 12, and 15-wk abstinence at weeks 9 - 24 In the non-psychiatric cohort, 78.9% completed treatment, and 78.4% completed the study In the psychiatric cohort, 74.2% completed treatment, and 77.8% completed the study
Treatment type	VARENICLINE / BUPROPION / NRT
Notes	Trial was funded by Pfizer and GlaxoSmithKline

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer- generated randomisation schedule ... 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	"Investigators obtained participant identification numbers via a web-based or telephone call-in drug management system"

EAGLES 2016 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"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 assignment" "The triple dummy design feature required participants to take study medication as masked tablets dispensed in separate varenicline and bupropion pill bottles each with matching placebo along with with either applying active or placebo patches on a daily basis"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses fully accounted for; ITT analysis conducted throughout
Selective reporting (reporting bias)	Low risk	All protocol-reported outcomes were addressed
Other bias	Low risk	None noted

Ebbert 2015

Methods	Country: 65 centres in 10 countries: USA (14), Australia (4), Canada (6), Czech Republic (7), Egypt (3), Germany (7), Japan (6), Mexico (4), Taiwan (7), UK (7) Setting: Clinics, hospitals, academic research centres Aim: To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction Study Design: Double-blind placebo-controlled multinational RCT Study name: Reduce to Quit Dates conducted: July 2011 - July 2013 Analysis: "A sample size of 1404 randomized participants in a 1:1 ratio (702 in each group) was estimated to provide 90% or more power to detect a difference between varenicline and placebo of 10.3% in the primary end point of CAR during weeks 15 through 24, assuming a CAR of 17.2% for varenicline and 6.9% for placebo using a 2-group, continuity-corrected, 2-sided χ^2 test. A P value of .05 or less was considered significant"
Participants	1510 adult smokers, unwilling to quit abruptly (within the next month), aged 18+, smoking mean 10+ CPD, interested in trying to quit within 3 months. Mean age 44. 5, 43.7% women, mean CPD 20.7, mean FTND 5.5. Allocated to varenicline (760) or placebo (750) Exclusions: suicidal behaviour in previous 2 years or history of suicide attempts; major depression, anxiety; diagnosis of psychosis, panic disorder, PTSD, schizophrenia
Interventions	1. Varenicline 24 wks, titrated 1st wk (12 wks to quit + 12 wks post-quit) 2. Placebo 24 wks, titrated 1st wk (12 wks to quit + 12 wks post-quit) All participants asked to reduce their smoking rate by 50% by wk 4, by 75%+ by wk 8,

	and 100% by wk 12. Individual 10-minute counselling at each visit (18 face-to-face and 10 phone calls), + a copy of *Clearing the air: quit smoking today.*
Outcomes	Primary: CAR at wks 15 - 24 Secondary: CAR at wks 21 - 24, 15 - 52, 21 - 52; 7-day PPA at wks 24, 52 Validation: CO < 10 ppm
Treatment type	Medication: VARENICLINE
Notes	New for 2016 update Funding: Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were randomized to receive varenicline or placebo for 24 weeks of treatment in a 1:1 ratio using a computer generated block randomization schedule within site"
Allocation concealment (selection bias)	Low risk	"Investigators obtained participant identification numbers and treatment group assignments through a web-based or telephone call-in drug management system"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Participants, investigators, and research personnel were blinded to randomization until after the database was locked"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported. ITT analyses conducted for efficacy (760 varenicline, 750 placebo), and treated denominators for safety outcomes (751 varenicline, 742 placebo)
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Eisenberg 2016

Methods	Country: 40 centres in USA and Canada Setting: Hospitals Aim: To determine the efficacy and safety of varenicline for increasing smoking abstinence rates through smoking reduction Study Design: Double-blind placebo-controlled multicentre RCT Study name: Evaluation of varenicline in smoking cessation for patients post-acute coronary syndrome (EVITA) Dates conducted: not stated Analysis: "The sample size was estimated assuming a 7 day point prevalence abstinence rate of 24% at 24 weeks in patients receiving placebo.With this assumption, 150 patients per study arm would achieve a >80% power to identify a >15% absolute increase in abstinence rates (24% to 39%) using a two-tailed α of 0.05"
Participants	302 adult smokers, aged 18+, smoking 10+ CPD, interested in trying to quit, hospitalised in USA or Canada for acute coronary syndrome (MI or unstable angina). Mean age 55, 25% women, mean CPD 21.5 Allocated to varenicline (151) or placebo (151) Exclusions: Excessive alcohol, history of panic disorder, psychosis, bipolar disease, dementia, renal or hepatic impairment, current or recent drug use, history of suicidal ideation/attempt or family history of suicide
Interventions	1. Varenicline 12 wks, titrated 1st wk 2. Placebo 12 wks, titrated 1st wk Medication was begun in hospital. All participants received low-intensity counselling Follow-up at wks 1, 2 and 8 by phone, and clinic visits at wks 4, 12 and 24
Outcomes	Primary: 7-day PPA at wk 24 Secondary: CAR at all follow-up visits, 7-day PPA at other follow-up visits, $\geq$ 50% reduction in CPD Measures of side effects and SAEs Validation: CO $\leq$ 10 ppm
Treatment type	Medication: VARENICLINE
Notes	New for 2016 update Funded by Pfizer

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomized to either varenicline or matching placebo... Randomization was performed by enrolling center personnel and stratified by center using a computer-generated list of permuted blocks of 2 and 4"
Allocation concealment (selection bias)	Unclear risk	Not stated

Eisenberg 2016 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind", but no further detail
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Evins 2014

Methods	Country: USA Setting: Massachussetts General Hospital and 9 other community mental health centres in Massachussetts, Michigan, New Hampshire, Indiana, Alabama, Minnesota Aim: To determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment Study Design: Double-blind placebo-controlled RCT Dates conducted: March 2008 - April 2012 Analysis: "The study was powered to show differences between varenicline and placebo for point-prevalence abstinence at week 52. Assuming a 35% to 40% relapse in the varenicline group and a 75% to 80% relapse in the placebo group, estimates based on trials of bupropion involving smokers with schizophrenia, we estimated that 48 participants per study group would provide 91% to 99% power and 40 patients per study group would provide 85% to 98% power to detect a treatment effect using a 2-group Fisher exact test with a .05, 2-sided significance level"
Participants	247 outpatient smokers with schizophrenia, schizoaffective or bipolar disorder, aged 18 - 70, CPD 10+, 87 of whom met the abstinence criteria after 12 wks of open-label varenicline to enter this relapse prevention trial. Randomised to varenicline (40) or control (47). Mean age 48, 37% women, 74% white, mean FTND 5.9, mean CPD 23.2
Interventions	All participants had received 12 wks open-label varenicline, and were confirmed abstinent at wks 11 and 12 1. Varenicline 1 mg x 2/day for a further 40 wks, + tapered CBT relapse prevention counselling 2. Placebo, same regimen, i.e. CBT alone
Outcomes	Primary: 7-day PPA at wk 52 (12 wks cessation treatment + 40 weeks relapse prevention treatment); Secondary: PPA and CAR at wk 64 (52 wks after achieving abstinence); effect of varenicline on psychiatric symptoms (Calgary Depression Scale for Schizophrenia, Brief Psychiatric Rating Scale, Schedule for Assessment of Negative Symptoms), nicotine withdrawal symptoms (Wisconsin SmokingWithdrawal Scale), health-related quality of life (SF-12), body mass index, and adverse events

Evins 2014 (*Continued*)

	Validation: CO < 9 ppm	
Treatment type	Medication: VARENICLINE	
Notes	New for 2016 update Funding: NIDA grant R01 DA021245, DHHS grant 05B1MACMHS, Pfizer	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was conducted via centralized computer-generated random sequence performed by Massachusetts General Hospital research pharmacy staff members, who were not otherwise involved in the trial, in double-blind fashion, in blocks of 4, stratified by study site and by a single categorical predictor that was a combination of psychiatric disorder and type of antipsychotic medication (eMethods 1 in the Supplement), using a permuted block design with 1:1 ratio"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	See above. "participants were followed up for biochemically verified abstinence and safety outcomes under double-blind conditions through week 64"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported; by wk 52, 33/40 varenicline participants completed study, and 28/42 placebo participants. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	"Telephone follow-up at week 76 for self report of smoking behavior from those who had achieved continuous abstinence from weeks 12 through 64 was added to the protocol after trial commencement to better evaluate the duration of continuous abstinence after discontinuation of maintenance treatment."

Gonzales 2006

Methods	Country: USA Setting: 19 research centres Aim: To test the efficacy and safety of varenicline for smoking cessation Dates conducted: June 2003 - April 2005 Study Design: Double-blind placebo-controlled parallel-group RCT Analysis: Power calculation (90%, alpha = 0.05); ITT denominators and logistic regression analysis (step-down procedure)
Participants	1025 healthy adult volunteers, recruited through media advertising. Allocated to varenicline (352), bupropion (329) or placebo (344). 54% men, 79% white, mean age 42.4, mean CPD 21, mean FTND score 5.3. No significant differences between groups at baseline Exclusion criteria: Standard pharmacotherapy trial criteria, + use of tobacco products other than cigarettes; use of NRT, clonidine, nortriptyline within last month; BMI < 15 or > 38 or weight < 45.5 kg; any prior use of bupropion or varenicline
Interventions	1. Varenicline 1 mg x 2/day 2. Bupropion 150 mg x 2/day 3. Placebo inactive tablets, same regimen Treatment period was 12 wks. All participants received *Clearing the Air* self-help booklet at baseline, and brief counselling (≤ 10 mins) at each clinic visit. Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at wks 13, 24, 36, 44 and 52, plus brief phone calls at wks 16, 20, 28, 32, 40 and 48
Outcomes	Primary outcome: CO-validated CAR at 9 - 12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks and 9 - 52 weeks; 7-day PPA at wks 12, 24 and 52 Other outcomes: Weight change, withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 31.5%, losses to follow-up 16% of treatment completers
Treatment type	Medication: VARENICLINE / BUPROPION
Notes	This trial had the same aims and study design as Jorenby 2006 The trial was funded by Pfizer Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"predefined ... computer-generated randomization sequence", 1:1:1, using block size of 6, stratified by centre
Allocation concealment (selection bias)	Low risk	Central allocation

Gonzales 2006 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"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	Considered abstinent if, at next non-missed visit, they reported no smoking... Missing CO but otherwise OK considered abstinent, except at end of study, where all criteria had to be present
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Gonzales 2014

Methods	Country: 37 centres in 8 countries: USA (8), Australia (4), Belgium (4), Canada (4), Czech Republic (4), France (3), Germany (5), UK (5) Setting: Clinics, hospitals, academic research centres Aim: To evaluate the efficacy and safety of retreatment with varenicline in smokers who had taken varenicline for $\geq$ 2 weeks in a previous smoking cessation attempt Study Design: Double-blind placebo-controlled multinational RCT Dates conducted: December 2010 - November 2012 Analysis: "A sample size of 490 participants randomized to varenicline or placebo in a 1:1 ratio was estimated to provide $\geq$90% power for a comparison of varenicline vs. placebo using a two-group continuity corrected two-sided χ^2 test at the 0.05 significance level for the primary end point (CAR for weeks 9-12), assuming an OR of 3.36 with a placebo CAR of 12% and a varenicline CAR of 31%. It was also estimated to provide 80% power for the treatment comparison in the key secondary end point (CAR for weeks 9-52) for an OR of at least 2.55 with a 6% CAR in the placebo group and 14% in the varenicline group."
Participants	498 adult smokers (varenicline 251, placebo 247) with previous use of 2+ wks of varenicline at least 3m prior to screening, aged 18+, CPD 10+, motivated to quit. Mean age 47.5, 50.4% women, 93% white, mean CPD 20.5, mean FTND 5.5
Interventions	1. Varenicline 12 wks, titrated in 1st wk, 1 mg x 2/day 2. Placebo, identical regimen Brief (< 10 mins) counselling at each contact. TQD set for wk 1 visit. Clinic visits at wks 1, 2, 3, 4, 6, 8, 9, 10, 11, 12; 13, 16, 24, 32, 40, 48, 52. Brief phone calls at wks 5, 7, 14, 20, 36, 44. Dosage could be halved if intolerable
Outcomes	Primary: CAR at wks 9 - 12, 9 - 52 Secondary: CAR at wks 9 - 24; 7-day PPA at wks 12, 24, 52 Validation: CO < 10 ppm

Gonzales 2014 (*Continued*)

Treatment type	Medication: VARENICLINE
Notes	New for 2016 update Funding: Pfizer

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible participants were randomly assigned to receive either varenicline or placebo at a 1:1 ratio for 12 weeks of drug treatment using computer-generated block randomization within each site"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up fully reported. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Hajek 2015

Methods	Country: UK Setting: Specialist stop-smoking clinic in London Aim: To determine whether increasing varenicline dose in people who show no response to the drug improves treatment efficacy in terms of tobacco withdrawal relief and abstinence rates Study Design: Double-blind placebo-controlled RCT Dates conducted: July 2011 - February 2013 Analysis: ANOVA for continuous end points and X^2 for categorical end points. Sample size of 200 for 80% power to detect a difference in 4-wk abstinence between 60% placebo and 80% varenicline. 2-tailed $P < 0.05$
Participants	200 non-responders to varenicline at day 12, from an initial cohort of 503 given varenicline while still smoking, randomised to varenicline (100) or placebo (100) add-on treatment. Treatment-seeking smokers, aged 18+; 28% women, 65% white, mean age 45.8 yrs, 20.5 cigs in previous wk, mean FTND 5.5

Hajek 2015 (*Continued*)

Interventions	503 eligible consented volunteers began taking varenicline at standard dosage; at day 12, 204 were rated as non-responders (no strong nausea, no reduction in smoking enjoyment, < 50% reduction in baseline smoking), and 200 were then randomised to additional varenicline or placebo. All participants received phone calls on days 15 and 18, with TQD at day 21 + phone call 24 hours later, and 4 x weekly supportive visits (as per standard NHS stop-smoking treatment protocol). participants were invited to a 12-week final visit for assessment 1. Varenicline: standard dose + initial increase of 0.5 mg x 2/day which could be increased by 0.5 twice daily up to a total of 5 mg/day. Dosage used at TQD was maintained for 3 wks, with an option to reduce it if necessary. From 4 wks, only standard dose was used 2. Placebo: same regimen, but with identical placebo pills
Outcomes	Smoking enjoyment and withdrawal symptoms weekly for 1st 4 wks; CAR at wks 1, 4, 12 after TQD Validation: CO < 9 ppm
Treatment type	Medication: VARENICLINE
Notes	Funding: Pfizer Although this study did not assess abstinence beyond 3m, we have included it for assessment of variation in dosing, and for safety data. We have not pooled the efficacy findings with the other included studies, apart from sensitivity analysis 13.2 (CAR at 9 - 12 wks) New for 2016 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participants were randomized to treatment arms using sequentially numbered prepackaged medication containers boxed according to a computer-generated randomization list prepared by an independent statistician"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	"The authors were unblinded only after the data analysis was completed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All losses during treatment and follow-up reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Heydari 2012

Methods	Country: Tehran, Iran Setting: Smoking cessation clinics in the Tobacco Prevention and Control Research Centre, Shahid Beheshti University of Medical Sciences Aim: To evaluate the effectiveness of varenicline in the Iranian community of tobacco quitters and compare it with other treatment methods Study Design: 3-arm randomised parallel clinical study Dates conducted: 2009 - 2010 Analysis: 91 participants per group were required
Participants	272 treatment-seeking participants: Brief advice (91), NRT (92), varenicline (89). 41. 2% women, mean age 42.5 yrs, mean FTND 5.5
Interventions	All participants were managed by the same physician. All received brief (5 mins) education and counselling at 4 x weekly sessions. TQD was day 14 1. Control group: no pharmacotherapy 2. NRT: 8 wks of 15 mg NRT patches 3. 8 wks of 1 mg x 2/day varenicline (titrated 1st wk)
Outcomes	Abstinence at 6m and 12m, in person or by phone, verified by expired CO (cut-off value not given)
Treatment type	Medication: VARENICLINE / NRT
Notes	Funding: Masih Daneshvari Hospital Research Institute, Tehran New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Smokers who attended the clinic for help in quitting were divided randomly"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label; blinding of outcome assessors not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition: "Participants entered the study of their own accord and none left the study"
Selective reporting (reporting bias)	High risk	No information on potential differences between phone- and in-person reporting of abstinence at 6m and 12m, nor of whether all such claims of abstinence were biochemically verified No information on SAEs, if any

Other bias	Unclear risk	Participants were all previous quit-attempters Varenicline was given for 8 wks, i.e. ⅔ of the normal regimen, presumably to align it with the NRT dosage pattern Abstinence-by-gender data (Table 2) appears to contain an error for women on NRT at 12m; we have ignored this finding in favour of the combined-genders data

Jorenby 2006

Methods	Country: USA Setting: 14 research centres Aim: To test the efficacy and safety of varenicline for smoking cessation Dates conducted: June 2003 - March 2005 Study Design: Double-blind placebo-controlled RCT. Analysis: Power calculation (90%, alpha = 0.05); ITT denominators and logistic regression analysis (step-down procedure)
Participants	1027 healthy adult volunteers. Allocated to varenicline (344), bupropion (342) or placebo (341). 58% men, 84% white, mean age 43.3, mean CPD 22, mean FTND score 5.3. No significant differences between groups at baseline Exclusion criteria: Standard pharmacotherapy trial criteria, + use of tobacco products other than cigarettes; use of NRT, clonidine, nortriptyline within last month; BMI < 15 or > 38 or weight < 45.5 kg; any prior use of bupropion or varenicline
Interventions	1. Varenicline 1 mg x2/day 2. Bupropion 150 mg x2/day 3. Placebo inactive tablets, same regimen Treatment period was 12 wks. All participants received brief counselling (≤ 10 mins) at each clinic visit Weekly visits throughout treatment phase, plus a phone call 3 days post-TQD In follow-up phase, clinic visits at wks 13, 24, 36, 44 and 52, plus brief phone calls at wks 16, 20, 28, 32, 40 and 48
Outcomes	Primary outcome: CO-validated CAR at 9 - 12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks and 9 - 52 wks; 7-day PPA at wks 12, 24 and 52 Other outcomes: Weight change, withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 29.3%, losses to follow-up 8% of treatment completers
Treatment type	Medication: VARENICLINE / BUPROPION

Jorenby 2006 (*Continued*)

Notes	This trial had the same aims and study design as Gonzales 2006. The trial was funded by Pfizer Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated list"
Allocation concealment (selection bias)	Low risk	"completed centrally ... and sites used an electronic system to assign participants to treatment"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"in a double-blind manner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	CA for missed visits: if self-reported abstinent at next visit, assumed abstinent, except at wk 52 visit when all criteria had to be met
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Nahvi 2014a

Methods	Country: USA Setting: 3 urban outpatient clinics for substance use disorder (SUD) in the Bronx, NY Aim: to test the efficacy and safety of varenicline for smoking cessation among opioid-dependent people on a maintenance regimen Study Design: Randomised quadruple-blind controlled trial Dates conducted: August 2009 - September 2011 Analysis: 50 participants in each arm would give 80% power to detect a 22% abstinence rate in the varenicline users (½ the expected rate in non-MM participants)
Participants	112 smokers in methadone treatment for substance abuse, aged 18+, CPD 5+, motivated to quit within next 6m. Allocated 57 varenicline, 55 placebo. 52% women, 54% Hispanic, mean CPD 15, mean FTND 4
Interventions	All participants set a TQD 1 wk after treatment began. All were offered structured, brief (≤ 10 mins) individual in-person counselling by a physician or tobacco specialist at baseline and at 2-, 4-, 8- and 12-wk visits. All participants were also offered free quitline support 1. Varenicline: 12-wk standard regimen, titrated for 1st wk

Nahvi 2014a (*Continued*)

	2. Control: Identical placebo tablets and regimen
Outcomes	7-day PPA at 12 and 24 wks Validation: Expired CO < 8 ppm
Treatment type	Medication: VARENICLINE
Notes	Funding: National Center for Research Resources grant UL1 RR025750 to SN, and the National Institute on Drug Abuse grants K23 DA025736 to SN and R25 DA023021 to SN and JHA New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Treatment group allocation was computer-generated, and stratified by the three clinic sites in blocks of six within each stratum"
Allocation concealment (selection bias)	Low risk	"a central data manager concealed the allocation sequence using a password-protected file, assigned subjects to treatment groups and faxed pre-printed medication orders to the study pharmacist. The pharmacist prepared the research medication by compounding varenicline tablets or placebo lactose powder to create identical-appearing capsules. The pharmacist marked medication bottles with subjects' study identification numbers, and delivered medications for individual study subjects to clinical sites, where they were distributed to each subject by the research assistant"
Blinding (performance bias and detection bias) All outcomes	Low risk	"The pharmacist prepared the research medication by compounding varenicline tablets or placebo lactose powder to create identical-appearing capsules. The pharmacist marked medication bottles with subjects' study identification numbers, and delivered medications for individual study subjects to clinical sites, where they were distributed to each subject by the research assistant" "All subjects, research assistants, counsellors and physicians were blinded to treat-

Nahvi 2014a (*Continued*)

		ment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses during treatment (varenicline 6, placebo 9) and during follow-up (varenicline 2, placebo 3) fully reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Nakamura 2007

Methods	Country: Japan Setting: 19 study sites Aim: To test efficacy, safety and tolerability of 3 doses of varenicline over 12 wks Dates conducted: not stated Study Design: Double-blind, placebo-controlled, parallel group RCT Analysis: Power calculation (90%, alpha = 0.05) for 0.5 or 1.0 mg vs placebo; ITT denominators; also logistic regression (step-down) with dose and study centre as categorical variables
Participants	619 healthy Japanese adult volunteers, aged 20 - 75, smoking ≥ 10 CPD. Allocated to varenicline 0.25 mg x 2/day (153), 0.5 mg x 2/day (156), 1.0 mg x 2/day (156) or placebo x 2/day (154). 1 participant withdrew before treatment, and is excluded from ITT denominator. 1 RTA death removed from varenicline group at 52 wks Participants stratified by level of nicotine dependence, measured by Tobacco Dependence Screener scale (≥ 5) and by FTND. 515 (83.3%) classified as nicotine dependent Demographic data only supplied for nicotine-dependent group (515/618): 75% men, mean age 39.8, mean CPD 24, mean FTND score 5.6 Exclusion criteria: Standard pharmacotherapy trial criteria, + use of NRT within last 30 days, use of pipe tobacco, snuff, chewing tobacco, cigars within last 30 days and throughout trial
Interventions	1. Varenicline 0.25 mg x 2/day 2. Varenicline 0.50 mg x 2/day 3. Varenicline 1.00 mg x 2/day 4. Placebo tablet x 2/day Treatment period 12 wks, 1st wk titrated dosage. All participants received a smoking cessation booklet *Clearing the Air* at baseline, + brief counselling (≤ 10 mins) at each clinic visit. Weekly visits throughout treatment phase, plus a 5-min phone call at TQD and +3 days post-TQD In follow-up phase, clinic visits at wks 13, 16, 24, 36, 44 and 52, plus brief phone calls at wks 20, 28, 32, 40 and 48
Outcomes	Primary outcome: CO-validated CAR at 9 - 12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks and 9 - 52 wks; 7-day PPA at wks 2, 12, 24 and 52 Validation was by expired CO ≤ 10 ppm

	Other outcomes: Withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 6.4%, losses to follow-up 11.4% of treatment completers (excluding 1 death)
Treatment type	Medication: VARENICLINE
Notes	Trial was funded by Pfizer Inc New for 2008 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated list of random numbers"
Allocation concealment (selection bias)	Low risk	"randomized to 1 of the 4 treatment groups in a 1:1:1:1 ratio using a central procedure"
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blinding of subjects and investigators was maintained throughout the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No comment on level or handling of missing data
Selective reporting (reporting bias)	High risk	CARs for all participants reported, but demographics, withdrawal and craving measures, and PPA for nicotine-dependent group only
Other bias	Unclear risk	None noted

NCT00828113

Methods	Randomised quadruple-blind placebo-controlled trial
Participants	101 adult smokers
Interventions	All get 13 weeks varenicline, then half continue and half switch to placebo, until week 52
Outcomes	Biochemically confirmed abstinence (at 52 weeks) CO-confirmed at $\leq$ 10 ppm

NCT00828113 (*Continued*)

Treatment type	VARENICLINE	
Notes	Study results posted on clinicaltrials.gov June 2012, updated October 2015	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Stated to be quadruple-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates: varenicline 30/50 (27 withdrawals, 3 lost), placebo 31/51 (26 withdrawals, 5 lost)
Selective reporting (reporting bias)	High risk	Results unpublished; available only on www.ClinicalTrials.gov

NCT01347112

Methods	Phase II/III randomised quadruple-blind placebo-controlled trial	
Participants	33 adult alcohol-dependent smokers	
Interventions	Varenicline 1 mg bid for 12 weeks vs placebo	
Outcomes	Prolonged abstinence at 12 weeks (end of treatment), and at 6m Abstinence self-reported, not biochemically confirmed	
Treatment type	VARENICLINE	
Notes	Study results posted on www.clinicaltrials.gov May 2014	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

NCT01347112 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition rates: 4/16 varenicline group (1 withdrawal, 3 lost), 12/17 placebo group (7 withdrawals, 5 lost)
Selective reporting (reporting bias)	High risk	Results unpublished; available only on www.ClinicalTrials.gov
Other bias	High risk	Trial planned to include 70 participants, but recruited only 33

Niaura 2008

Methods	Country: USA Setting: 5 research centres Aim: To test the efficacy and safety of varenicline in smokers allowed to modify their own dosage regimen Dates conducted: December 2001 - June 2003 Study Design: Double-blind placebo-controlled RCT Analysis: Power calculation (90%, alpha = 0.05); ITT denominators and logistic regression analysis (step-down procedure)
Participants	320 healthy adult volunteers, aged 18 - 65, smoking ≥ 10 CPD. Allocated to varenicline (160), or placebo (160) 52% men, 91% white, mean age 42, mean CPD 22, mean FTND score 5.4 Exclusion criteria: Standard pharmacotherapy trial criteria, + use of NRT within last 3m
Interventions	1. 0.5 mg varenicline ad lib, from 1 to 4 per day as wished 2. Placebo tablets ad lib, from 1 to 4 per day as wished Treatment period 12 wks, 1st wk titrated dosage up to 0.5 mg x 2/day. All participants received a smoking cessation booklet *Clearing the Air* at baseline, + brief counselling (≤ 10 mins) at each clinic visit. Weekly visits throughout treatment phase In follow-up phase, clinic visits at wks 13, 24, and 52 wks, plus monthly phone calls between visits
Outcomes	Primary outcome: CAR at 4 - 7, 9 - 12 and 9 - 52 wks Validation was by expired CO ≤ 10 ppm Secondary outcomes: CO-confirmed CAR at 9 - 24 wks; CO-confirmed 7-day PPA Other outcomes: Mean modal dosage; withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 22% in varenicline group and 29% in placebo group; losses to follow-up by wk 52 were 36% from varenicline group and 43% from placebo group

Niaura 2008 (*Continued*)

Treatment type	Medication: VARENICLINE	
Notes	The trial was funded by Pfizer Inc New for 2010 update.	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly permuted blocks and a pseudo-random number generator"
Allocation concealment (selection bias)	Low risk	"participants were assigned in a 1:1 ratio to varenicline treatment or placebo in the numerical order that they were accepted to the study"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind" but no further information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data imputed if prior and subsequent abstinence confirmed, otherwise assumed still smoking
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Nides 2006

Methods	Country: USA Setting: 7 research centres Aim: To test efficacy, tolerability and safety of 3 doses of varenicline over 6 wks Dates conducted: February 2000 - January 2003 Study Design: Phase 2 double-blind placebo-controlled RCT Analysis: Power calculation (80%, 2-tailed, alpha = 0.05); Dunnett adjustment for multiple comparisons used for primary endpoint (CQR within treatment phase). ORs and CIs least squares mean estimates. Not powered for varenicline/bupropion comparison
Participants	638 healthy volunteer smokers, aged 18 - 65, smoking at least 10 CPD on average. 48% men, 87% white, av age 42, av CPD 20, mean FTND 5.5. Allocated to varenicline group 1 (128), group 2 (128), group 3 (127), bupropion (128), placebo≤ (127) Exclusion criteria: Standard pharmacotherapy trial criteria, + use of bupropion within previous 12m, use of NRT within past 3m

Interventions	1. varenicline tartrate 0.3 mg x 1/day for 6wks, + 1 wk placebo 2. varenicline tartrate 1.0 mg x 1/day for 6 wks, + 1 wk placebo 3. varenicline tartrate 1.0 mg x 2/day for 6 wks, + 1 wk placebo 4. bupropion 150 mg x 2/day (titrated in wk 1) for 7 wks 5. placebo tablets x 2/day for 7 wks All groups received self-help booklet *Clearing the Air* at baseline, + brief (≤ 10 mins) counselling at weekly clinic visits throughout treatment phase. At each visit smoking status reported and verified; lab samples taken at screening, baseline and wks 1, 2, 4, 6 and 7 Follow-up phase (optional): Clinic visits at wks 12, 24, 52 for brief counselling, smoking status and vital signs. Phone calls every 4 wks from wk 16
Outcomes	Primary outcome: Continuous verified 4-wk abstinence for any part of treatment period Secondary outcomes: CQR wks 4 - 7; CQR from wk 4 to wks 12, 24, and 52 Other outcomes: Weight change; reduction of craving and withdrawal using MNWS, QSU-brief and mCEQ; adverse events Validation was by expired CO ≤ 10 ppm Trial report ITT analysis based on numbers treated (N = 626); for consistency our MA used numbers randomised (N = 638). Attrition was 30% during treatment period, 25% of follow-up consenters lost during follow-up phase
Treatment type	Medication: VARENICLINE / BUPROPION
Notes	Previous users of bupropion > 12m before were not excluded, unlike Gonzalez and Jorenby trials; prior use ranged from 13% to 20.6% across groups Denominator in trial report is all treated; we have used all randomised in our MA The trial was funded by Pfizer Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"computer-generated using a method of randomly permuted blocks and a pseudo-random number generator"
Allocation concealment (selection bias)	Low risk	"assigned ... medication to subjects in numerical order of acceptance into the study"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind", "to preserve treatment blinding"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered

Nides 2006 (*Continued*)

Other bias	Unclear risk	None noted

Oncken 2006

Methods	Country: USA Setting: 10 research centres Aim: To evaluate efficacy and safety of 4 varenicline dose regimens Dates conducted: Not stated Study Design: Phase 2 double-blind placebo-controlled RCT Analysis: Power calculation (90%, 2-tailed, alpha = 0.05); Logistic regression with treatment and centre as independent variables. Likelihood ratio Chi^2 statistic
Participants	647 healthy volunteer smokers, aged 18 - 65, smoking at least 10 CPD. 49.5% men, 80% white, av CPD 21, mean FTND 5.5. Allocated to group 1 (129), group 2 (130), group 3 (129), group 4 (130) or placebo (129) Exclusion criteria: Standard pharmacotherapy trial criteria, + use of NRT or bupropion within last 3m; use of marijuana or tobacco other than cigarettes with last month
Interventions	1. 0.5 mg nontitrated (2/day for 12 wks) 2. 0.5 mg titrated (wk1 1/day, wks 2 - 12 2/day) 3. 1.0 mg nontitrated (2/day for 12 wks) 4. 1.0 mg titrated (0.5 mg 1/day for 3 days, 0.5 mg 2/day for 4 days, 1.0 mg 2/day wks 2 - 12) 5. placebo tablets 2/d 12 wks All groups received self-help booklet at baseline, + brief (≤ 10 mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; vital signs, weight and adverse events. Urine, blood tests and ECGs at screening, baseline, wks 1, 2, 4, 7 and 12. Follow-up phase: smoking status + CO measured at wks 13, 24, 52; self-reported status by phone at wks 16, 20, 28, 32, 36, 40, 44
Outcomes	Primary outcome: Continuous verified 4-wk abstinence at wks 4 - 7 and 9 - 12 Secondary outcomes: Continuous verified abstinence at wks 2 - 12 and 9 - 52; 7-day PPA throughout treatment phase and at wks 12, 24 and 52 Other outcomes: weight change; craving and withdrawal changes using MNWS and mCEQ; adverse events Validation was by expired CO ≤ 10 ppm Cessation analyses were ITT (all participants randomised), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 627) . Attrition was 27% during treatment phase, and 22% of follow-up consenters lost in follow-up phase
Treatment type	Medication: VARENICLINE
Notes	For cessation analyses, titrated and nontitrated results were reported separately and pooled. 24-wk continuous cessation data supplied by authors The trial was funded by Pfizer Inc

Oncken 2006 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	"Eligible subjects were randomly assigned to 1 of 5 groups"
Blinding (performance bias and detection bias) All outcomes	Low risk	"Subjects and investigators were blinded to the study drug treatment [, and] were not encouraged to guess their treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing COs or visits OK if confirmed abstinent before and after missed measure
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Rennard 2012

Methods	Countries: Argentina, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, Italy, Korea, Mexico, Taiwan, UK, USA Setting: 33 research centres Aim: To evaluate efficacy and safety of varenicline allowing a self-selected quit date Dates conducted: September 2008 - December 2009 Study Design: Double-blind placebo-controlled RCT Analysis: Power calculation (90%, alpha = 0.05) assuming a true abstinence rate at 9 - 12 wks of 0.24 (placebo) and 0.46 (varenicline); Logistic regression with treatment and centre as independent variables
Participants	659 healthy volunteer smokers, aged 18 - 75, motivated to quit, smoking at least 10 CPD. 60% men, mean age 43, 68% white, mean CPD 21, mean FTND 5.5, 66% had tried to quit at least once before. Allocated to varenicline (493) or placebo (166) Exclusion criteria: Standard pharmacotherapy trial criteria, + use of NRT, bupropion, clonidine or nortriptyline within last 3m, ever use of varenicline; use of marijuana or tobacco other than cigarettes with last month
Interventions	1. Varenicline 1 mg x 2/day, titrated in 1st wk 2. Placebo inactive tablets, same regimen Participants could choose their own quit date between days 8 and 35 Treatment period was 12 wks. All participants received *Clearing the Air: Quit smoking today* booklet at baseline, + brief counselling (≤ 10 mins) at each clinic visit. Weekly visits throughout treatment phase, and in follow-up phase clinic visits at wks 13, 16, 20

Rennard 2012 (*Continued*)

	and 24. Phone calls at wks 14, 18 and 22
Outcomes	Primary outcome: CO-validated CAR at 9 - 12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks; 7-day PPA at wks 12 and 24 Other outcomes: Adverse events, SAEs; timing and number of quit attempts Validation was by expired CO $\leq$ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition to end of study (24 wks) was 12.4% from varenicline, 20.5% from placebo
Treatment type	Medication: VARENICLINE
Notes	New for 2012 update. Additional information supplied by the authors The study was funded and managed by Pfizer Inc

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"a predefined, central, computer-generated randomization sequence...assigned subjects in a 3:1 ratio". Block size: 4, stratified by centre
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-blind (participant, care-giver, investigator)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts and attrition rates fully reported
Selective reporting (reporting bias)	Low risk	All predicted and expected outcomes reported
Other bias	Unclear risk	None noted

Rigotti 2010

Methods	Country: 15 countries in Europe, Asia, Americas Setting: 39 research centres Aim: To evaluate efficacy and safety of varenicline in patients with stable CVD Dates conducted: February 2006 - August 2008 Study Design: Phase 3 double-blind placebo-controlled RCT Analysis: Logistic regression with treatment group and study site as independent variables

Participants	714 adult smokers, aged 35 - 75, smoking at least 10 CPD, with stable CVD and motivated to quit. 79% men, 80% white, mean CPD 22, mean FTND 5.6. Allocated to varenicline (355) or placebo (359), stratified by site Exclusion criteria: Standard pharmacotherapy trial criteria, + use of NRT or bupropion within previous month. All had been diagnosed for at least 2m with CVD, but not hypertension alone
Interventions	1. Varenicline 1.0 mg 2/day for 12 wks, including wk 1 at titrated dose 2. Placebo tablets as above Both groups received brief (≤ 10mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; vital signs, weight and adverse events. Urine, blood tests and ECGs at screening, baseline, wks 12 and 52 Follow-up phase: smoking status + CO measured at wks 13, 16, 24, 32, 40 and 52; counselling and self-reported status by phone at wks 14, 20, 28, 36 and 44
Outcomes	Primary outcome: CO-validated CAR at wks 9 - 12 Secondary outcomes: CO-validated CAR at wks 9 - 52 and 9 - 24; 7-day PPA at wks 12, 24 and 52 Other outcomes: Adverse events; serious adverse events; cardiovascular events; changes in blood pressure and heart rate Validation was by expired CO ≤ 10 ppm Cessation analyses were ITT (all participants randomised minus deaths), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 703). Attrition was 17.5% from the varenicline group and 20.3% from the placebo group during treatment phase, and 14.9% varenicline and 19.5% placebo who did not complete the study. This includes 2 deaths in the varenicline group and 5 in the placebo group by 52-wk follow-up
Treatment type	Medication: VARENICLINE
Notes	The study was funded by Pfizer Inc New for 2010 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The study sponsor conducted the randomization centrally using a computer-generated list that prespecified the order of treatment allocation"
Allocation concealment (selection bias)	Low risk	See above
Blinding (performance bias and detection bias) All outcomes	Low risk	Described as "double-blind" (participants and study implementation). Cardiovascular outcomes "were reviewed separately and

		adjudicated under blinded conditions by an independent event committee made up of 3 board-certified cardiologists"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analyses conducted; participants who missed a visit but had validated abstinence at next visit were considered continuously abstinent. But 52-wk status had to be attended and confirmed
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Rose 2013

Methods	Country: USA Setting: Duke University Medical Center, Durham, NC Aim: "Given the safety and tolerability profile of nicotine replacement therapy, our rationale in this study was to use nicotine replacement therapy as an initial line of treatment, and then identify early on which smokers are unlikely to benefit from nicotine alone" Study Design: Randomised double-blind parallel-arm adaptive treatment trial in 2 phases Dates conducted: Not stated Analysis: Logistic regression
Participants	606 adult smokers, motivated to quit, aged 18 - 65, mean CPD 10+ for 3 yrs, expired CO level 10+ ppm. 46% women, 63% white, mean CPD 21.7, mean FTND 5.8. Participants could receive up to USD 320 for study participation
Interventions	Two phase study: All participants seen weekly for 2 wks before TQD, and attended 4 - 6 sessions after the TQD. At each session, participant received brief (< 15 mins) support, + clinical trial materials. Smoking diaries, expired CO, withdrawal symptoms and reports of adverse events were collected each time. Participants were recontacted at 6m, and those reporting abstinence were invited to return to give a CO sample All participants were given open-label active NRT patch, either 42 mg/day (baseline CO > 30 ppm) or 21 mg/day (baseline CO < 30 ppm) for 2 wks; dose reductions allowed if side effects dictated. At 1 wk, participants were classified as 'responders' (reduced ad lib smoking by > 50%, CO-verified) or 'non-responders' (< 50%) *Phase 1 (12 weeks):* Non-responders only (N = 371 - 36 who withdrew, = 335) allocated to: 1. Double-blind varenicline, stopping NRT (N = 112) 2. Double-blind augmentation of NRT with bupropion (N = 109) 3. Continuation on open-label NRT alone (N = 114) All participants received dummy (placebo) versions of the other 2 treatments as well as their own active treatment *Phase 2:*

	235 responders after wk 1 assessed at 1st wk after TQD (wk 3). Lapsers (N = 105) were assigned a 2nd TQD 1 wk later, and were allocated to the same 3 double-blind treatment conditions as Phase 1 non-responders 1. Double-blind varenicline, stopping NRT (N = 36) 2. Double-blind augmentation of NRT with bupropion (N = 34) 3. Continuation on open-label NRT alone (N = 35) Non-lapsers (N = 130) remained on open-label NRT throughout study duration All participants received dummy (placebo) versions of the other 2 treatments as well as their own active treatment 47 participants were excluded from the analysis (27 Phase 1, 20 Phase 2) because of using contra-indicated medications during the study or failing to meet other entry requirements. 1 individual died before end of treatment, and 1 was excluded for extreme CO change from the mean sample range
Outcomes	Primary: CAR at wks 8 - 11 Secondary: CA from TQD for 11 wks (EoT); 7-day PPA at 6m: CA from TQD to 6m Validation: CO $\leq$ 10 ppm AEs and SAEs (reported, but not by treatment group)
Treatment type	Medication: VARENICLINE, BUPROPION, NRT
Notes	Funding by a grant from Philip Morris USA, with NRT supplied free by GSK Phase 1 and Phase 2 groups combined for varenicline vs NRT analysis New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"randomly assigned"
Allocation concealment (selection bias)	Unclear risk	No information
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported; exclusions for protocol violations or contra-indicated medicines. 1 death and 1 'rogue' CO reading excluded
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Unclear risk	Unexplained disparity between CONSORT (N = 103) and Results table (N = 108) denominators for rescue varenicline group

Stein 2013

Methods	Country: USA Setting: 9 methadone-maintained treatment centres in New England Aim: "[to] test varenicline versus placebo, and include a comparison condition of combination nicotine replacement therapy" Study Design: Randomised 3-armed double-blind controlled trial Dates conducted: December 2008 - January 2012 Analysis: Sample sizes of 132 (varenicline) and 44 (placebo) estimated to give 80% power to detect quit rates of 20% and 2.5% respectively; the study was not powered to detect differences between varenicline and combination NRT
Participants	315 adult methadone-maintained smokers, smoking 10+ CPD, willing to set a quit date within the 1st wk Allocated 3:1:3 to varenicline (137): placebo (45): combination NRT (133). Mean age 39.9, 47.6% women, 78.5% white, mean CPD 20, mean FTND 5.7
Interventions	All participants received a standardised 15-min session of advice to quit (5As model), and were asked to set a TQD for 8 days time. All made monthly visits for support and top-up medication 1. Varenicline: 24-wk course of varenicline tablets, 1st wk titrated 2. Placebo: 24-wk course of identical tablets and regimen 3. Combination NRT: 24-wk course of NRT patch (42 mg for > 30 CPD, 21 mg if < 30 CPD), + ad lib nicotine gum (4 mg) as needed Participants were paid USD 30 for the baseline assessment and USD 40 for the 6m assessment
Outcomes	Primary: 7-day PPA at 6m Secondary: CA from wk 2 to 6m; for non-quitters: CPD reduction in the 28 days prior to 6m assessment Validation: CO < 8 ppm; urinary cotinine in varenicline and placebo participants claiming abstinence
Treatment type	Medication: VARENICLINE / NRT
Notes	Funding: NCI grant RO1 CA129226; MDS supported by a NIDA mid-career investigator award K24 DA000512 New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Participants were randomized to treatment after completing the baseline assessment". No further information
Allocation concealment (selection bias)	Unclear risk	No information

Stein 2013 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind"; research assistants were "blind to participant group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to treatment and follow-up reported; ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Steinberg 2011

Methods	Country: New Jersey, USA Setting: Robert Wood Johnson Hospital (584-bed University-based) Aim: To evaluate efficacy and safety of varenicline in hospital inpatients Dates conducted: August 2007 - March 2009 Study Design: Phase III triple-blind pilot RCT
Participants	79 adult smokers, aged 18+, smoking 10+ CPD; randomised to varenicline (40) or placebo (39) 59% men, mean age: 51, 72% white, 57% > 20 cpd, 40% FTND > 6 Admission diagnoses 57% CVD, 14% orthopaedic, 13% pulmonary, 16% other Exclusion criteria: Standard pharmacotherapy criteria, + current use of any SC medications
Interventions	1. Varenicline 1.0 mg x 2/day for 12 wks, including wk 1 at titrated dose 2. Placebo tablets as above Initial visit by Clinic Co-ordinator of local Tobacco Dependence Program for 5 - 10 min counselling Subsequent sessions of 15 mins post-discharge After discharge, data collection sessions at 4, 12 and 26 wks, + 1 phone call at 2 wks with research nurse USD 25 gift card for attendance at each follow-up visit
Outcomes	Primary outcome: 7-day PPA at 26 wks Secondary outcomes: 7-day PPA at 4, 12 wks. Repeated PPA at 4, 12 and 24 wks. AEs and SAEs; withdrawal and craving on MNWS; motivation; CPD; utilisation of OP services; composite medical outcome Validation: CO validation $\leq$ 8 ppm. Self report accepted if unable to attend
Treatment type	Medication: VARENICLINE
Notes	Study was funded and support by Robert Wood Johnson Foundation and Pfizer Repeated PPA at 4, 12 and 24 wks used as strictest definition of abstinence and included in main MA New for 2012 update
Risk of bias	

Steinberg 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"randomized in a 1:1 ratio through centralized telephone randomization process by the study statistician and hospital research pharmacist"
Allocation concealment (selection bias)	Low risk	see above
Blinding (performance bias and detection bias) All outcomes	Low risk	"The subject, research nurse, and treatment staff were blinded to treatment assignment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis conducted; unvalidated smoking status included where ascertained for non-attenders, but % of unvalidated status not reported
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered, except for detailed identification of SAEs
Other bias	Unclear risk	None noted

Tashkin 2011

Methods	Country: USA (17 centres), Spain (3 centres), France (4 centres), Italy (3 centres) Setting: 27 research centres. Aim: To test efficacy and safety of varenicline in smokers with COPD Dates conducted: May 2006 - April 2009 Study Design: Double-blind placebo-controlled RCT Analysis: Power calculation (81% to detect a diff in CAR 9 - 52 wks based on an OR of 2.21 and a placebo rate of 9%); ITT denominators. Logistic regression with treatment group and study site as independent variables
Participants	504 adult smokers with mild-to-moderate COPD, aged 35+, smoking 10+ CPD, motivated to quit; allocated to varenicline (250), or placebo (254). 62% men, mean age 57, CPD 24 - 25, FTND score 5.9 - 6.2 Treatment groups were comparable at baseline Exclusion criteria: Standard pharmacotherapy trial criteria, + treatment with systemic corticosteroids or hospitalised for COPD in previous 4 wks
Interventions	1. Varenicline 1.0 mg x 2/day for 12 wks, preceded by 1 wk titrated dose 2. Placebo tablets as above Both groups received SC educational booklet, + brief ($\leq$ 10mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3 days post-TQD. At each visit smoking status reported and CO verified; throughout treatment and at wk 52 lung function, respiratory symptoms, weight, BP, pulse, temperature, ECGs, haematology and serum chemistry assessed, + adverse events

	Follow-up phase: smoking status + CO measured at wks 13, 16, 24, 32, 40, 48 and 52; counselling and self-reported status by phone at wks 14, 20, 28, 36 and 44
Outcomes	Primary outcome: CO-validated CAR at wks 9 - 12 Secondary outcomes: CO-validated CAR at wks 9 - 52 and 9 - 24; 7-day PPA at wks 12, 24 and 52 Other outcomes: Adverse events; serious adverse events; weight change Validation was by expired CO $\leq$ 10 ppm Cessation analyses were ITT (all participants randomised), while tolerability and safety analyses were based only on those known to have used the intervention drug (N = 499) . Attrition was 17% in the varenicline group and 24% in the placebo group during treatment phase, and 29% varenicline and 38% placebo who did not complete the study. This includes 2 deaths in the varenicline group and 1 in the placebo group
Treatment type	Medication: VARENICLINE
Notes	The study was funded by Pfizer Inc New for 2010 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"participants were randomized"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double blind" but details not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Tønnesen 2013

Methods	Country: Denmark Setting: 1 hospital-based smoking cessation specialist clinic Aim: "to evaluate whether varenicline used for 12 weeks would be more effective than placebo to get long-term NRT users to stop using NRT" Study Design: Randomised placebo-controlled quadruple-blind trial Dates conducted: Not given Analysis: Sample sizes of 66 in each group, estimated to give 80% power to detect quit rates of 50% and 25% respectively at 12 weeks in active and placebo groups
Participants	139 adult ex-smokers, aged 18+, reporting long-term (> 11m) abstinence, using flexible-dose NRT (i.e. > 4 pieces of nicotine gum/sublingual tablets or lozenges per day, or > 3 inhaler cartridges per day, or > 10 puffs of nasal spray per day), wishing and willing to try to stop using NRT; allocated to varenicline (70) or placebo (69) Participants used gums (2 mg 68.3%; 4 mg 11.5%), inhalers (5.8%), sublingual tablets (7.2%), lozenge (9.4%); mean daily NRT unit intake was 16 (SD 8.1), and mean NRT usage had lasted 6 years. Mean age 54.6, 54% women, mean CPD when smoking 23.5, mean FTND (recalled) 6.5
Interventions	All participants attended clinic visits at wks 0, 2, 4, 6, 9, 12, 52, + 2 phone calls at wks 26 and 38. Each visit included assessments, < 5 mins counselling from SC nurses. All participants advised to gradually reduce NRT and to stop completely by TQD at 1 - 2 wks 1. Varenicline: standard 12-wk regimen, titrated 1st wk 2. Placebo: identical tablets, same regimen
Outcomes	7-day PPA at 12 weeks, not smoking or on NRT; also no NRT (7-day PPA) + abstinence at 52 wks. CAR from wk 2 to wk 52, proven abstinent at all clinic visits Validation: expired CO < 7 ppm and plasma cotinine < 15 ng/ml
Treatment type	Medication: VARENICLINE
Notes	Not included in the main analysis, as smoking cessation was not the aim Funding was from an Independent Investigator Grant from Pfizer A/S, Denmark and Pfizer, Europe New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects were randomized to active or placebo using a computer-generated list with random numbers"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as a "double-blind" trial. No additional information

Tønnesen 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	By 52 wks, 9 had dropped out of the varenicline group and 15 out of the placebo group (PRISMA flow diagram says 15, text says 14). ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Tonstad 2006

Methods	Country: USA (6 centres) and 'international' (18 centres, across Canada, Czech Republic, Denmark, Norway, Sweden, UK*) Setting: 24 research centres Aim: To test the efficacy and safety of extended varenicline treatment for preventing relapse in adults who have quit smoking on open-label varenicline Dates conducted: April 2003 - February 2004 (initial recruitment phase) Study Design: Double-blind placebo-controlled RCT. Analysis: Power calculation (80%, alpha = 0.05); ITT denominators and logistic regression analysis for binary data, and Kaplan-Meier curve for time to first lapse
Participants	1210 successful quitters (62.8% of initial cohort) following a 12-wk open-label course of varenicline for smoking cessation, randomised to varenicline (603) or placebo (607) for a further 12 wks. 49% men, 97% white, mean age 45, BMI < 15 or > 38 or weight < 45.5 kg, mean CPD 21, mean FTND score 5.4 Exclusion criteria: Standard pharmacotherapy trial criteria, + use of marijuana or tobacco products other than cigarettes within last month; use of NRT, bupropion, clonidine, nortriptyline within last month
Interventions	1. Varenicline 1 mg x 2/day for 11 wks after 1 wk titrated dosage 2. Placebo tablets, same regimen All participants also received brief counselling (≤ 10 mins) at each clinic visit throughout treatment phase (wks 13 - 24). Treatment phase clinic visits were at wks 13, 14, 16, 20 and 24 Follow-up phase: 5 visits and 4 phone calls from wks 25 - 52
Outcomes	Primary outcome: Relapse prevention: maintenance of CO-validated CAR at 24 wks Secondary outcome: CO-validated CAR at wk 52; 7-day PPA at wks 24 and 52. 2 deaths removed from varenicline denominator at 52 wks Other outcomes: weight change, withdrawal symptoms (using MNWS), time to first lapse, adverse events Validation was by expired CO ≤ 10 ppm Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition was 12% during treatment phase, and 10% of treatment completers lost during follow-up phase
Treatment type	Medication: VARENICLINE

Tonstad 2006 (*Continued*)

Notes	* additional information supplied by author The trial was funded by Pfizer Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"computer-generated randomization sequence (stratified by center with a block size of 4)"
Allocation concealment (selection bias)	Low risk	"a single, centralised [system]"
Blinding (performance bias and detection bias) All outcomes	Low risk	"double-blind treatment phase"; "participant blinding was maintained during this [non-treatment follow-up] phase"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing COs were considered abstinent if other criteria OK; at wk 52 all criteria had to be met
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Tsai 2007

Methods	Country: Taiwan and Korea Setting: 5 sites in each country Aim: To test the efficacy and safety of varenicline for smoking cessation in Taiwanese and Korean smokers Dates conducted: February 2005 - March 2006 Study Design: Double-blind placebo-controlled RCT Analysis: Power calculation (I am happy to talk to the CEU team and Jo while you're away, to keep things moving forward. (≥ 90%, alpha = 0.05); ITT denominators and logistic regression model including treatment and centre
Participants	250 healthy adult volunteers, motivated to quit, aged 18 - 75; allocated to varenicline (126), or placebo (124). 89% men, mean age 40.3, BMI < 15 or > 38 or weight < 45. 5 kg, mean CPD 24, mean FTND score 5.1. Treatment groups were comparable at baseline Exclusion criteria: Standard pharmacotherapy trial criteria
Interventions	1. Varenicline 1.0 mg x 2/day 2. Placebo tablet x 2/day Treatment period 12 wks, 1st wk titrated dosage. All participants received a smoking cessation booklet *Clearing the Air* at baseline, + brief counselling (≤ 10 mins) at each

	clinic visit. Clinic visits at baseline and at wks 1, 2, 3, 4, 6, 8, 10, 12, plus a 5-min phone call at +3 days post-TQD, and at wks 5, 7, 9, 11 In follow-up phase, clinic visits at wks 13, 16, 20, 24 plus brief phone calls at wks 14, 18, 22
Outcomes	Primary outcome: CO-validated CAR at 9 - 12 wks Secondary outcomes: CO-validated CAR at 9 - 24 wks; 7-day PPA at wks 12 and 24 Validation was by expired CO $\leq$ 10 ppm Other outcomes: Withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 2.8%, losses to follow-up 2.5% of treatment completers
Treatment type	Medication: VARENICLINE
Notes	Trial was funded by Pfizer Inc New for 2008 update.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"randomly permuted blocks" (block size= 4)
Allocation concealment (selection bias)	Low risk	web- and telephone-based assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Subjects, investigators, study staff and sponsor personnel
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information, but very high compliance rates
Selective reporting (reporting bias)	Unclear risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Tsukahara 2010

Methods	Country: Japan Setting: Cessation clinic in Fukuoka University Hospital Aim: To test the efficacy and safety of varenicline for smoking cessation in Japanese smokers Dates conducted: Aug 2008 - November 2009 Study Design: Randomised controlled open-label trial Study name: The VN-SEESAW Study
Participants	32 adult smokers, motivated to quit, allocated to varenicline (16) or nicotine patch (16). 75% men, mean age 46, mean CPD 28 (varenicline), 25 (patch), mean TDS (addiction) score 7.6, mean Brinkman index score (CPD x yrs smoking) 702. 71% had tried to quit previously, and 7% had used nicotine patches before Standard pharmacotherapy trial exclusion criteria, plus attendance at any smoking cessation clinic during previous 12m
Interventions	1. Open-label varenicline 1.0 mg x 2/day for 12 wks, following 1 wk titration 2. Open-label nicotine patch for 8 wks (52.5 mg/day for 4 wks, 35 mg/day for 2 wks, 17.5 mg/day for 2 wks) No non-treatment or placebo control group Varenicline group received 8 clinic visits and nicotine group 5 visits over 12 wks, with 5 brief counselling sessions (≤ 10 mins)
Outcomes	CO-confirmed CAR at 9 - 12 wks, and self-reported at 9 - 24 wks by phone interview Validation by expired CO < 8 ppm at 12 wks, but not at 24 wks Other outcomes: Safety and tolerability by wk 12, using MNWS at wks 2, 4, 8 and 12. Also used Stress Check List and Strait-trait Anxiety Inventory Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 12.5% from each group
Treatment type	Medication: VARENICLINE / NRT OPEN-LABEL
Notes	The study was supported by the Japanese Ministry of Education, Science and Culture, Fukuoka University and FU-Global program Not included in main MA, as no placebo group New for 2010 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"by computer" allocating men: women 3:1 to reflect Japanese smoking prevalence (M: 40%, F: 12%)
Allocation concealment (selection bias)	Unclear risk	Not stated

Tsukahara 2010 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	Participants and personnel were not blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Wang 2009

Methods	Country: China (10 sites), Singapore (3 sites), Thailand (2 sites) Aim: To test the efficacy and safety of varenicline for smoking cessation in Chinese, Singaporean and Thai smokers Dates conducted: Not stated Study Design: Double-blind placebo-controlled RCT. Analysis: Power calculation (≥ 90%, alpha = 0.05); ITT denominators and logistic regression model including treatment with site, country, FTND score, CPD and time to first cigarette. No interactions found
Participants	333 healthy adult volunteers, aged 18 - 75; allocated to varenicline (165), or placebo (168). 97% men, mean age 39, BMI > 15 and < 38 or weight > 45.5 kg, mean CPD 20, mean FTND score 5.4. Treatment groups were comparable at baseline. 58% had never tried to quit before Exclusion criteria: Standard pharmacotherapy trial criteria, plus any use of NRT or bupropion in previous 6m
Interventions	1. Varenicline 1.0 mg x 2/day 2. Placebo tablet x 2/day Treatment period 12 wks, 1st wk titrated dosage. All participants received a smoking cessation booklet at baseline, + brief counselling (≤ 10 mins) at each clinic visit, except for wks 5 and 7, when counselling was conducted by phone In follow-up phase, clinic visits at wks 13, 16, 20, 24 plus brief phone calls at wks 14, 18, 22. Dosing and CO checked at each visit, and lab samples taken at wks 12 and 24
Outcomes	Primary outcome: CO-confirmed CAR for wks 9 - 12 Secondary outcomes: CO-confirmed CAR for wks 9 - 24; 7-day PPA at 24 wks Validation by expired CO < 10 ppm Other outcomes: adverse events; long-term quit rates Dropouts and losses to follow-up were included in the analyses as continuing smokers (ITT analysis) Attrition in treatment phase was 3.0% in varenicline group, and 3.6% in placebo group. By wk 24, 4.2% of had dropped out of each group
Treatment type	Medication: VARENICLINE

Wang 2009 (*Continued*)

Notes	The trial was funded by Pfizer Inc New for 2010 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"eligible subjects were randomized in a 1:1 ratio"
Allocation concealment (selection bias)	Unclear risk	See above
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"double-blind", but no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information, but very high compliance rates
Selective reporting (reporting bias)	Low risk	All expected and predicted outcomes covered
Other bias	Unclear risk	None noted

Westergaard 2015

Methods	Country: Denmark Aim: To evaluate the effect of varenicline on tobacco cessation in young smokers suffering from asthma Dates conducted: Not stated Study Design: Double-blind placebo-controlled RCT
Participants	52 young (aged 19 - 40) smokers with asthma, randomised to varenicline (26) or placebo (26). CPD $\geq$ 10; FTND 5.6
Interventions	1. Varenicline: presumed standard regimen: Varenicline 1.0 mg x 2/day 2. Placebo tablet x 2/day No further details
Outcomes	Primary: presumed PPA at 12 wks Secondary: presumed PPA at 0, 6, 24 wks Validation by expired CO < 10 ppm Also assessed asthma symptom score, general health quality score (15D) and methacholine challenge
Treatment type	Medication: VARENICLINE
Notes	Author supplied further details

Westergaard 2015 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated. “”randomized, placebo-controlled, double-blinded trial“
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not stated. ”double-blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated; ITT analysis conducted
Selective reporting (reporting bias)	Unclear risk	Not stated
Other bias	Unclear risk	Not stated

Williams 2007

Methods	Country: USA and Australia Setting: 9 research centres (8 USA, 1 Aus) Aim: To test the safety of long-term (12m) use of varenicline in smokers trying to quit Study Design: Double-blind placebo-controlled RCT Dates conducted: October 2003 - March 2005
Participants	377 adult smokers, aged 18 - 75, smoking at least 10 CPD. 49.9% men, 88.6% white, av CPD at baseline 23, mean FTND 5.5 in treatment group, 6.05 in control group. Allocated to varenicline (251) or placebo (126) Exclusion criteria: Standard pharmacotherapy trial criteria, + no use of NRT, antidepressants, antipsychotics, naltrexone during study period
Interventions	1. Varenicline 1mg x 2/day, titrated for first wk 2. Placebo inactive tablets, same regimen All participants received S-H booklet *Clearing the Air*. Brief counselling (≤ 10 mins) at each visit TQD was 1st day of wk 1 visit (7 - 10 days post-randomisation) Treatment period was 52 wks. Weekly visits throughout wks 1 - 8, then every 4 wks to wk 52, + wk 53 assessment Blood and urine samples taken at screening, baseline, wks 2, 12, 24, 36, 52 (or early termination) Complete physical exam at baseline, wks 24 and 52; BP, pulse and weight measured at all visits, ECG at screening, baseline, wks 2, 24 and 52 (or early termination)
Outcomes	Primary outcome: Safety of smokers treated continuously with varenicline over 52 wks, measured at wk 53 by level and tolerability of adverse events and incidence of SAEs Secondary outcome: 7-day CO-verified PPA at all clinic visits (expired CO ≤ 10 ppm)

Williams 2007 (*Continued*)

	Other outcomes: Weight change; changes in vital signs Attrition was 46.2% in varenicline group, 53.2% in control group by end of study
Treatment type	Medication: VARENICLINE
Notes	This was a safety study, with cessation rates collected as a secondary outcome The trial was funded and conducted by Pfizer Inc In the first version of this review, this trial appeared as Reeves 2006 (unpublished data)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation 2:1 varenicline to placebo. No detailed information reported
Allocation concealment (selection bias)	Unclear risk	No information reported
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing CO and/or visit taken as smokers
Selective reporting (reporting bias)	Low risk	Primary outcome was safety, so minimal cessation data
Other bias	Unclear risk	None noted

Williams 2012

Methods	Countries: Canada, USA Setting: 12 sites Aim: To evaluate primarily safety, but also efficacy of varenicline in smokers with schizophrenia or schizoaffective disorders Dates conducted: May 2008 - April 2010 Study Design: Double-blind placebo-controlled RCT. Sample size [120] was considered sufficient to detect a between-group difference in 7-day PPA "for a medium effect size"
Participants	128 adults, diagnosed with stable schizophrenia or schizoaffective disorders, smoking at least 15 CPD and motivated to quit. Randomised to varenicline (85) or placebo (43). 77% men aged 18 - 75
Interventions	1. Varenicline 1.0 mg x 2/d for 12 wks, including wk 1 at titrated dose 2. Placebo tablets as above. Weekly clinic visits, for safety and efficacy, ≤ 30-min counselling sessions; after treatment phase, clinic visits at wks 13, 16, 20, 24, with brief phone calls at wks 14, 18 and 22.

Williams 2012 (*Continued*)

	Follow-up sessions included brief (≤ 10 mins) counselling. AEs collected to 30 days after treatment, and neuropsychiatric AEs to wk 24
Outcomes	Primary outcome: N of participants with adverse and serious adverse events from baseline to 30 days after end of treatment (12 wks). N of participants with psychiatric adverse events, including suicidal ideation or behaviour Secondary outcomes: CO-confirmed PPA at wks 12 and 24; 50%+ reduction in CPD; change in CPD from baseline. Assessments on mood and psychiatric scales Validation was by exhaled CO ≤ 10 ppm Dropouts in treatment phase: 14 (varenicline), 3 (placebo); follow-up phase: 10 (varenicline), 3 (placebo) 1 varenicline participant died during follow-up phase
Treatment type	Medication: VARENICLINE
Notes	The study was funded by Pfizer New for 2012 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Subjects were randomized (2:1) to varenicline or placebo ... and were stratified according to antipsychotic medication type (typical vs atypical)."
Allocation concealment (selection bias)	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not yet reported

Wong 2012

Methods	Country: Canada Setting: 2 Toronto hospitals Aim: "to determine the effectiveness and safety of a perioperative smoking cessation intervention including varenicline and counseling versus placebo and counseling to increase short- and long-term abstinence in surgical patients" Study Design: Randomised placebo-controlled double-blind trial Dates conducted: June 2008 - November 2010 Analysis: Sample sizes of 145 in each group, estimated to give 80% power to detect a risk difference of 15% at 12 months between active and placebo groups
Participants	286 non-cardiac elective surgery patients, smoking 10+ CPD, no abstinence > 3m in last year, scheduled for surgery in the next 8 - 30 days. Allocated to varenicline (151) or placebo (135). Mean age 52.6, 47% women, mean CPD 17.4, mean FTND 4.8

Wong 2012 (*Continued*)

Interventions	All participants received 2 standardised 15-min counselling sessions by researchers, 1 in pre-op clinic and 1 24 hours after surgery, supplemented by written materials. All participants retained the same counsellor throughout the process Weekly counselling phone calls for 4 weeks, and at the end of 8 weeks. From 3 - 12 months, phone calls every 4 weeks for smoking status, nicotine dependence, stage of change, CPD, brief (< 5 mins) counselling. TQD was set for 24 hours before surgery, and medication begun 7 days before TQD 1. Varenicline: 12 wks standard regimen, 1st wk titrated 2. Placebo: Identical-looking tablets and regimen Participants were invited to visit the hospital at 3, 6, and 12m, for assessment and testing. Participants unable to visit the hospital were sent a self-test urinary kit
Outcomes	7-day PPA at 12m; abstinence on TQD; 7-day PPA at 3m and 6m. Self-reported changes in CPD and stage of change at 3, 6 and 12m Validation: Expired CO and urinary cotinine (cut-offs not given)
Treatment type	Medication: VARENICLINE
Notes	Supported by Canadian academic institutes and Pfizer Canada New for 2016 update

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Smokers were randomly assigned to receive varenicline (Pfizer Inc., Kirkland, Quebec, Canada) or matching placebo using a computer-generated randomization list at each center. A stratified randomization with blocks of 40, based on the smoker's stage of change, was employed because the stage of change may predict successful abstinence from smoking."
Allocation concealment (selection bias)	Low risk	"The patient assignments were placed into sequentially numbered, opaque sealed envelopes, and were kept by an independent research pharmacist at each center who was not involved with patient care or outcome assessments. For each patient, the research pharmacist opened the envelope and provided the research coordinator with the medication or placebo (lactose, identical in appearance) according to the randomization schedule."

Wong 2012 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"The patients, healthcare personnel, and research staff were blinded to the randomization throughout the study period."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses fully reported: Varenicline: 6 discontinued treatment, 11 discontinued follow-up. Placebo: 6 discontinued treatment, 10 discontinued follow-up. ITT analyses conducted
Selective reporting (reporting bias)	Low risk	None noted
Other bias	Low risk	None noted

Brandon 2011*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: Short-term (15 days) RCT, to test craving and psychological reward; cessation was not an outcome

Ebbert 2011*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: Pilot study of varenicline for smokeless tobacco users. 12-wk outcome (EoT) reported, not long-term post-treatment

Faessel 2009*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: Outcomes were safety, tolerability and pharmacokinetics, not smoking cessation

Fagerström 2010*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: 431 smokeless tobacco users in Norway and Sweden, randomised to varenicline or placebo; CAR assessed at 12 and 26 weeks

Garza 2011*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: 110 abstinent smokers treated with varenicline or placebo, to assess incidence and severity of neuropsychiatric symptoms; not a cessation trial

Hughes 2011*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: 218 smokers not ready to quit assigned to varenicline or placebo for 2 - 8 weeks for cigarette reduction; abstinence was not the outcome of interest, although measured in those who made a quit attempt. Primary outcome was incidence of quit attempts over 6m

McClure 2013* NCT00944554

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: New for 2016 update. Laboratory study following an RCT of varenicline in a programmed lapse; abstinence only to 4 weeks

Meszaros 2013*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: New for 2016 update. Pilot study (10 participants, only 4 completers), only followed to 3m; objective was reduction, not cessation

Mitchell 2012*

Methods	
Participants	
Interventions	
Outcomes	
Treatment type	
Notes	Treated as an included study in order to contribute to adverse event meta-analyses; Excluded for efficacy: New for 2016 update. Varenicline was for drinking reduction, not smoking cessation; only followed for 12 weeks

BMI: Body Mass Index (kg/m^2)
CAR: Continuous Abstinence Rate
CO: carbon monoxide
COPD: chronic obstructive pulmonary disease
CPD: cigarettes per day
CQR: continuous quit rate
CVD: cardiovascular disease
EoT: end of treatment
FTND: Fagerström Test for Nicotine Dependence
ITT: intention-to-treat
LOCF: last observation carried forward
MA: meta-analysis
MDD: major depressive disorder
MI: motivational interviewing
mCEQ: Modified Cigarette Evaluation Questionnaire
MNWS: Minnesota Nicotine Withdrawal Scale
PA prolonged abstinence
PPA: point-prevalence abstinence
QoL: quality of life
QSU-brief: Brief Questionnaire of Smoking Urges
RCT: randomised controlled trial
SAE: serious adverse event
SC: smoking cessation
TQD: target quit date

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

Study	Reason for exclusion
Burstein 2006	RCT of tolerability and safety of varenicline in 24 elderly (≥ 65) smokers for 1 week. Not a cessation trial
Chantix 2006	39 smokers randomised to NRT alone (17) or varenicline + NRT (22) for 12 days to test safety and side effects of co-administration. 36% of combined group discontinued, compared with 6% of NRT alone group
Cui 2012	Open-label non-randomised pre/post study of 36 HIV+ participants; all got varenicline, assessed at wks 12 and 24
Dezee 2013	New for 2016 update. RCT in which all participants were given varenicline; intervention tested was in-person vs internet counselling
Dutra 2012	53 participants with schizophrenia given varenicline + CBT. Abstinence assessed at 12 weeks (end of treatment)
Ebbert 2009a	Open-label, single-arm Phase II study, for safety and efficacy of varenicline plus bupropion
Ebbert 2009b	Cohort analysis of 104 participants on varenicline + NRT and 135 participants treated prior to release of varenicline (93% used NRT)
Ebbert 2014	New for 2016 update. RCT in which all participants were given varenicline; the intervention being tested was bupropion vs placebo. See also Hong 2011 NCT00492349
Falk 2014	Varenicline was used for alcohol reduction, not for smoking
Fatemi 2013 NCT01111149	New for 2016 update. 3-arm RCT of varenicline, bupropion and placebo; only assessed to end of treatment (12 weeks)
Ferketich 2012	New for 2016 update. Pilot study of varenicline vs NRT; participants could choose their treatment; intervention being tested was the addition of a lung cancer screening programme
Ferketich 2013	New for 2016 update. Safety of varenicline among smokers enrolled in the Lung HIV study. Participants could choose varenicline or NRT, and were only followed for 3 months
Frye 2013	New for 2016 update. Small (9 participants) feasibility study in bipolar participants, open-label, followed only until end of treatment (12 weeks)
Fucito 2011	RCT of 30 heavy-drinking smokers, assigned to pre-treatment varenicline or placebo, prior to 4 wks varenicline; primary outcome was effects on drinking behaviour, but smoking status at end of study (8 wks) was also measured
Granatowicz 1976	Polish uncontrolled study of 1968 smokers, 71% taking cytisine, followed for 6m
Gray 2012	New for 2016 update. Pilot study of varenicline vs bupropion in older adolescents; outcome was reduction rather than cessation, and participants were only followed for 3 months

(*Continued*)

Hajek 2011	101 smokers randomised to preloaded varenicline or placebo; abstinence not measured beyond 12 weeks
Hajek 2013	New for 2016 update. All were given varenicline, with the intervention tested being the addition of a NRT patch. Only followed to 3 months
Hartwell 2014	Varenicline for drinking and smoking; smoking topography and pharmacogenetics rather than smoking cessation
Hawk 2012 NCT00835900	New for 2016 update. RCT of extended pre-TQD varenicline vs standard regimen; all participants got varenicline, and were followed only until end of treatment (12 weeks)
Hong 2011 NCT00492349	New for 2016 update. Secondary analysis to Ebbert 2014, looking at depression in recipients of varenicline + bupropion vs varenicline alone
Hoogsteder 2014	New for 2016 update. All participants were given open-label varenicline; the intervention being tested was the addition of NicVAX
Hsueh 2014	New for 2016 update. Open-label cohort study of smokers taking varenicline or NRT
Jain 2014	New for 2016 update. RCT of smokeless tobacco users in India (to be covered in our review of interventions for smokeless tobacco)
Jennings 2014	New for 2016 update. The EUROACTION PLUS study; a complex nurse-led intervention for smokers at high risk of CVD. Varenicline was a treatment option. Only followed to 16 weeks
Jiménez-Ruiz 2013	New for 2016 update. Cohort study of smokers not responding to standard varenicline dosage by 8 weeks treated with varenicline 3 mg/day in 2 Spanish smoking cessation clinics
Kempe 1967	Bulgarian 1965 observational uncontrolled study of 30 male smokers given cytisine (Tabex) for 25 days and followed up for 6m
Koegelenberg 2014	New for 2016 update. All participants took varenicline; the intervention being tested was the addition of NRT
Maliszewski 1972	Polish uncontrolled study of 14 smokers on a 25-day course of cytisine (Tabex); followed up for 2 wks
Marakulin 1984	Russian trial of 620 smokers; no placebo, but autogenic training for control group. Follow-up 6 wks
McColl 2008	RCT of varenicline's potential as an abuse drug in smokers and non-smokers; not a smoking cessation trial
McNaughton 2013	New for 2016 update. All participants received varenicline; the intervention being tested, as a relapse prevention aid, was interactive voice response phone calls
Metelitsa 1987	Russian uncontrolled study of 281 smokers, comparing anabasine hydrochloride, cytisine or a combination of both drugs, taken as biosoluble film on a paper or fabric patches. Followed for 6 - 14m

(*Continued*)

Mocking 2013	New for 2016 update. 7-day administration of varenicline for emotional and cognitive processing in non-smokers
Mocking 2014	New for 2016 update. 7-day administration of varenicline for cortisol levels, not for smoking cessation
Monova 2004	Bulgarian RCT of 150 moderate+ smokers; investigators did not instruct participants to stop smoking, but monitored their smoking behaviour during and after a 25-day course of cytisine (Tabex). Follow-up was 60 days
NCT00502216	New for 2016 update. Study of varenicline and naltrexone for tolerability and weight gain in smokers, not cessation
NCT01308736	Outcome was 50% reduction in smoking, not abstinence (none succeeded in quitting completely)
NCT01806779	All participants got varenicline; the addition of bupropion was the intervention being tested
Nollen 2011	RCT of 72 black smokers; all received varenicline, but half got extended counselling and half a single session. Cessation only measured to 3m endpoint
Ostrovskaia 1994	Russian uncontrolled study of 74 smokers, comparing anabasin, cytisine or combination therapy, in film patches. (Relates to Metelitsa 4-stage study). Followed for 6 - 14m
Park 2011	RCT of 49 smokers with lung cancer randomised to varenicline or placebo; Follow-up only for 12 weeks to end of treatment
Patterson 2010	New for 2016 update. Short-term (3-week) study of propensity to relapse with working memory deficits after 10 days of varenicline
Paun 1968	Bulgarian controlled trial of cytisine (Tabex) (366 smokers) vs placebo (239 smokers) but followed only for 8 wks. Observational study of 230 cytisine-users followed for 26 wks, but no comparator group
Pfizer 2006	Phase II flexible-dosing trial of varenicline in 312 participants. Treatment lasted 12 weeks, and cessation outcomes reported for continuous abstinence through weeks 9 - 12
Poling 2010	RCT of varenicline in 31 methadone-maintained smokers; trial lasted 3m, and reduction was an outcome of interest (though 3m abstinence was reported)
Ramon 2014	New for 2016 update. RCT in which all participants received varenicline; intervention being tested was the addition of NRT
Rose 2014	New for 2016 update. RCT of varenicline versus varenicline + bupropion, in smokers who had failed to quit on NRT. All got varenicline
Schlienz 2014	New for 2016 update. 4 weeks treatment with varenicline; outcome was impact on behavioural economic indices, not smoking cessation

(*Continued*)

Schmidt 1974	Non-randomised trial of 16 smoking cessation preparations, including cytisine (Tabex) (200 smokers) ; participants allocated to treatment 'by chance', and followed up over 3m. Placebo group not directly matched to cytisine (Tabex) group
Schnoll 2011	New for 2016 update. RCT of open-label varenicline + counselling; intervention being tested was recruitment strategies, not smoking cessation
Shim 2011	60 smokers with schizophrenia randomised to varenicline or placebo for 8 weeks; assessment at end of treatment, reduction but not abstinence rates reported
Sicras-Mainar 2010	Multicentre observational non-randomised non-controlled study
Stapleton 2008	Non-randomised trial of 412 attenders at a London smoking cessation clinic, choosing either NRT (single product or combination) or varenicline. NRT arm were historical controls. Effectiveness and safety were assessed separately in a subset of 111 participants receiving treatment for mental illness
Stoyanov 1972	87 smokers (17 of them psychiatric patients); observational study with no comparator group and short but unstated length of follow-up
Swan 2010	All participants were given varenicline (treated as an included study for 2012 update)
Weiner 2011	9 smokers with schizophrenia randomised to varenicline or placebo; final assessment was at 12 weeks (end of treatment)
Zatonski 2006	Polish uncontrolled observational study of 342 smokers; at 12 months 13.8% abstinent

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

Wiratmoko 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract only; further details awaited

Yujie 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	Abstract only; further details awaited

Zincir 2013

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not in English; may be too short-term to include

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

ACTRN12613000854730

Trial name or title	TALANOA Samoa: A randomised controlled trial to evaluate the efficacy of a cessation support programme for smokers delivered by radio
Methods	Open-label parallel-group efficacy RCT
Participants	Up to 130 adults (16+), tobacco smoker, speaking Samoan, resident in Auckland NZ
Interventions	10 weekly ½-hour radio programmes of behavioural advice
Outcomes	Prevalence of quitting at 3m, CO-verified (< 10 ppm). N of quit attempts, successful or not
Starting date	September 2013
Contact information	PI: v.nosa@auckland.ac.nz; Scientific enquiries: d.gentles@auckland.ac.nz
Notes	

ACTRN12614000329662

Trial name or title	Examination of mechanism of action of pre-quit use of nicotine patch and varenicline for smoking cessation [PQT]
Methods	Open-label parallel-group efficacy RCT
Participants	Up to 216 adults (18+), smoking 15+ CPD, high motivation to quit, willing and able to take either medication
Interventions	(i) Varenicline, 2 wks before TQD and 4 wks after; or (ii) NRT 21 mg patch, starting 2 wks before TQD
Outcomes	Primary: 1. CPD reduction in 1st 2 wks 2. Measures of craving 3. Smoking satisfaction Secondary: 1. CO-validated abstinence at 28 days post-TQD
Starting date	March 2014
Contact information	PI and enquiries: stuart.ferguson@utas.edu.au
Notes	

ACTRN12614000876695

Trial name or title	Improving radiotherapy outcomes with smoking cessation: feasibility trial in head and neck cancer patients [Health Steps]
Methods	Parallel blinded safety/efficacy RCT
Participants	Up to 40 head-and-neck cancer patients, smoking at least 5 CPD, scheduled for radiotherapy
Interventions	3m varenicline + 10 sessions manual-based MI; control get TAU, no varenicline
Outcomes	Feasibility and acceptability, i.e. compliance, tolerability Continuous abstinence up to 6m post-radiotherapy, CO-validated
Starting date	August 2014
Contact information	PI and enquiries: ben.britton@hnehealth.nsw.gov.au
Notes	

Ameridian 2007

Trial name or title	Efficacy and safety of dianicline treatment as an aid to smoking cessation in cigarette smokers (AMERIDIAN)
Methods	Double-blind placebo-controlled RCT; companion study to EURODIAN trial (see Tonstad 2011).
Participants	600 adult smokers in USA, Canada
Interventions	Dianicline 40 mg bid for 7 wks, vs placebo (same regimen)
Outcomes	CAR at wks 4 - 7. Craving and withdrawal symptoms
Starting date	September 2006
Contact information	Sanofi-Aventis
Notes	Information taken from ClinicalTrials.gov; results not yet reported.

EUCTR2009-017599-26-IT

Trial name or title	Efficacy and safety of smoking cessation with varenicline tartrate in diabetic smokers: a double-blind, placebo-controlled randomised trial
Methods	RCT
Participants	Elderly adults, aged 75+, with type 2 diabetes
Interventions	1 mg x 2/day
Outcomes	CQR at wk 24
Starting date	22nd January 2010
Contact information	
Notes	

ISRCTN25441641

Trial name or title	Evaluation of the impact of systematic delivery of cessation interventions on delivery of smoking cessation in secondary care [Exploring ways to help hospital patients stop smoking]
Methods	RCT
Participants	Adult smokers
Interventions	NRT + counselling, with varenicline or bupropion offered to those who do not wish to take NRT
Outcomes	1m abstinence after discharge from hospital

ISRCTN25441641 (*Continued*)

Starting date	October 2010
Contact information	Kapka Nilan, University of Nottingham, UK
Notes	

Nahvi 2014b

Trial name or title	Varenicline smoking cessation treatment for methadone maintenance patients
Methods	Open-label parallel-group efficacy RCT
Participants	100 adult methadone-maintained smokers, at least 5 CPD, interested in quitting
Interventions	Directly-observed varenicline treatment versus TAU (self-administered varenicline)
Outcomes	CO-verified abstinence at 12 wks Varenicline adherence; tobacco use measures; reduction in CPD
Starting date	July 2011
Contact information	Shadi Nahvi
Notes	

NCT00554840

Trial name or title	Comparison of varenicline and placebo for smoking cessation in schizophrenia
Methods	Randomised double-blind placebo-controlled trial
Participants	44 smokers with schizophrenia
Interventions	12 weeks varenicline 1.0 mg x 2/day vs placebo
Outcomes	PPA at 12 weeks, neuropsychiatric symptoms
Starting date	November 2007
Contact information	E Weiner
Notes	

NCT00580853

Trial name or title	The effect of varenicline (Chantix) and bupropion (Zyban) on smoking lapse behavior
Methods	Randomised triple-blind factorial trial
Participants	60 adult smokers
Interventions	8-day course of varenicline, bupropion or placebo
Outcomes	Latency to initiate ad-lib smoking
Starting date	April 2007
Contact information	SA McKee
Notes	

NCT00683280

Trial name or title	Contingency management and pharmacotherapy for smoking cessation (Donaghue)
Methods	Open-label parallel-group efficacy RCT
Participants	59 adults, smoking 10+ CPD, motivated to quit (intended to recruit 70)
Interventions	All on 12 wks varenicline + brief counselling; tested intervention is the addition of contingent prizes for quitting
Outcomes	CO- and cotinine-verified abstinence at wks 5, 12 and 24
Starting date	May 2008
Contact information	Sheila M Alessi
Notes	

NCT00786149

Trial name or title	Improving varenicline adherence and outcomes in homeless smokers
Methods	Open-label parallel-group efficacy RCT
Participants	428 adult homeless smokers, at least 5 CPD
Interventions	Varenicline + MI sessions vs varenicline + brief advice (testing MI)
Outcomes	7-day PPA at 6m Adherence at 12 wks and 6m; moderating effects of psychiatric comorbidities

NCT00786149 (*Continued*)

Starting date	September 2007
Contact information	Kolawole S Okuyemi
Notes	

NCT00879177

Trial name or title	Smoking study with behavioural therapy for hypertensive patients (VANQUISH)
Methods	Open-label parallel-group efficacy RCT
Participants	260 hypertensive adult smokers
Interventions	Varenicline alone vs varenicline + behavioural therapy
Outcomes	Abstinence at 5, 6, 8, 12, 24, 36, 52 wks
Starting date	April 2009
Contact information	William B White
Notes	

NCT00906386

Trial name or title	Methadone maintenance treatment and smoking cessation (MMTASC)
Methods	Randomised double-blind placebo-controlled trial
Participants	112 smokers on methadone maintenance for opioid dependence
Interventions	Varenicline 1.0 mg x 2/day vs placebo for 12 wks
Outcomes	7-day PPA at 26 weeks
Starting date	May 2009
Contact information	Milan Khara
Notes	

NCT00918307

Trial name or title	Comparison of the efficacy and safety of varenicline versus placebo for smoking cessation among HIV-infected patients (Inter-ACTIV)
Methods	Randomised quadruple-blind placebo-controlled trial
Participants	254 smokers diagnosed with HIV infection
Interventions	Varenicline 1.0 mg x 2/day vs placebo for 12 weeks
Outcomes	CAR for wks 9 - 48
Starting date	October 2009
Contact information	Patrick Mercie
Notes	

NCT00921388

Trial name or title	Exercise or relaxation for smoking cessation
Methods	Open-label parallel-group efficacy RCT
Participants	364 postmenopausal (aged 45+) women smokers, 10+ CPD, motivated to quit and to exercise
Interventions	Varenicline + counselling + exercise programme vs varenicline + counselling + relaxation programme
Outcomes	Abstinence at wks 12 and 64
Starting date	March 2009
Contact information	Cheryl Oncken
Notes	

NCT00931021

Trial name or title	Smoking cessation treatment for head and neck cancer patients
Methods	Randomised open-label trial
Participants	30 smokers diagnosed with head and neck cancer
Interventions	Varenicline 1.0 mg x 2/day vs 21 mg nicotine patch for 8 weeks
Outcomes	CAR at wks 5 - 8

NCT00931021 (*Continued*)

Starting date	July 2009
Contact information	Benjamin Toll
Notes	

NCT00937235

Trial name or title	Treatment of smoking among individuals with PTSD
Methods	Single-blind parallel-group RCT
Participants	166 treatment-seeking smokers, aged 18 - 75, ≥ 10 CPD, diagnosed with chronic PTSD
Interventions	Varenicline + SC counselling + CBT vs varenicline + SC counselling
Outcomes	7-day PPA at end of treatment and at 6m
Starting date	January 2009
Contact information	Edna B Foa
Notes	

NCT00943618

Trial name or title	Effectiveness of varenicline vs. varenicline plus bupropion or placebo for smoking cessation
Methods	Randomised triple-blind placebo-controlled trial
Participants	350 adult smokers
Interventions	(Varenicline + bupropion) vs (varenicline + placebo) vs double placebo, for 12 weeks
Outcomes	Quit rate at 12 weeks
Starting date	May 2010
Contact information	Paul Cinciripini
Notes	

NCT01067612

Trial name or title	Extended treatment for smoking cessation
Methods	Randomised open-label trial
Participants	400 adult smokers
Interventions	10-wk open-label phase of CBT + bupropion and NRT; those still smoking at 10 wks will be switched to 16 wks of varenicline. All will get CBT to 26 wks
Outcomes	Smoking abstinence at 52 and 104 wks
Starting date	March 2010
Contact information	Joel D Killen
Notes	

NCT01093937

Trial name or title	Varenicline for smoking cessation/reduction in patients with bipolar disorder
Methods	Randomised placebo-controlled quadruple-blind trial
Participants	30 adult smokers with bipolar disorder
Interventions	Varenicline flexible dosing (0.5 to 2.0 mg/day) vs placebo for 10 weeks. All get group CBT
Outcomes	Smoking cessation and safety at 10 weeks
Starting date	November 2009
Contact information	Tony George
Notes	

NCT01162239

Trial name or title	Maintaining nonsmoking
Methods	Open-label 4-arm randomised trial
Participants	271 adult smokers (5+ CPD), who have all completed 12-wk course of varenicline + counselling
Interventions	After treatment, participants are randomised to: 1. Extended brief contact, or 2. Extended health education, or 3. Extended relapse prevention + varenicline, or

NCT01162239 (*Continued*)

	4. Extended relapse prevention
Outcomes	Smoking status at 12, 24, 52, 64 and 104 wks
Starting date	May 2010
Contact information	Not named (U of California, San Francisco)
Notes	

NCT01170338

Trial name or title	Safety and efficacy of varenicline in patients with acute coronary syndrome
Methods	Randomised placebo-controlled double-blind trial
Participants	100 adult smokers with acute coronary syndrome
Interventions	Varenicline 100 [sic] mg bid
Outcomes	Nicotine levels at 1 month; recurrent myocardial ischaemia
Starting date	January 2008
Contact information	Marc Cohen
Notes	

NCT01243203

Trial name or title	Smoking cessation program in the preadmission clinic: the use of a teachable moment
Methods	Double-blind parallel-group RCT
Participants	300 smokers scheduled for elective surgery, aged 18+, smoking 10+ CPD
Interventions	Varenicline vs placebo
Outcomes	Abstinence at 24 and 52 wks
Starting date	November 2007
Contact information	Francis Chung
Notes	

NCT01286584

Trial name or title	Varenicline in residential treatment (ViRT)
Methods	Phase IV randomised triple-blind controlled trial
Participants	50 smokers undergoing inpatient treatment for alcohol dependence
Interventions	Varenicline 1 mg x 2/day for 12 weeks vs placebo
Outcomes	Abstinence at end of treatment and 30-day CAR at 6m
Starting date	June 2011
Contact information	Laurie Zawertailo
Notes	

NCT01312909

Trial name or title	Smoking cessation study in healthy adolescent smokers
Methods	Phase IV randomised triple-blind placebo-controlled trial
Participants	300 healthy adolescents (12 - 19 yrs) smoking at least 5 CPD, with at least 1 failed quit attempt
Interventions	Varenicline 1 mg x 2/day vs varenicline 0.5 mg x 2/day vs placebo
Outcomes	CAR at weeks 9 - 12, 9 - 24, 9 - 52; 7-day PPA at wks 12, 24, 52; CPD reduction
Starting date	April 2011
Contact information	Pfizer Inc
Notes	

NCT01314001

Trial name or title	Pharmacogenetics of nicotine addiction treatment
Methods	Phase III randomised triple-blind placebo-controlled trial
Participants	1350 adult smokers, stratified by nicotine metabolite ratio (NMR)
Interventions	Varenicline 1 mg x 2/day + placebo patch vs NRT patch + placebo pills vs placebo pills + placebo patch
Outcomes	7-day PPA at 11 weeks, CAR at 11 weeks, cost effectiveness, time to relapse
Starting date	January 2011

NCT01314001 (*Continued*)

Contact information	Caryn Lerman
Notes	

NCT01320462

Trial name or title	Smoking cessation program in the preadmission clinic: the combination of counseling, pharmacotherapy and quit line
Methods	Randomised open-label controlled trial
Participants	296 adult smokers scheduled for elective surgery
Interventions	Counselling + 12 weeks varenicline + proactive telephone support, vs standard care (brief information + smokers help line)
Outcomes	4-wk CAR at 4, 12, 24 and 52 weeks; 24 hr PPA
Starting date	December 2010
Contact information	Francis Chung
Notes	

NCT01387425

Trial name or title	Efficacy and safety of smoking cessation with varenicline tartrate in diabetic smokers (DIASMOKE)
Methods	Randomised double-blind placebo-controlled trial
Participants	300 adult smokers with type 2 diabetes
Interventions	Varenicline 1 mg x 2/day for 12 weeks vs placebo
Outcomes	CAR at week 24; safety; CAR at week 52; adverse events
Starting date	June 2011
Contact information	Riccardo Polosa
Notes	

NCT01413516

Trial name or title	Varenicline inpatient study [VIP]
Methods	Double-blind parallel-group RCT
Participants	80 (40m, 40f) smokers hospitalised, 10+ CPD, with admission of at least 3 days
Interventions	Varenicline + counselling vs placebo + counselling
Outcomes	7-day PPA after 4 wks of treatment
Starting date	August 2011
Contact information	Judith J Prochaska
Notes	

NCT01509547

Trial name or title	Varenicline for adolescent smoking cessation
Methods	Double-blind parallel-group RCT
Participants	166 adolescents aged 14 - 21, daily smoker for 6+ months, motivated to quit and failed at least 1 quit attempt
Interventions	Varenicline vs placebo for 12 wks
Outcomes	Self-reported CPD; CO-validated smoking status at 26 wks; adverse events
Starting date	August 2012
Contact information	Kevin M Gray
Notes	

NCT01531049

Trial name or title	Smoking habits and smoking cessation in young adults
Methods	Single-blind 4-arm parallel-group RCT
Participants	300 young adults (18 - 26), smoking at least 1 CPD
Interventions	Varenicline, 10 mg nicotine patch, 15 mg nicotine patch, placebo
Outcomes	CAR at 12m
Starting date	May 2012

NCT01531049 (*Continued*)

Contact information	Tuula Toljamo
Notes	

NCT01532232

Trial name or title	Tobacco dependence in beast cancer patients trial of varenicline (Chantix)
Methods	Double-blind parallel-group RCT
Participants	30 women smokers diagnosed with breast cancer, scheduled for mastectomy and breast reconstruction
Interventions	Varenicline + counselling vs placebo + counselling
Outcomes	PPA and CA at 2 yrs
Starting date	February 2012
Contact information	Jamie Ostroff
Notes	

NCT01538394

Trial name or title	Clinical trial to evaluate the efficacy of smoking cessation (COMBIVAR)
Methods	Double-blind parallel-group RCT
Participants	Adult smokers (18 - 65), smoking 20+ CPD
Interventions	Varenicline + nicotine patches versus varenicline + placebo patches
Outcomes	CAR at wk 12, 24, 36. 52; safety
Starting date	February 2012
Contact information	Josep Maria Ramon Torrell
Notes	Will be excluded, as intervention being tested is nicotine patches

NCT01553136

Trial name or title	Varenicline treatment of alcohol dependence in smokers
Methods	Double-blind parallel-group RCT
Participants	Smokers seeking treatment for alcohol dependence
Interventions	Varenicline versus placebo, 16 weeks
Outcomes	Primarily N of drinking days, but also self-reported abstinence in the last month of treatment
Starting date	February 2012
Contact information	SS O'Malley
Notes	May be excluded, as primarily about alcohol abuse

NCT01574703

Trial name or title	Study to evaluate cardiac assessments following different treatments of smoking cessation medications in subjects with and without psychiatric disorders [CATS]
Methods	Double-blind 4-arm parallel-group RCT
Participants	6800 adult smokers, 10+ CPD, motivated to quit; Neuropsychiatric subgroup must have 'proper diagnosis as outlined in protocol'
Interventions	Placebo, varenicline, NRT patch, bupropion
Outcomes	1. Time to major adverse cardiac event (MACE) up to 52 wks 2. Abstinence at wk 12, 24
Starting date	May 2012
Contact information	Pfizer,GSK
Notes	

NCT01592695

Trial name or title	Tailored tobacco quitline for rural veterans
Methods	Double-blind parallel-group RCT
Participants	50 adult smokers, rural-dwelling veterans
Interventions	Tailored behavioural and pharmacotherapy group vs Enhanced standard of care + pharmacotherapy group

NCT01592695 (*Continued*)

Outcomes	Treatment satisfaction; 7-day PPA and PA at 6m
Starting date	June 2012
Contact information	Mark VanderWeg
Notes	

NCT01623505

Trial name or title	Reducing cardiovascular disease by combining smoking cessation pharmacotherapy and behavioural counseling (RW)
Methods	Open-label parallel-assignment RCT
Participants	Adult smokers, 10+ CPD
Interventions	Nicotine patch versus nicotine patch + gum or inhaler versus varenicline
Outcomes	CO-confirmed CAR at 10, 22 and 52 weeks
Starting date	July 2011
Contact information	Heather Tulloch
Notes	May be related to Tulloch 2014

NCT01639560

Trial name or title	Varenicline for light smokers (ChanLight)
Methods	Double-blind parallel-group RCT
Participants	Adult smokers, smoking 5 - 10 CPD for last 6m
Interventions	Varenicline versus placebo
Outcomes	Abstinence at 12 weeks (end of treatment)
Starting date	July 2012
Contact information	Jon Ebbert
Notes	

NCT01694732

Trial name or title	Efficacy of varenicline on smoking cessation at the acute phase of an exacerbation of chronic obstructive pulmonary disease (SAVE)
Methods	Double-blind parallel-group RCT
Participants	276 adult patients hospitalised with acute COPD, smoking 10+ CPD, motivated to quit
Interventions	Varenicline + counselling vs placebo + counselling
Outcomes	Abstinence at 1 yr; side effects and tolerance at 3m
Starting date	August 2012
Contact information	Francis Couturaud
Notes	

NCT01710137

Trial name or title	Varenicline for nicotine dependence among those with HIV/AIDS
Methods	Double-blind parallel-group RCT
Participants	350 adult smokers diagnosed with HIV, 5+ CPD
Interventions	Varenicline + counselling vs placebo + counselling
Outcomes	7-day PPA and CA cotinine-confirmed at 24 wks
Starting date	October 2012
Contact information	Robert A Schnoll
Notes	

NCT01756885

Trial name or title	Extended varenicline treatment for smoking among cancer patients
Methods	Double-blind parallel-group RCT
Participants	400 adult smokers with a current or last 5 years cancer diagnosis, 5+ CPD
Interventions	24 wks varenicline + counselling vs 12 wks varenicline + 12 wks placebo + counselling
Outcomes	7-day PPA, CA, PA CO-verified at wk 24, wk 52

NCT01756885 (*Continued*)

Starting date	January 2013
Contact information	
Notes	

NCT01771627

Trial name or title	Varenicline or nicotine patch in promoting smoking cessation among current smokers
Methods	Open-lable parallel-group RCT
Participants	300 adult smokers calling quitline
Interventions	Varenicline + counselling vs nicotine patch + counselling
Outcomes	4m quit rate
Starting date	October 2012
Contact information	Martin Mahoney
Notes	

NCT01772641

Trial name or title	A smoking intervention study using scheduled gradual reduction with varenicline to help with cessation
Methods	Double-blind factorial RCT
Participants	192 adult smokers, 10+ CPD
Interventions	4-wk scheduled gradual reduction programme + varenicline vs 4-wk scheduled gradual reduction programme + placebo
Outcomes	PA at 4, 12 wks
Starting date	December 2012
Contact information	Joel Erblich
Notes	

NCT01800019

Trial name or title	The Canadian HIV Quit Smoking Trial: tackling the co-morbidities of depression and cardiovascular disease in HIV+ smokers (CANQUIT)
Methods	Open-label 4-arm factorial RCT
Participants	256 adults HIV+ smokers, 5+ CPD, willing to set a quit date
Interventions	NRT, NRT + HIV-tailored quit smoking counselling, varenicline, varenicline + HIV-tailored quit smoking counselling
Outcomes	7-day PPA and 4-wk CA at wk 48, CO-verified
Starting date	January 2014
Contact information	
Notes	

NCT01850953

Trial name or title	Varenicline lapse study
Methods	Double-blind cross-over RCT
Participants	50 adult smokers, 10+ CPD, not trying to quit, with schizophrenia or schizoaffective disorder; controls not on psychotropic meds or diagnosed with any Axis 1 disorder
Interventions	Varenicline vs placebo
Outcomes	Time to lapse
Starting date	June 2013
Contact information	Tony George
Notes	

NCT01892813

Trial name or title	Dissemination of a tailored tobacco quitline for rural veteran smokers
Methods	Double-blind parallel-group RCT
Participants	500 adult veteran daily smokers, willing to try to quit
Interventions	Tailored intervention (behavioural and meds) vs Enhanced standard of care

NCT01892813 (*Continued*)

Outcomes	7-day and 30-day PPA at 6m
Starting date	July 2013
Contact information	Mark W Vander Weg
Notes	

NCT01898195

Trial name or title	Improving adherence to smoking cessation medication among PLWHA (HIV)
Methods	Open-label RCT
Participants	220 adult HIV+ smokers, 5+ CPD, willing to quit
Interventions	Varenicline (standard care), vs varenicline: text messages + adherence behavioural therapy
Outcomes	Adherence to treatment; abstinence at wks 1, 4, 8, EoT, 3m
Starting date	March 2013
Contact information	Donna Shelley
Notes	

NCT02048917

Trial name or title	Smoking cessation strategies in community cancer programs for lung and head and neck cancer patients
Methods	Open-label 12-arm RCT
Participants	180 adult smoking patients with current lung, head and neck cancer diagnosis, smoked at least 1 cigarette within 4 wks of enrolment
Interventions	High vs low intensity counselling, long-acting vs PRN NRT, bupropion, varenicline in various combinations
Outcomes	7-day CO-confirmed PPA at 8 wks
Starting date	July 2014
Contact information	Joseph Valentino
Notes	May be too short

NCT02106637

Trial name or title	Early in-hospital initiation of pharmacotherapy for smoking cessation, Patients after ACS
Methods	Double-blind parallel-group RCT
Participants	300 adult smokers with ACS
Interventions	Varenicline vs placebo
Outcomes	CAR at 1m, 6m, 1 yr after hospitalisation; SAE rate
Starting date	June 2014
Contact information	Haim Lotan
Notes	

NCT02136498

Trial name or title	Internet-based medication adherence program for nicotine dependence treatment
Methods	Double-blind parallel-group RCT
Participants	70 adult members of Group Health insurance, smoking 10+ CPD, motivated to quit, smart phone access
Interventions	Online self help + varenicline vs augmented online self help + varenicline
Outcomes	7-day PPA at 5m
Starting date	October 2014
Contact information	Sherryl Catz, Larry An
Notes	

NCT02146911

Trial name or title	The MATCH (medication aids for tobacco cessation) Study
Methods	Open-label RCT
Participants	1500 adult smokers, 10+ CPD, motivated to quit
Interventions	Bupropion + weekly motivational emails vs varenicline + weekly motivational emails
Outcomes	CA at 12, 26, 52 wks
Starting date	May 2014

NCT02146911 (*Continued*)

Contact information	Laurie Zawertailo
Notes	

NCT02147132

Trial name or title	Pilot study of nicotine nasal spray and varenicline on smoking in methadone-maintained patients
Methods	Double-blind 4-arm cross-over RCT
Participants	20 adult smokers on methadone maintenance, 10+ CPD
Interventions	Nasal spray (active and placebo), varenicline (active and placebo), taken in different orders
Outcomes	Proportion of CPD taken within 4 hours of receiving methadone dose; abstinence, CO-verified
Starting date	December 2014
Contact information	Theresa Winhusen
Notes	

NCT02162849

Trial name or title	Reward sensitivity and pharmacotherapy for smoking cessation
Methods	Double-blind parallel-group RCT
Participants	90 adults smokers, 5+ CPD,
Interventions	Varenicline + placebo patch vs nicotine patch + placebo tablet; all get behavioural counselling
Outcomes	CAR at EoT, 3m, 6m
Starting date	April 2015
Contact information	Paul Cinciripini
Notes	

NCT02271919

Trial name or title	Varenicline and combined nicotine replacement therapy (NRT) for smoking cessation
Methods	Double-blind 5-arm cross-over RCT
Participants	310 adult smokers, 5+ CPD
Interventions	Varenicline vs nicotine patch + lozenge vs extra tablets or patches vs switch to different therapy vs extra tablet or patch
Outcomes	7-day PPA at 12 wks
Starting date	May 2015
Contact information	Paul Cinciripini
Notes	

NCT02328794

Trial name or title	Randomised clinical trial to reduce harm from tobacco
Methods	Single-blind parallel-group RCT
Participants	6000 adult smokers, Vitality beneficiaries
Interventions	Standardised Vitality program vs Vitality + choice of e-cigarette/varenicline/bupropion/NRT vs Vitality + choice of meds + deposit-refund programme
Outcomes	CO-verified abstinence at 6m, 12m
Starting date	January 2015
Contact information	Scott Halpern
Notes	

NCT02351167

Trial name or title	Genetically informed smoking cessation trial
Methods	Double-blind 3-arm parallel-group RCT
Participants	720 adults, 5+ CPD, motivated to quit smoking
Interventions	NRT + counselling vs varenicline + counselling vs combination NRT + counselling
Outcomes	7-day PPA at wk 12, wk 24

NCT02351167 (*Continued*)

Starting date	May 2015
Contact information	Li-Shiun Chen
Notes	

NCT02360631

Trial name or title	Advancing tobacco use treatment for African-American smokers (KIS-IV)
Methods	Double-blind parallel-group RCT
Participants	500 adult A-A smokers, 5+ CPD, motivated to quit
Interventions	Varenicline vs placebo
Outcomes	7-day PPA at 6m
Starting date	April 2015
Contact information	Lisa Sanderson Cox
Notes	

NCT02367391

Trial name or title	Penn State TXT2Quit study
Methods	Single-blind parallel-group RCT
Participants	150 adult smokers, 4+ CPD, motivated to quit
Interventions	Varenicline + motivation text messages vs varenicline alone
Outcomes	7-day PPA CO-verified at wk 12
Starting date	January 2015
Contact information	Jonathan Foulds
Notes	

Reid 2010

Trial name or title	Varenicline versus transdermal nicotine patch for smoking cessation in patients with coronary heart disease
Methods	Randomised open-label trial
Participants	60 adult smokers
Interventions	Varenicline or NRT patch for 12 weeks
Outcomes	CO-confirmed CAR for wks 12 - 26
Starting date	April 2009
Contact information	Robert Reid
Notes	

Rohsenow 2015

Trial name or title	Varenicline helps smokers with SUD stop smoking without harming recovery
Methods	Randomised quadruple-blind placebo-controlled trial
Participants	274 adult smokers with substance use disorders
Interventions	Varenicline vs NRT patches for 12 weeks, plus motivational advice
Outcomes	7-day PPA at 3, 6 and 12m
Starting date	
Contact information	Damaris_Rohsenow@brown.edu
Notes	New for 2016 update; extraction based on Powerpoint slides in 137 participants

Smith 2013b

Trial name or title	Varenicline for cognitive deficits and cigarette smoking in schizophrenia
Methods	Randomised double-blind placebo-controlled trial
Participants	60 adult smokers with schizophrenia
Interventions	Varenicline 1 - 2 mg/day vs placebo
Outcomes	Cotinine-verified cessation, + Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), Positive and Negative Syndrome Scale (PANNS), Hamilton Depression Scale

Smith 2013b (*Continued*)

Starting date	September 2008
Contact information	RC Smith
Notes	

Tulloch 2014

Trial name or title	Flexible and extended dosing of nicotine replacement therapy or varenicline in comparison to fixed dose nicotine replacement therapy for smoking cessation: the FLEX trial
Methods	Randomised controlled trial
Participants	737 adult smokers
Interventions	NRT vs combination NRT vs varenicline
Outcomes	CAR wks 5 - 52, + neuropsychiatric and withdrawal symptoms
Starting date	
Contact information	hetulloch@ottawaheart.ca
Notes	New for 2016 update

Van Rossem 2015

Trial name or title	Helping more smokers to quit by combining varenicline with counselling for smoking cessation. The COV-ACO randomized controlled trial
Methods	Open-label RCT
Participants	295 primary-care smoking patients, no minimum CPD
Interventions	Varenicline + brief GP advice vs varenicline + PN or GP extended counselling
Outcomes	PA at wk 52
Starting date	
Contact information	C van Rossem
Notes	

This list does not include all registered studies of varenicline, dianicline and cytisine. It covers only those studies expected to be eventual candidates for inclusion within future updates of this review, i.e. RCTs of smoking cessation interventions with a minimum follow-up of six months, or for shorter duration if safety issues are the main outcome.

ACS: acute coronary syndrome

CAR: continuous abstinence rate

COPD: chronic obstructive pulmonary disease

CPD: cigarettes per day

CQR: continuous quit rate

MI: motivational interviewing

PLWHA: people living with HIV/AIDS

PN: psychiatric nurse

PPA: point prevalence abstinence

PTSD: post-traumatic stress disorder

TAU: treatment as usual

DATA AND ANALYSES

Comparison 1. Cytisine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CAR at longest follow-up	2	937	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [2.01, 7.87]
2 Point prevalence abstinence at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 2. Cytisine vs NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous abstinence at 6m	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 3. Dianicline vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CAR at weeks 4 - 26	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Varenicline (1.0 mg 2/d) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous or sustained abstinence at longest follow-up (24+ weeks)	27	12625	Risk Ratio (M-H, Fixed, 95% CI)	2.24 [2.06, 2.43]
2 Abstinence at six months	25	12304	Risk Ratio (M-H, Fixed, 95% CI)	2.25 [2.08, 2.44]
3 Abstinence for long-term use (up to 52 weeks) of varenicline	4	2170	Risk Ratio (M-H, Fixed, 95% CI)	3.64 [2.81, 4.72]

Comparison 5. Varenicline vs bupropion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Varenicline vs bupropion at 6m	5	5877	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.25, 1.54]
2 Continuous abstinence at 52 weeks	3	1618	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.22, 1.88]
3 Varenicline vs bupropion at 3m	5	5877	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [1.35, 1.58]

Comparison 6. Varenicline vs NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Point prevalence abstinence at 24 weeks	8	6264	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.14, 1.37]

Comparison 7. Variations in usage

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Flexible quit date	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Non-standard dose varenicline versus placebo at 52 weeks	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low-dose varenicline vs placebo at 52 weeks	4	1266	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.56, 2.78]
2.2 Variable dosage at participant's or physician's discretion	6	1789	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.81, 2.89]
3 Standard dose varenicline versus low dose at 52 weeks	3	1079	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.55]
4 Standard dose varenicline versus high dose at 12 weeks	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.54, 1.44]
5 Reducing to quit	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Varenicline as maintenance therapy (relapse prevention) to sustain quitting	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Abstinence at 52 weeks	2	1295	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.08, 1.42]
6.2 Abstinence at 24 weeks	1	1210	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.29, 1.56]

Comparison 8. Varenicline in specific patient groups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiovascular disease	2	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.44, 2.47]
2 COPD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Schizophrenia/bipolar/ psychiatric disorder	4	2332	Risk Ratio (M-H, Fixed, 95% CI)	2.28 [1.82, 2.87]
5 Depression	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6 Substance use disorder/ methadone-maintained at 24 weeks	2	294	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [0.50, 27.59]
7 Alcohol-dependent smokers	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
8 Long-term use of NRT	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 9. Varenicline in different settings/subgroups

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital inpatients/perioperative patients	3	744	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [1.09, 1.77]
2 Smokers who have failed on other cessation therapies	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Light or heavy smokers	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 10. Adverse event meta-analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	32	14963	Risk Ratio (M-H, Fixed, 95% CI)	3.27 [3.00, 3.55]
2 Insomnia	29	14447	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [1.35, 1.65]
3 Abnormal dreams	26	13682	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.88, 2.38]
4 Headache	25	13835	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [1.07, 1.29]
5 Depression	36	16189	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.77, 1.14]
6 Suicidal ideation	24	11193	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.07]

Comparison 11. Serious adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 SAEs in the varenicline trials	29	15370	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.04, 1.49]
2 SAEs in the varenicline trials, exc post-treat events	26	15000	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.02, 1.52]
3 Neuropsychiatric SAEs (not deaths)	23	8955	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.57, 1.19]
4 Cardiac SAEs, including deaths	21	8587	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.91, 2.04]

Comparison 12. Losses to follow-up

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants remaining at end of varenicline trials			Other data	No numeric data

Comparison 13. Sensitivity analysis

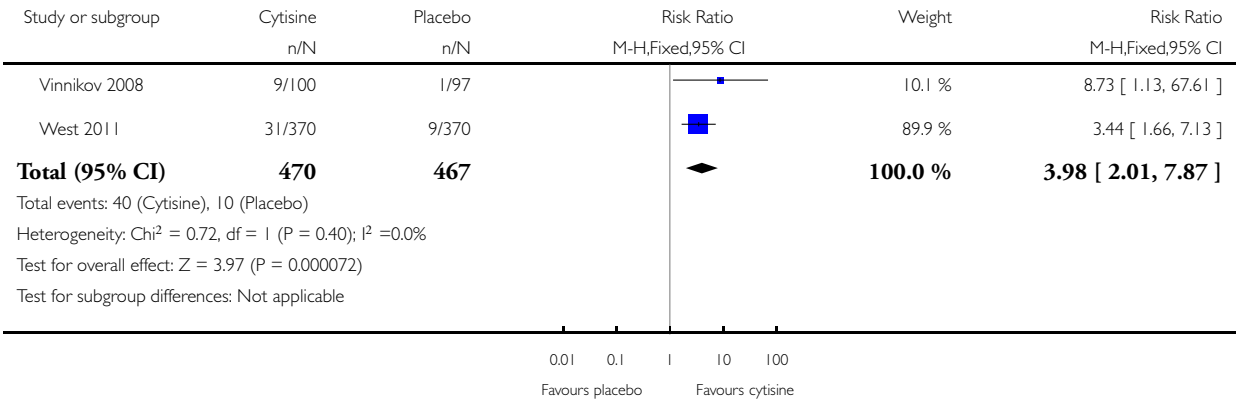
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ITT treatment vs per protocol control	28	12422	Risk Ratio (M-H, Fixed, 95% CI)	1.79 [1.65, 1.94]
2 Continuous abstinence at 9 - 12 weeks	24	12339	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [2.33, 2.65]
3 Continuous abstinence at 24 weeks	26	14016	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [2.26, 2.63]

Analysis 1.1. Comparison 1 Cytisine vs placebo, Outcome 1 CAR at longest follow-up.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Cytisine vs placebo

Outcome: 1 CAR at longest follow-up

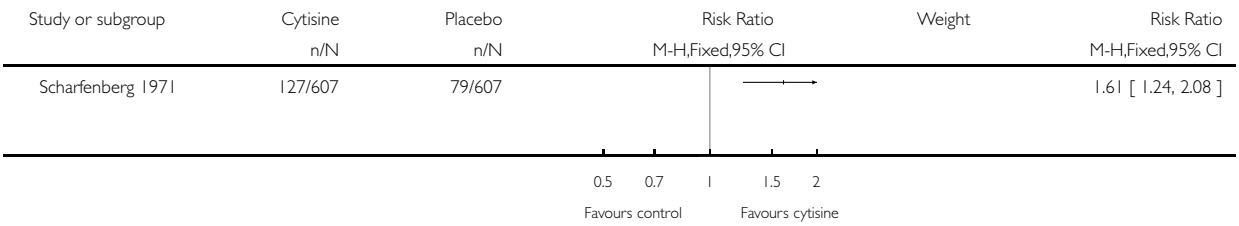


Analysis 1.2. Comparison 1 Cytisine vs placebo, Outcome 2 Point prevalence abstinence at 2 years.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Cytisine vs placebo

Outcome: 2 Point prevalence abstinence at 2 years



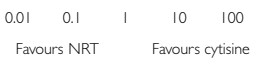
Analysis 2.1. Comparison 2 Cytisine vs NRT, Outcome 1 Continuous abstinence at 6m.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 2 Cytisine vs NRT

Outcome: 1 Continuous abstinence at 6m

Study or subgroup	Cytisine n/N	NRT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Walker 2014	143/655	100/655			1.43 [1.13, 1.80]
Test for subgroup differences: Not applicable					



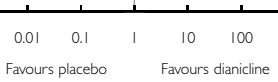
Analysis 3.1. Comparison 3 Dianicline vs placebo, Outcome 1 CAR at weeks 4 - 26.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 3 Dianicline vs placebo

Outcome: 1 CAR at weeks 4 - 26

Study or subgroup	Dianicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Tonstad 2011	50/300	42/302		1.20 [0.82, 1.75]



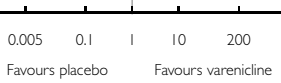
Analysis 4.1. Comparison 4 Varenicline (1.0 mg 2/d) vs placebo, Outcome 1 Continuous or sustained abstinence at longest follow-up (24+ weeks).

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 4 Varenicline (1.0 mg 2/d) vs placebo

Outcome: 1 Continuous or sustained abstinence at longest follow-up (24+ weeks)

Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
De Dios 2012 (1)	3/10	0/11		0.1 %	7.64 [0.44, 131.75]
Nahvi 2014a (2)	3/57	0/55		0.1 %	6.76 [0.36, 127.89]
Chengappa 2014	6/31	2/29		0.3 %	2.81 [0.61, 12.81]
Westergaard 2015 (3)	5/26	4/25		0.6 %	1.20 [0.36, 3.97]
Evins 2014	12/40	5/47		0.7 %	2.82 [1.09, 7.32]
Heydari 2012 (4)	29/89	6/91		0.9 %	4.94 [2.16, 11.32]
Nides 2006	18/125	6/123		0.9 %	2.95 [1.21, 7.19]
Oncken 2006	58/259	5/129		1.0 %	5.78 [2.38, 14.05]
Gonzales 2014	50/249	8/245		1.2 %	6.15 [2.98, 12.70]
NCT00828113	10/50	11/51		1.6 %	0.93 [0.43, 1.99]
Steinberg 2011 (5)	8/40	11/39		1.6 %	0.71 [0.32, 1.57]
Niaura 2008	35/160	12/160		1.7 %	2.92 [1.57, 5.41]
Cinciripini 2013	24/86	15/106		2.0 %	1.97 [1.11, 3.52]
Tashkin 2011	46/248	14/253		2.0 %	3.35 [1.89, 5.94]
Rigotti 2010	68/353	26/354		3.8 %	2.62 [1.71, 4.02]
Anthenelli 2013	52/254	28/269		3.9 %	1.97 [1.28, 3.01]
Tsai 2007	59/126	27/124		3.9 %	2.15 [1.47, 3.15]
Gonzales 2006	77/352	29/344		4.3 %	2.59 [1.74, 3.87]
Rennard 2012	171/493	21/166		4.6 %	2.74 [1.81, 4.16]
Bolliger 2011	155/394	26/199		5.0 %	3.01 [2.06, 4.40]
Nakamura 2007	56/155	35/154		5.1 %	1.59 [1.11, 2.28]
Jorenby 2006	79/344	35/341		5.1 %	2.24 [1.55, 3.24]
Wong 2012 (6)	55/151	34/135		5.2 %	1.45 [1.01, 2.07]
Carson 2014 (7)	56/190	36/189		5.2 %	1.55 [1.07, 2.23]
Eisenberg 2016	53/148	39/151		5.6 %	1.39 [0.98, 1.96]



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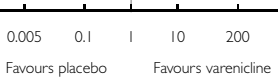
Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 2009	63/165	42/168		6.0 %	1.53 [1.10, 2.12]
EAGLES 2016 (8)	444/2037	191/2035		27.7 %	2.32 [1.98, 2.72]
Total (95% CI)	**6632**	**5993**		**100.0 %**	**2.24 [2.06, 2.43]**

Total events: 1695 (Varenicline), 668 (Control)

Heterogeneity: Chi^2 = 64.85, df = 26 (P = 0.00004); I^2 =60%

Test for overall effect: Z = 19.01 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) 7-day PPA at 6m

(2) 7-day PPA at 24 wks

(3) PPA at 24 wks

(4) PPA at 12m

(5) 7-day PPA at 24 weeks

(6) 7-day PPA at 12m

(7) 24-month follow-up

(8) Extrapolated from % reported quit

Analysis 4.2. Comparison 4 Varenicline (1.0 mg 2/d) vs placebo, Outcome 2 Abstinence at six months.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 4 Varenicline (1.0 mg 2/d) vs placebo

Outcome: 2 Abstinence at six months

Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	64/256	33/269		4.3 %	2.04 [1.39, 2.99]
Bolliger 2011	155/394	26/199		4.6 %	3.01 [2.06, 4.40]
Carson 2014	78/191	54/194		7.2 %	1.47 [1.10, 1.95]
Chengappa 2014	6/31	2/29		0.3 %	2.81 [0.61, 12.81]
Cinciripini 2013	24/86	15/106		1.8 %	1.97 [1.11, 3.52]
De Dios 2012 (1)	3/10	0/11		0.1 %	7.64 [0.44, 131.75]
EAGLES 2016 (2)	444/2037	191/2035		25.5 %	2.32 [1.98, 2.72]
Eisenberg 2016	53/148	39/151		5.2 %	1.39 [0.98, 1.96]
Gonzales 2006	104/352	36/344		4.9 %	2.82 [1.99, 4.00]
Gonzales 2014	72/249	19/245		2.6 %	3.73 [2.32, 5.99]
Jorenby 2006	102/344	45/341		6.0 %	2.25 [1.64, 3.09]
Nahvi 2014a (3)	3/57	0/55		0.1 %	6.76 [0.36, 127.89]
Nakamura 2007	63/155	44/154		5.9 %	1.42 [1.04, 1.95]
NCT01347112	4/16	0/17		0.1 %	9.53 [0.55, 164.01]
Niaura 2008	44/160	14/160		1.9 %	3.14 [1.80, 5.50]
Nides 2006	26/125	9/123		1.2 %	2.84 [1.39, 5.82]
Oncken 2006	75/259	7/129		1.2 %	5.34 [2.53, 11.24]
Rennard 2012	171/493	21/166		4.2 %	2.74 [1.81, 4.16]
Rigotti 2010	100/353	34/359		4.5 %	2.99 [2.09, 4.29]
Steinberg 2011 (4)	8/40	11/39		1.5 %	0.71 [0.32, 1.57]
Tashkin 2011	64/248	18/254		2.4 %	3.64 [2.22, 5.96]
Tsai 2007 (5)	59/126	27/124		3.6 %	2.15 [1.47, 3.15]
Wang 2009	63/165	42/168		5.6 %	1.53 [1.10, 2.12]
Westergaard 2015 (6)	5/26	4/25		0.5 %	1.20 [0.36, 3.97]
Wong 2012 (7)	54/151	35/135		4.9 %	1.38 [0.97, 1.97]
Total (95% CI)	**6472**	**5832**		**100.0 %**	**2.25 [2.08, 2.44]**

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Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 1844 (Varenicline), 726 (Control)					
Heterogeneity: Chi² = 71.43, df = 24 (P<0.00001); I² =66%					
Test for overall effect: Z = 20.20 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) 7-day PPA

(2) Extrapolated from % reported quit

(3) 7-day PPA

(4) 7-day PPA

(5) Extrapolated from graphical data

(6) 7-day PPA

(7) 7-day PPA

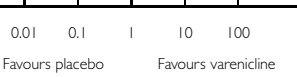
Analysis 4.3. Comparison 4 Varenicline (1.0 mg 2/d) vs placebo, Outcome 3 Abstinence for long-term use (up to 52 weeks) of varenicline.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 4 Varenicline (1.0 mg 2/d) vs placebo

Outcome: 3 Abstinence for long-term use (up to 52 weeks) of varenicline

Study or subgroup	varenicline n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ebbert 2015 (1)	182/760	45/750		65.7 %	3.99 [2.93, 5.44]
NCT00828113 (2)	10/50	11/51		15.8 %	0.93 [0.43, 1.99]
Stein 2013 (3)	2/137	0/45		1.1 %	1.67 [0.08, 34.08]
Williams 2007 (4)	88/251	9/126		17.4 %	4.91 [2.56, 9.42]
Total (95% CI)	**1198**	**972**		**100.0 %**	**3.64 [2.81, 4.72]**
Total events: 282 (varenicline), 65 (placebo)					
Heterogeneity: Chi² = 13.77, df = 3 (P = 0.003); I² =78%					
Test for overall effect: Z = 9.78 (P < 0.00001)					
Test for subgroup differences: Not applicable					



(1) 24 wks of treatment; PPA

(2) PPA at 52 wks (52 wks treatment)

(3) 24 wks of treatment

(4) 52 wks of treatment

Analysis 5.1. Comparison 5 Varenicline vs bupropion, Outcome 1 Varenicline vs bupropion at 6m.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 5 Varenicline vs bupropion

Outcome: 1 Varenicline vs bupropion at 6m

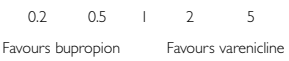
Study or subgroup	Varenicline n/N	Bupropion n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cinciripini 2013	24/86	23/102		4.2 %	1.24 [0.75, 2.03]
EAGLES 2016 (1)	444/2037	330/2034		65.6 %	1.34 [1.18, 1.53]
Gonzales 2006	104/352	68/329		14.0 %	1.43 [1.10, 1.87]
Jorenby 2006	102/344	69/342		13.7 %	1.47 [1.13, 1.92]
Nides 2006	26/125	13/126		2.6 %	2.02 [1.09, 3.74]
Total (95% CI)	**2944**	**2933**		**100.0 %**	**1.39 [1.25, 1.54]**

Total events: 700 (Varenicline), 503 (Bupropion)

Heterogeneity: $Chi^2 = 2.08$, df = 4 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 6.25 (P < 0.00001)

Test for subgroup differences: Not applicable



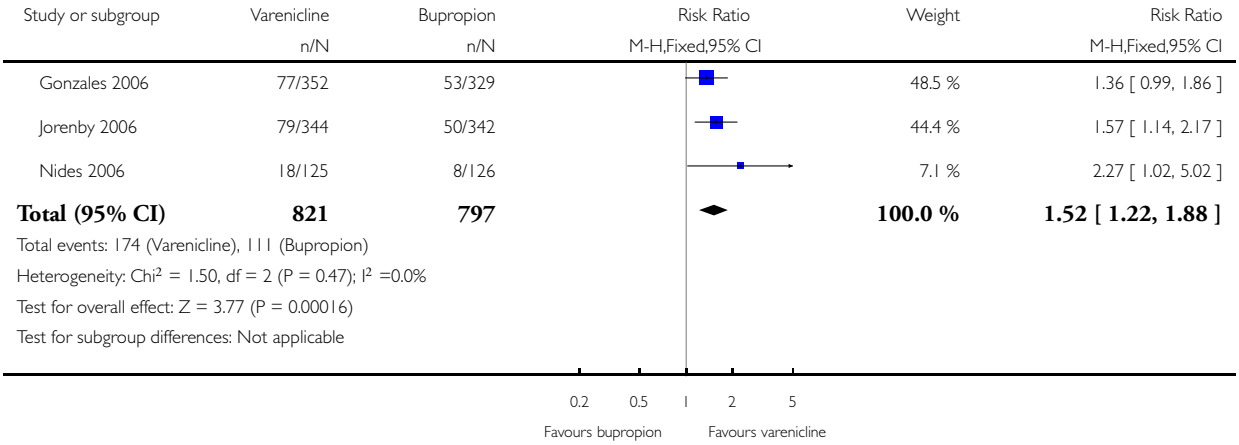
(1) Extrapolated from % reported quit

Analysis 5.2. Comparison 5 Varenicline vs bupropion, Outcome 2 Continuous abstinence at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 5 Varenicline vs bupropion

Outcome: 2 Continuous abstinence at 52 weeks



Analysis 5.3. Comparison 5 Varenicline vs bupropion, Outcome 3 Varenicline vs bupropion at 3m.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 5 Varenicline vs bupropion

Outcome: 3 Varenicline vs bupropion at 3m

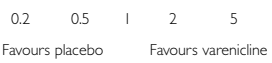
Study or subgroup	Varenicline n/N	Bupropion n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cinciripini 2013	34/86	36/102		4.6 %	1.12 [0.77, 1.62]
EAGLES 2016 (1)	682/2037	460/2034		63.9 %	1.48 [1.34, 1.64]
Gonzales 2006	155/352	97/329		13.9 %	1.49 [1.22, 1.83]
Jorenby 2006	151/344	102/342		14.2 %	1.47 [1.20, 1.80]
Nides 2006	36/125	25/126		3.5 %	1.45 [0.93, 2.27]
Total (95% CI)	**2944**	**2933**		**100.0 %**	**1.46 [1.35, 1.58]**

Total events: 1058 (Varenicline), 720 (Bupropion)

Heterogeneity: $Chi^2 = 2.09$, df = 4 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 9.39 (P < 0.00001)

Test for subgroup differences: Not applicable



(1) Extrapolated from % reported quit

Analysis 6.1. Comparison 6 Varenicline vs NRT, Outcome 1 Point prevalence abstinence at 24 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 6 Varenicline vs NRT

Outcome: 1 Point prevalence abstinence at 24 weeks

Study or subgroup	Varenicline n/N	NRT n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Aubin 2008 (1)	145/376	126/370		21.5 %	1.13 [0.94, 1.37]
Baker 2016	100/424	55/241		11.9 %	1.03 [0.77, 1.38]
De Dios 2012	3/10	0/11		0.1 %	7.64 [0.44, 131.75]
EAGLES 2016 (2)	444/2037	320/2038		54.1 %	1.39 [1.22, 1.58]
Heydari 2012 (3)	52/89	47/92		7.8 %	1.14 [0.88, 1.49]
Rose 2013 (4)	11/138	9/136		1.5 %	1.20 [0.52, 2.81]
Stein 2013	5/137	11/133		1.9 %	0.44 [0.16, 1.24]
Tsukahara 2010 (5)	7/16	7/16		1.2 %	1.00 [0.46, 2.19]
Total (95% CI)	**3227**	**3037**		**100.0 %**	**1.25 [1.14, 1.37]**

Total events: 767 (Varenicline), 575 (NRT)

Heterogeneity: Chi^2 = 11.44, df = 7 (P = 0.12); I^2 =39%

Test for overall effect: Z = 4.70 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Open-label, unblinded

(2) CAR at 24 weeks; extrapolated from % reported quit

(3) Open-label, unblinded

(4) Rescue treatments for non-responders or relapsers, Phases 1 and 2 combined

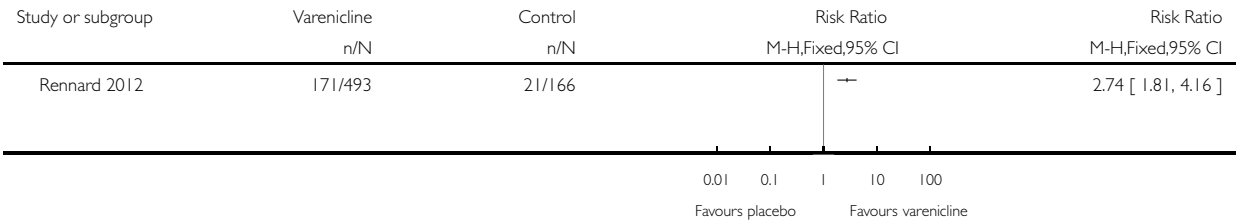
(5) Open-label, unblinded

Analysis 7.1. Comparison 7 Variations in usage, Outcome 1 Flexible quit date.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 1 Flexible quit date

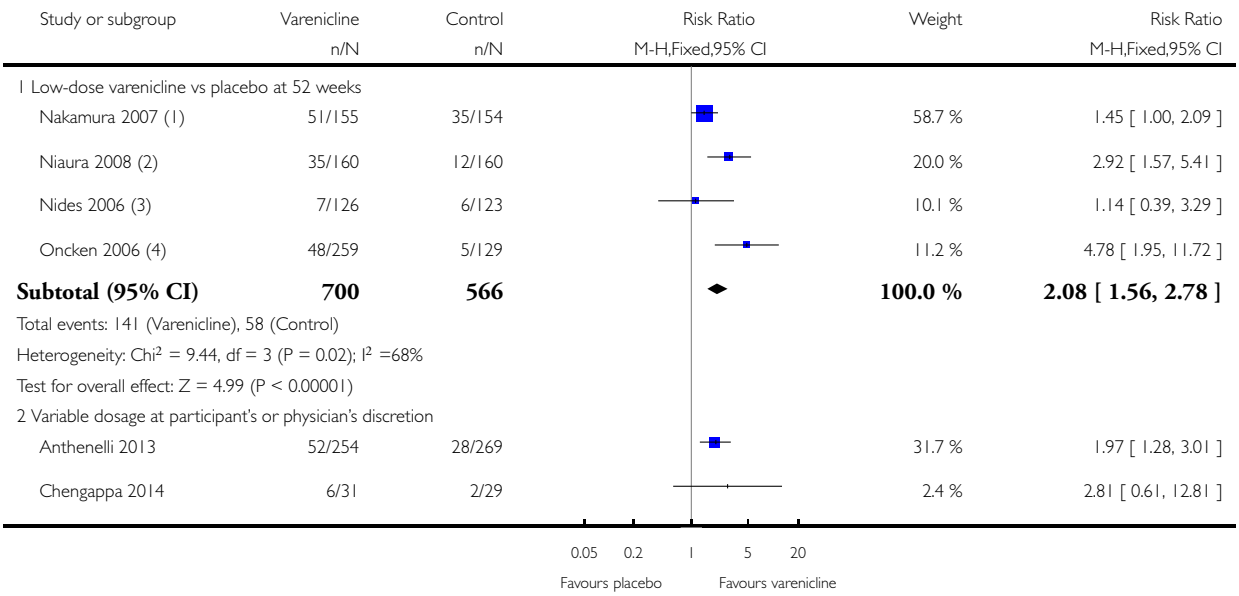


Analysis 7.2. Comparison 7 Variations in usage, Outcome 2 Non-standard dose varenicline versus placebo at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 2 Non-standard dose varenicline versus placebo at 52 weeks



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Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cinciripini 2013	24/86	15/106		15.7 %	1.97 [1.11, 3.52]
Gonzales 2014	50/249	8/245		9.4 %	6.15 [2.98, 12.70]
Hajek 2015 (5)	26/100	23/100		26.8 %	1.13 [0.69, 1.84]
Niaura 2008	35/160	12/160		14.0 %	2.92 [1.57, 5.41]
Subtotal (95% CI)	**880**	**909**		**100.0 %**	**2.29 [1.81, 2.89]**
Total events: 193 (Varenicline), 88 (Control)					
Heterogeneity: Chi^2 = 16.58, df = 5 (P = 0.01); I^2 =70%					
Test for overall effect: Z = 6.93 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.25, df = 1 (P = 0.62), I^2 =0.0%					

(1) 0.5 mg twice a day

(2) ad lib, between 0.5 and 2.0 mg daily

(3) 1 mg once a day

(4) 0.5 mg twice a day (titrated and non-titrated combined)

(5) 12 weeks

Analysis 7.3. Comparison 7 Variations in usage, Outcome 3 Standard dose varenicline versus low dose at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 3 Standard dose varenicline versus low dose at 52 weeks

Study or subgroup	Standard dose n/N	low dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nakamura 2007 (1)	56/155	51/155		48.1 %	1.10 [0.81, 1.49]
Nides 2006 (2)	18/125	7/126		6.6 %	2.59 [1.12, 5.99]
Oncken 2006 (3)	58/259	48/259		45.3 %	1.21 [0.86, 1.70]
Total (95% CI)	**539**	**540**		**100.0 %**	**1.25 [1.00, 1.55]**

Total events: 132 (Standard dose), 106 (low dose)

Heterogeneity: $Chi^2 = 3.62$, $df = 2$ ($P = 0.16$); $I^2 = 45\%$

Test for overall effect: $Z = 1.95$ ($P = 0.051$)

Test for subgroup differences: Not applicable

(1) 1 mg twice a day vs 0.5 mg twice a day

(2) 1 mg twice a day vs 1 mg once a day

(3) 1 mg twice a day vs 0.5 mg twice a day (titrated and non-titrated combined)

Analysis 7.4. Comparison 7 Variations in usage, Outcome 4 Standard dose varenicline versus high dose at 12 weeks.

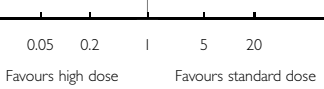
Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 4 Standard dose varenicline versus high dose at 12 weeks

Study or subgroup	Standard dose n/N	High dose n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hajek 2015 (1)	23/100	26/100		100.0 %	0.88 [0.54, 1.44]
Total (95% CI)	**100**	**100**		**100.0 %**	**0.88 [0.54, 1.44]**

Total events: 23 (Standard dose), 26 (High dose)
Heterogeneity: not applicable
Test for overall effect: Z = 0.49 (P = 0.62)
Test for subgroup differences: Not applicable



(1) 12 weeks sustained abstinence

Analysis 7.5. Comparison 7 Variations in usage, Outcome 5 Reducing to quit.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 5 Reducing to quit

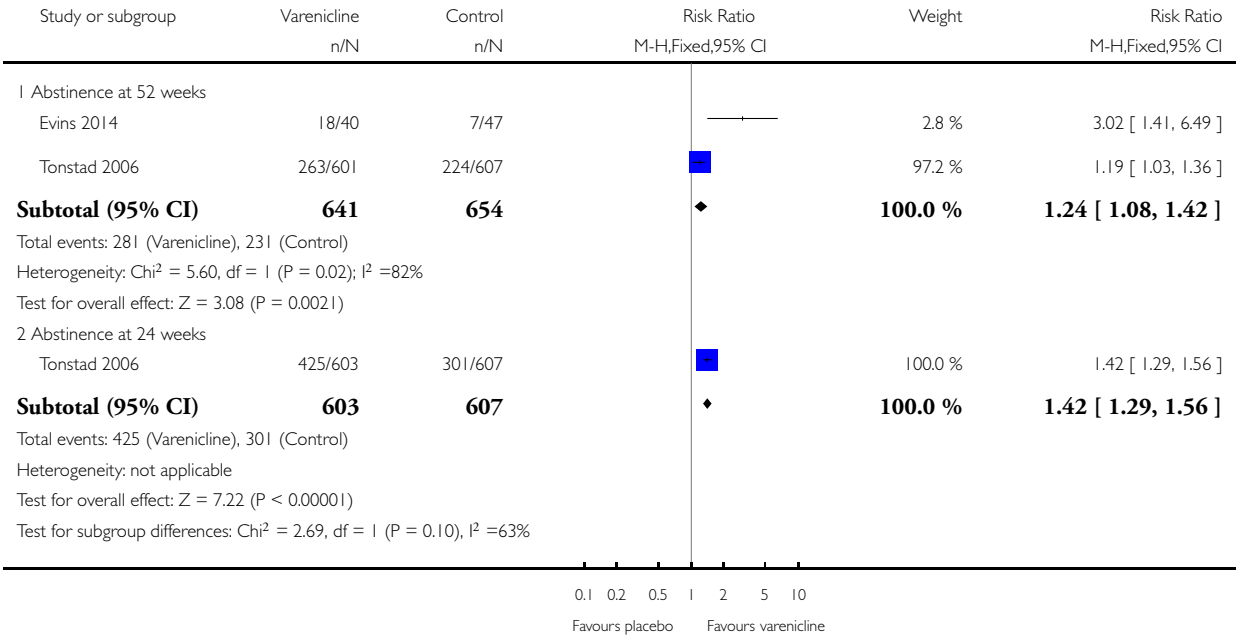
Study or subgroup	Varenicline n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Ebbert 2015	182/760	45/750		3.99 [2.93, 5.44]

Analysis 7.6. Comparison 7 Variations in usage, Outcome 6 Varenicline as maintenance therapy (relapse prevention) to sustain quitting.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Variations in usage

Outcome: 6 Varenicline as maintenance therapy (relapse prevention) to sustain quitting



Analysis 8.1. Comparison 8 Varenicline in specific patient groups, Outcome 1 Cardiovascular disease.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 1 Cardiovascular disease

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Eisenberg 2016 (1)	53/148	39/151		59.8 %	1.39 [0.98, 1.96]
Rigotti 2010 (2)	68/353	26/354		40.2 %	2.62 [1.71, 4.02]
Total (95% CI)	**501**	**505**		**100.0 %**	**1.88 [1.44, 2.47]**

Total events: 121 (Varenicline), 65 (Placebo)

Heterogeneity: $Chi^2 = 5.32$, df = 1 (P = 0.02); $I^2 = 81\%$

Test for overall effect: Z = 4.61 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) 24 wk follow-up

(2) 52 wk follow-up

Analysis 8.2. Comparison 8 Varenicline in specific patient groups, Outcome 2 COPD.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 2 COPD

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Tashkin 2011	46/248	14/253		3.35 [1.89, 5.94]

Analysis 8.3. Comparison 8 Varenicline in specific patient groups, Outcome 3 Asthma.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 3 Asthma

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Westergaard 2015	5/26	4/26		1.25 [0.38, 4.14]

Analysis 8.4. Comparison 8 Varenicline in specific patient groups, Outcome 4 Schizophrenia/bipolar/psychiatric disorder.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 4 Schizophrenia/bipolar/psychiatric disorder

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Chengappa 2014	6/31	2/29		2.2 %	2.81 [0.61, 12.81]
EAGLES 2016 (1)	188/1032	85/1026		91.4 %	2.20 [1.73, 2.80]
Evins 2014	12/40	5/47		4.9 %	2.82 [1.09, 7.32]
Williams 2012 (2)	10/84	1/43		1.4 %	5.12 [0.68, 38.69]
Total (95% CI)	**1187**	**1145**		**100.0 %**	**2.28 [1.82, 2.87]**
Total events: 216 (Varenicline), 93 (Placebo)					
Heterogeneity: Chi^2 = 0.97, df = 3 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 7.05 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) Extrapolated from % reported quit

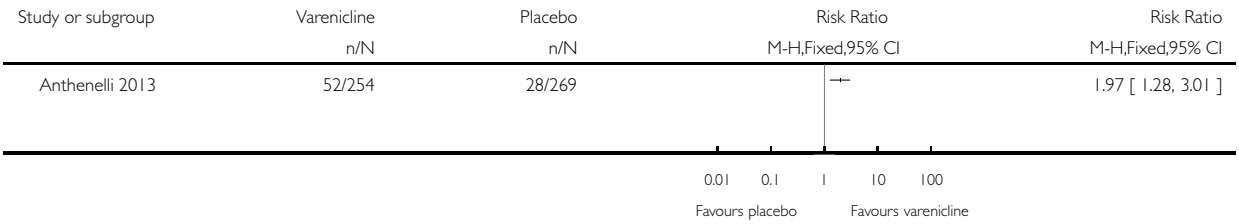
(2) 7-day PPA at 24 weeks

Analysis 8.5. Comparison 8 Varenicline in specific patient groups, Outcome 5 Depression.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 5 Depression

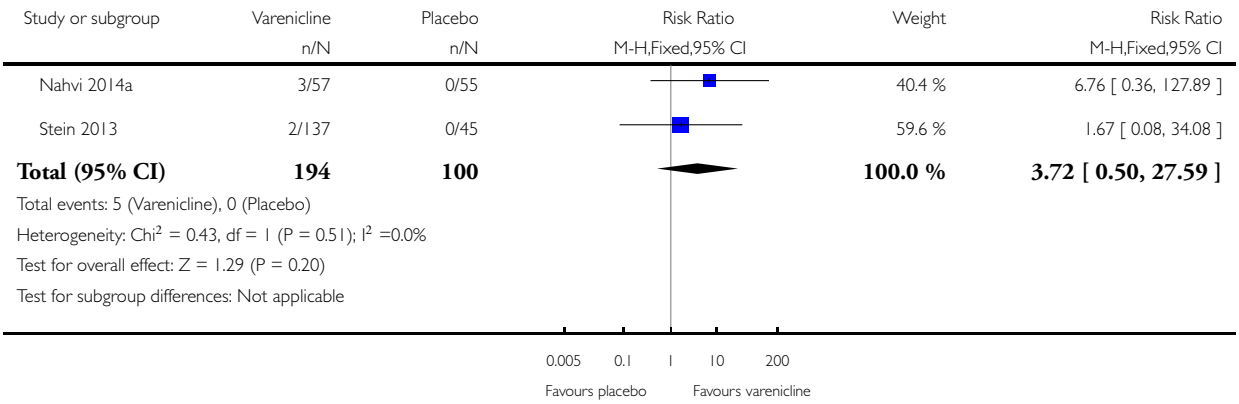


Analysis 8.6. Comparison 8 Varenicline in specific patient groups, Outcome 6 Substance use disorder/methadone-maintained at 24 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 6 Substance use disorder/methadone-maintained at 24 weeks



Analysis 8.7. Comparison 8 Varenicline in specific patient groups, Outcome 7 Alcohol-dependent smokers.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 7 Alcohol-dependent smokers

Study or subgroup	Varenicline n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
NCT01347112	4/16	0/17			12.60 [0.62, 255.76]
Test for subgroup differences: Not applicable					

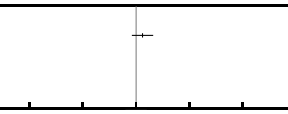
Analysis 8.8. Comparison 8 Varenicline in specific patient groups, Outcome 8 Long-term use of NRT.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 8 Varenicline in specific patient groups

Outcome: 8 Long-term use of NRT

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
T nnesen 2013	28/70	21/69		1.31 [0.83, 2.08]



Analysis 9.1. Comparison 9 Varenicline in different settings/subgroups, Outcome 1 Hospital inpatients/perioperative patients.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 9 Varenicline in different settings/subgroups

Outcome: 1 Hospital inpatients/perioperative patients

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Carson 2014	56/190	36/189		43.4 %	1.55 [1.07, 2.23]
Steinberg 2011 (1)	8/40	11/39		13.4 %	0.71 [0.32, 1.57]
Wong 2012 (2)	55/151	34/135		43.2 %	1.45 [1.01, 2.07]
Total (95% CI)	**381**	**363**		**100.0 %**	**1.39 [1.09, 1.77]**
Total events: 119 (Experimental), 81 (Control)					
Heterogeneity: Chi^2 = 3.12, df = 2 (P = 0.21); I^2 =36%					
Test for overall effect: Z = 2.66 (P = 0.0077)					
Test for subgroup differences: Not applicable					

(1) 7-day PPA at 24 weeks

(2) 7-day PPA at 12m

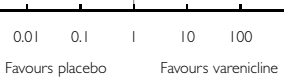
Analysis 9.2. Comparison 9 Varenicline in different settings/subgroups, Outcome 2 Smokers who have failed on other cessation therapies.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 9 Varenicline in different settings/subgroups

Outcome: 2 Smokers who have failed on other cessation therapies

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Gonzales 2014	50/249	8/245		6.15 [2.98, 12.70]

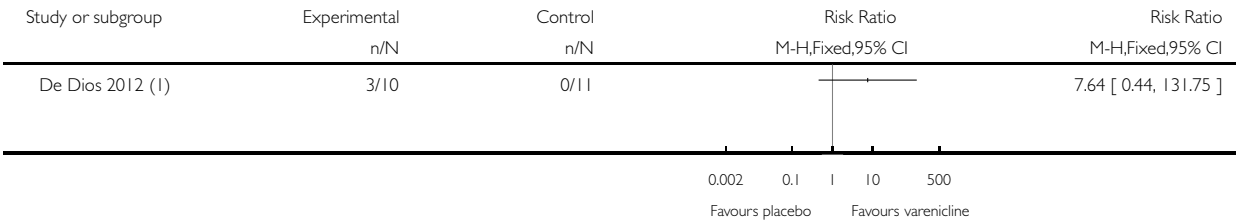


Analysis 9.3. Comparison 9 Varenicline in different settings/subgroups, Outcome 3 Light or heavy smokers.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 9 Varenicline in different settings/subgroups

Outcome: 3 Light or heavy smokers



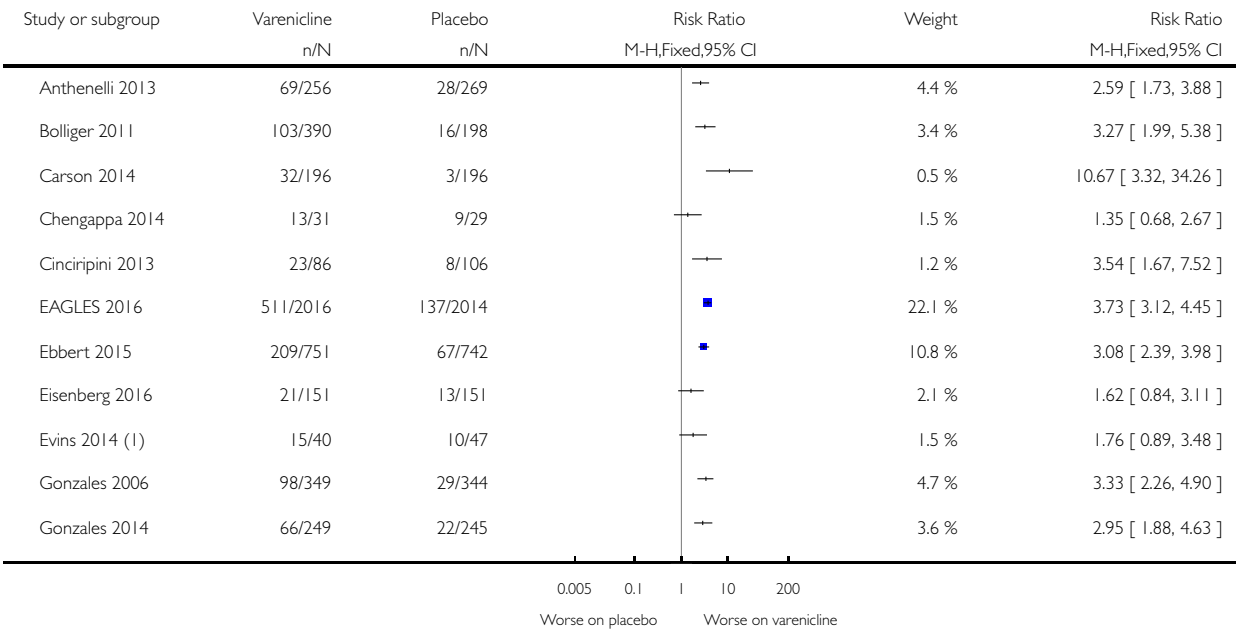
(1) 7-day PPA at 6m

Analysis 10.1. Comparison 10 Adverse event meta-analyses, Outcome 1 Nausea.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 1 Nausea



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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Hajek 2015	80/100	18/100		2.9 %	4.44 [2.89, 6.83]
Heydari 2012	8/89	0/91		0.1 %	17.38 [1.02, 296.64]
Jorenby 2006	101/343	33/340		5.3 %	3.03 [2.11, 4.36]
Nahvi 2014a	29/57	14/55		2.3 %	2.00 [1.19, 3.36]
Nakamura 2007	38/156	12/154		1.9 %	3.13 [1.70, 5.75]
NCT00828113	2/33	0/34		0.1 %	5.15 [0.26, 103.33]
NCT01347112	4/16	0/17		0.1 %	9.53 [0.55, 164.01]
Niaura 2008	21/157	8/155		1.3 %	2.59 [1.18, 5.67]
Nides 2006	65/125	23/123		3.7 %	2.78 [1.85, 4.17]
Oncken 2006	97/253	18/121		3.9 %	2.58 [1.64, 4.06]
Rennard 2012	142/486	15/165		3.6 %	3.21 [1.95, 5.31]
Rigotti 2010	104/353	30/350		4.8 %	3.44 [2.35, 5.02]
Stein 2013	7/111	2/33		0.5 %	1.04 [0.23, 4.77]
Steinberg 2011	11/40	2/39		0.3 %	5.36 [1.27, 22.65]
Tashkin 2011	67/248	20/251		3.2 %	3.39 [2.12, 5.41]
Tsai 2007	55/126	14/124		2.3 %	3.87 [2.27, 6.58]
T nnesen 2013	40/70	8/69		1.3 %	4.93 [2.49, 9.75]
Wang 2009	48/165	20/168		3.2 %	2.44 [1.52, 3.93]
Williams 2007	101/251	10/126		2.1 %	5.07 [2.75, 9.36]
Williams 2012	7/84	2/43		0.4 %	1.79 [0.39, 8.26]
Wong 2012	20/151	5/135		0.8 %	3.58 [1.38, 9.27]
Total (95% CI)	**7929**	**7034**		**100.0 %**	**3.27 [3.00, 3.55]**

Total events: 2207 (Varenicline), 596 (Placebo)
Heterogeneity: Chi^2 = 39.89, df = 31 (P = 0.13); I^2 =22%
Test for overall effect: Z = 27.50 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) maintenance phase (12 - 40 wks post-quit)

Analysis 10.2. Comparison 10 Adverse event meta-analyses, Outcome 2 Insomnia.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 2 Insomnia

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	28/256	13/269		2.2 %	2.26 [1.20, 4.27]
Bolliger 2011	50/390	13/198		2.9 %	1.95 [1.09, 3.51]
Carson 2014	10/196	4/196		0.7 %	2.50 [0.80, 7.84]
Chengappa 2014	14/31	8/29		1.4 %	1.64 [0.81, 3.32]
Cinciripini 2013	20/86	21/106		3.2 %	1.17 [0.68, 2.02]
EAGLES 2016	189/2016	139/2014		23.8 %	1.36 [1.10, 1.68]
Ebbert 2015	80/751	51/742		8.8 %	1.55 [1.11, 2.17]
Eisenberg 2016	27/151	19/151		3.2 %	1.42 [0.83, 2.44]
Evins 2014 (1)	11/40	11/47		1.7 %	1.18 [0.57, 2.42]
Gonzales 2006	49/349	44/344		7.6 %	1.10 [0.75, 1.60]
Gonzales 2014	17/249	10/245		1.7 %	1.67 [0.78, 3.58]
Hajek 2015	21/100	20/100		3.4 %	1.05 [0.61, 1.81]
Heydari 2012 (2)	3/89	0/91		0.1 %	7.16 [0.37, 136.56]
Jorenby 2006	49/343	42/340		7.2 %	1.16 [0.79, 1.70]
Nahvi 2014a	15/57	13/55		2.3 %	1.11 [0.58, 2.12]
NCT01347112	2/16	0/17		0.1 %	5.29 [0.27, 102.49]
Niaura 2008	34/157	17/155		2.9 %	1.97 [1.15, 3.38]
Nides 2006	44/125	27/123		4.7 %	1.60 [1.06, 2.41]
Oncken 2006	75/253	14/121		3.2 %	2.56 [1.51, 4.34]
Rennard 2012	43/486	6/165		1.5 %	2.43 [1.05, 5.61]
Rigotti 2010	42/353	23/350		3.9 %	1.81 [1.11, 2.94]
Stein 2013	39/111	12/33		3.2 %	0.97 [0.58, 1.62]
Steinberg 2011	3/40	3/39		0.5 %	0.98 [0.21, 4.54]
Tashkin 2011	24/248	15/251		2.5 %	1.62 [0.87, 3.01]
Tsai 2007	19/126	17/124		2.9 %	1.10 [0.60, 2.02]
Wang 2009	10/165	5/168		0.8 %	2.04 [0.71, 5.83]

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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Williams 2007	48/251	12/126		2.7 %	2.01 [1.11, 3.64]
Williams 2012	8/84	2/43		0.5 %	2.05 [0.45, 9.23]
Wong 2012	2/151	1/135		0.2 %	1.79 [0.16, 19.50]
Total (95% CI)	**7670**	**6777**		**100.0 %**	**1.49 [1.35, 1.65]**

Total events: 976 (Varenicline), 562 (Placebo)
Heterogeneity: Chi^2 = 26.48, df = 28 (P = 0.55); I^2 =0.0%
Test for overall effect: Z = 7.98 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) maintenance phase (12 - 40 wks post-quit)

(2) described as "abnormal sleep and bad dreams"

Analysis 10.3. Comparison 10 Adverse event meta-analyses, Outcome 3 Abnormal dreams.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 3 Abnormal dreams

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	29/256	22/269		5.6 %	1.39 [0.82, 2.35]
Bolliger 2011	66/390	15/198		5.2 %	2.23 [1.31, 3.81]
Carson 2014	12/196	2/196		0.5 %	6.00 [1.36, 26.46]
Chengappa 2014	18/31	9/29		2.4 %	1.87 [1.01, 3.48]
Cinciripini 2013	13/86	11/106		2.6 %	1.46 [0.69, 3.09]
EAGLES 2016	201/2016	92/2014		24.0 %	2.18 [1.72, 2.77]
Ebbert 2015	86/751	43/742		11.3 %	1.98 [1.39, 2.81]
Eisenberg 2016	23/151	7/151		1.8 %	3.29 [1.45, 7.43]

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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Evins 2014 (1)	1/40	2/47		0.5 %	0.59 [0.06, 6.24]
Gonzales 2006 (2)	36/349	19/344		5.0 %	1.87 [1.09, 3.19]
Gonzales 2014	36/249	8/245		2.1 %	4.43 [2.10, 9.33]
Hajek 2015	15/100	18/100		4.7 %	0.83 [0.45, 1.56]
Jorenby 2006	45/343	12/340		3.1 %	3.72 [2.00, 6.90]
Nahvi 2014a	18/57	22/55		5.8 %	0.79 [0.48, 1.30]
NCT01347112	1/16	1/17		0.3 %	1.06 [0.07, 15.60]
Nides 2006	19/125	10/123		2.6 %	1.87 [0.91, 3.86]
Oncken 2006	46/253	6/121		2.1 %	3.67 [1.61, 8.35]
Rennard 2012	61/486	5/165		1.9 %	4.14 [1.69, 10.13]
Rigotti 2010	28/353	6/350		1.6 %	4.63 [1.94, 11.04]
Stein 2013	23/111	8/33		3.2 %	0.85 [0.42, 1.73]
Tashkin 2011	27/248	7/251		1.8 %	3.90 [1.73, 8.80]
Tsai 2007	7/126	1/124		0.3 %	6.89 [0.86, 55.17]
T nnesen 2013	35/70	26/69		6.8 %	1.33 [0.90, 1.95]
Williams 2007	57/251	9/126		3.1 %	3.18 [1.63, 6.21]
Williams 2012	6/84	4/43		1.4 %	0.77 [0.23, 2.58]
Wong 2012	3/151	0/135		0.1 %	6.26 [0.33, 120.16]
Total (95% CI)	**7289**	**6393**		**100.0 %**	**2.12 [1.88, 2.38]**

Total events: 912 (Varenicline), 365 (Placebo)

Heterogeneity: Chi^2 = 65.97, df = 25 (P = 0.00002); I^2 =62%

Test for overall effect: Z = 12.61 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) maintenance phase (12 - 40 wks post-quit)

(2) Bolliger 2011 groups all sleep disorders together

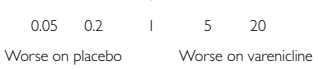
Analysis 10.4. Comparison 10 Adverse event meta-analyses, Outcome 4 Headache.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 4 Headache

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	43/256	30/269		4.2 %	1.51 [0.98, 2.32]
Bolliger 2011	64/390	24/198		4.6 %	1.35 [0.87, 2.10]
Carson 2014	12/196	3/196		0.4 %	4.00 [1.15, 13.96]
Chengappa 2014	11/31	12/29		1.8 %	0.86 [0.45, 1.63]
Cinciripini 2013	10/86	12/106		1.5 %	1.03 [0.47, 2.26]
EAGLES 2016	245/2016	199/2014		28.5 %	1.23 [1.03, 1.47]
Ebbert 2015	62/751	54/742		7.8 %	1.13 [0.80, 1.61]
Eisenberg 2016	8/151	12/151		1.7 %	0.67 [0.28, 1.58]
Evins 2014 (1)	17/40	11/44		1.5 %	1.70 [0.91, 3.18]
Gonzales 2006	54/349	42/344		6.1 %	1.27 [0.87, 1.84]
Gonzales 2014	26/249	24/245		3.5 %	1.07 [0.63, 1.80]
Hajek 2015	7/100	6/100		0.9 %	1.17 [0.41, 3.35]
Jorenby 2006	44/343	43/340		6.2 %	1.01 [0.68, 1.50]
Nahvi 2014a	11/57	18/55		2.6 %	0.59 [0.31, 1.13]
Nakamura 2007	16/156	4/154		0.6 %	3.95 [1.35, 11.54]
Niaura 2008	25/157	20/155		2.9 %	1.23 [0.72, 2.13]
Nides 2006	30/125	33/123		4.8 %	0.89 [0.58, 1.37]
Oncken 2006	59/253	21/121		4.1 %	1.34 [0.86, 2.10]
Rennard 2012	55/486	20/165		4.3 %	0.93 [0.58, 1.51]
Rigotti 2010	45/353	39/350		5.6 %	1.14 [0.76, 1.71]
Stein 2013	7/111	6/33		1.3 %	0.35 [0.13, 0.96]
Tashkin 2011	20/248	20/251		2.8 %	1.01 [0.56, 1.83]
Wang 2009	9/165	7/168		1.0 %	1.31 [0.50, 3.43]
Williams 2012	9/84	8/43		1.5 %	0.58 [0.24, 1.39]
Wong 2012	5/151	0/135		0.1 %	9.84 [0.55, 176.35]
Total (95% CI)	**7304**	**6531**		**100.0 %**	**1.17 [1.07, 1.29]**



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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 894 (Varenicline), 668 (Placebo)					
Heterogeneity: Chi^2 = 32.90, df = 24 (P = 0.11); I^2 =27%					
Test for overall effect: Z = 3.30 (P = 0.00097)					
Test for subgroup differences: Not applicable					

(1) maintenance phase (12 - 40 wks post-quit)

Analysis 10.5. Comparison 10 Adverse event meta-analyses, Outcome 5 Depression.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 5 Depression

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	17/256	13/269		6.5 %	1.37 [0.68, 2.77]
Bolliger 2011	8/390	4/198		2.7 %	1.02 [0.31, 3.33]
Brandon 2011* (1)	0/46	0/54			Not estimable
Carson 2014	4/196	2/196		1.0 %	2.00 [0.37, 10.79]
Chengappa 2014	8/31	2/29		1.1 %	3.74 [0.87, 16.18]
Cinciripini 2013	6/86	14/106		6.4 %	0.53 [0.21, 1.32]
EAGLES 2016	7/2016	6/2014		3.1 %	1.17 [0.39, 3.46]
Ebbert 2011*	0/38	1/38		0.8 %	0.33 [0.01, 7.93]
Ebbert 2015	25/751	35/742		18.1 %	0.71 [0.43, 1.17]
Eisenberg 2016	1/151	0/151		0.3 %	3.00 [0.12, 73.06]
Evins 2014	1/40	1/47		0.5 %	1.18 [0.08, 18.19]
Faessel 2009*	0/14	0/7			Not estimable
Fagerström 2010*	2/213	5/218		2.5 %	0.41 [0.08, 2.09]

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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Garza 2011*	1/55	1/55		0.5 %	1.00 [0.06, 15.59]
Gonzales 2006	4/349	7/344		3.6 %	0.56 [0.17, 1.91]
Gonzales 2014	5/249	2/245		1.0 %	2.46 [0.48, 12.56]
Hajek 2015	7/100	8/100		4.1 %	0.88 [0.33, 2.32]
Hughes 2011*	1/107	2/111		1.0 %	0.52 [0.05, 5.64]
Jorenby 2006	6/343	1/340		0.5 %	5.95 [0.72, 49.14]
McClure 2013* NCT00944554	17/41	20/42		10.1 %	0.87 [0.54, 1.41]
Meszaros 2013*	1/5	1/5		0.5 %	1.00 [0.08, 11.93]
Nahvi 2014a	2/57	1/55		0.5 %	1.93 [0.18, 20.68]
NCT01347112	0/16	1/17		0.7 %	0.35 [0.02, 8.08]
Niaura 2008	3/157	2/155		1.0 %	1.48 [0.25, 8.74]
Nides 2006	2/125	1/123		0.5 %	1.97 [0.18, 21.42]
Oncken 2006	6/253	4/121		2.8 %	0.72 [0.21, 2.50]
Rennard 2012	4/486	5/165		3.8 %	0.27 [0.07, 1.00]
Rigotti 2010	5/353	3/350		1.5 %	1.65 [0.40, 6.86]
Stein 2013	17/111	7/33		5.5 %	0.72 [0.33, 1.59]
Steinberg 2011	2/40	2/39		1.0 %	0.98 [0.14, 6.58]
Tashkin 2011	6/248	5/251		2.5 %	1.21 [0.38, 3.93]
Tonstad 2006	15/602	17/604		8.7 %	0.89 [0.45, 1.76]
Tsai 2007	1/126	2/124		1.0 %	0.49 [0.05, 5.36]
Williams 2007	12/251	4/126		2.7 %	1.51 [0.50, 4.58]
Williams 2012	4/84	3/43		2.0 %	0.68 [0.16, 2.91]
Wong 2012	2/151	2/135		1.1 %	0.89 [0.13, 6.26]
Total (95% CI)	**8537**	**7652**		**100.0 %**	**0.94 [0.77, 1.14]**

Total events: 202 (Varenicline), 184 (Placebo)
Heterogeneity: Chi² = 22.93, df = 33 (P = 0.90); I² =0.0%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable

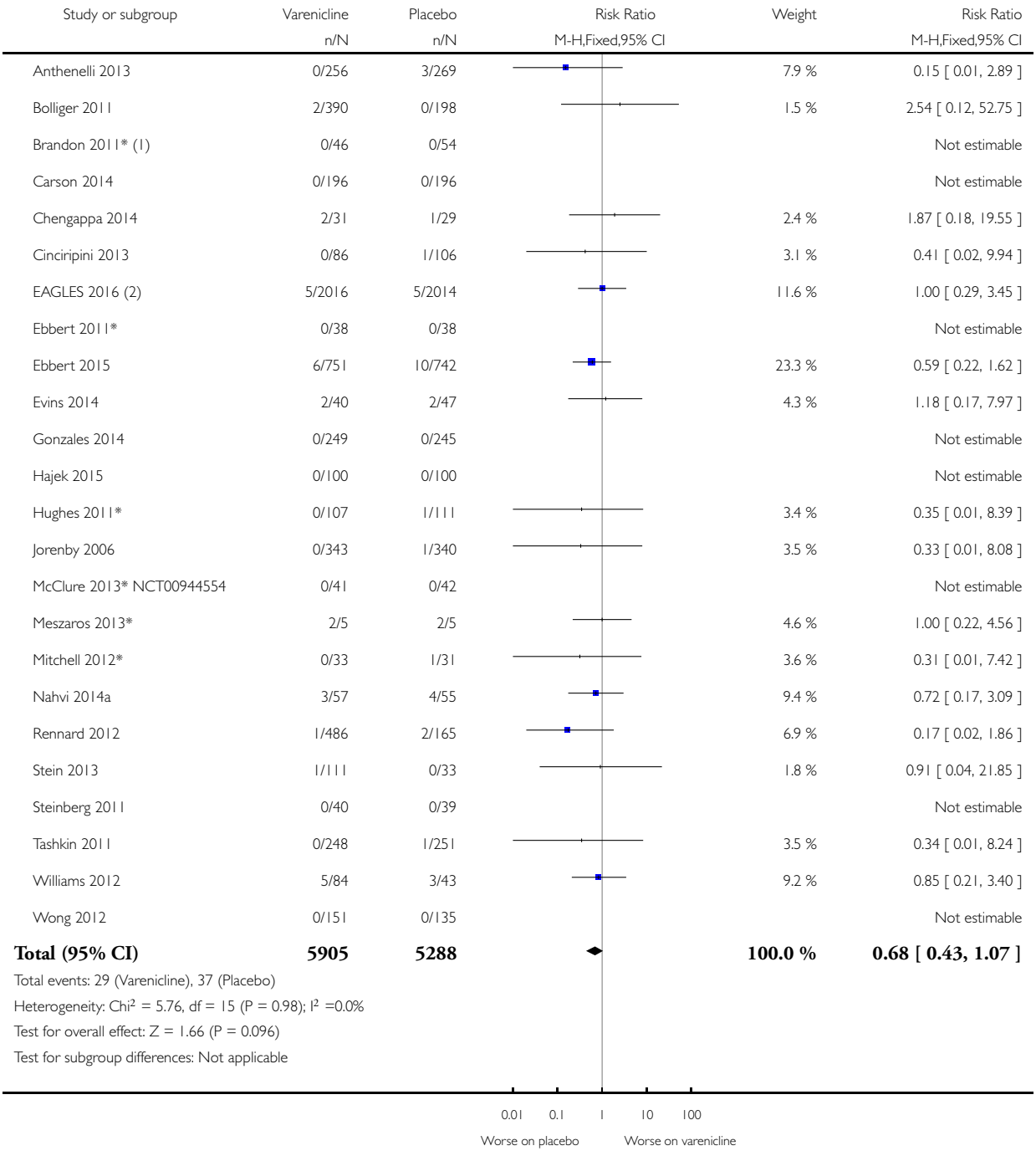
(1) Studies marked with an asterisk (*) contribute data to the neuropsychiatric adverse events analyses, but not to efficacy results

Analysis 10.6. Comparison 10 Adverse event meta-analyses, Outcome 6 Suicidal ideation.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 10 Adverse event meta-analyses

Outcome: 6 Suicidal ideation



(1) Studies marked with an asterisk (*) contribute data to the neuropsychiatric adverse events analyses, but not to efficacy results

(2) All 5 events occurred in the psychiatric cohort

Analysis 11.1. Comparison 11 Serious adverse events, Outcome 1 SAEs in the varenicline trials.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 11 Serious adverse events

Outcome: 1 SAEs in the varenicline trials

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	8/256	8/269		3.9 %	1.05 [0.40, 2.76]
Bolliger 2011	11/394	2/199		1.3 %	2.78 [0.62, 12.41]
Carson 2014	10/119	8/117		4.0 %	1.23 [0.50, 3.00]
Chengappa 2014	6/31	4/29		2.0 %	1.40 [0.44, 4.47]
Cinciripini 2013	2/86	2/106		0.9 %	1.23 [0.18, 8.57]
EAGLES 2016	39/2016	41/2014		20.3 %	0.95 [0.62, 1.47]
Ebbert 2015	28/751	16/742		8.0 %	1.73 [0.94, 3.17]
Eisenberg 2016	18/151	17/151		8.4 %	1.06 [0.57, 1.97]
Evins 2014	4/40	7/47		3.2 %	0.67 [0.21, 2.13]
Gonzales 2006	6/352	9/344		4.5 %	0.65 [0.23, 1.81]
Gonzales 2014	7/249	4/245		2.0 %	1.72 [0.51, 5.81]
Jorenby 2006	8/344	6/341		3.0 %	1.32 [0.46, 3.77]
Nahvi 2014a	5/57	3/55		1.5 %	1.61 [0.40, 6.41]
Nakamura 2007	10/155	3/154		1.5 %	3.31 [0.93, 11.80]
NCT00828113	1/33	1/34		0.5 %	1.03 [0.07, 15.80]
Niaura 2008	3/160	0/160		0.2 %	7.00 [0.36, 134.43]
Nides 2006	2/127	0/127		0.2 %	5.00 [0.24, 103.12]
Oncken 2006	11/259	2/129		1.3 %	2.74 [0.62, 12.18]
Rennard 2012	6/493	1/166		0.7 %	2.02 [0.25, 16.66]
Rigotti 2010	23/353	21/354		10.4 %	1.10 [0.62, 1.95]

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Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Stein 2013	4/111	0/33		0.4 %	2.73 [0.15, 49.48]
Steinberg 2011	6/40	5/39		2.5 %	1.17 [0.39, 3.52]
Tashkin 2011	12/248	15/253		7.4 %	0.82 [0.39, 1.71]
Tonstad 2006	10/603	5/607		2.5 %	2.01 [0.69, 5.86]
Tsai 2007	3/126	3/124		1.5 %	0.98 [0.20, 4.78]
T nnesen 2013	5/70	4/69		2.0 %	1.23 [0.35, 4.40]
Wang 2009	0/165	2/168		1.2 %	0.20 [0.01, 4.21]
Williams 2007	15/251	3/126		2.0 %	2.51 [0.74, 8.51]
Williams 2012	6/85	4/43		2.6 %	0.76 [0.23, 2.55]
Total (95% CI)	**8125**	**7245**		**100.0 %**	**1.25 [1.04, 1.49]**

Total events: 269 (Varenicline), 196 (Placebo)

Heterogeneity: Chi^2 = 18.78, df = 28 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 2.36 (P = 0.018)

Test for subgroup differences: Not applicable

Analysis 11.2. Comparison 11 Serious adverse events, Outcome 2 SAEs in the varenicline trials, exc post-treat events.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 11 Serious adverse events

Outcome: 2 SAEs in the varenicline trials, exc post-treat events

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	7/256	7/269		4.0 %	1.05 [0.37, 2.95]
Bolliger 2011	11/394	2/199		1.6 %	2.78 [0.62, 12.41]
Carson 2014	5/119	3/117		1.8 %	1.64 [0.40, 6.70]
Chengappa 2014	5/31	3/29		1.8 %	1.56 [0.41, 5.95]
Cinciripini 2013	2/86	2/106		1.1 %	1.23 [0.18, 8.57]
EAGLES 2016	39/2016	41/2014		24.3 %	0.95 [0.62, 1.47]
Ebbert 2015	18/751	10/742		6.0 %	1.78 [0.83, 3.83]
Eisenberg 2016	18/151	17/151		10.1 %	1.06 [0.57, 1.97]
Gonzales 2006	4/352	7/344		4.2 %	0.56 [0.16, 1.89]
Gonzales 2014	7/249	4/245		2.4 %	1.72 [0.51, 5.81]
Jorenby 2006	6/344	5/341		3.0 %	1.19 [0.37, 3.86]
Nahvi 2014a	3/57	2/55		1.2 %	1.45 [0.25, 8.33]
Nakamura 2007	10/155	3/154		1.8 %	3.31 [0.93, 11.80]
NCT00828113	0/33	1/34		0.9 %	0.34 [0.01, 8.13]
Niaura 2008	3/160	0/160		0.3 %	7.00 [0.36, 134.43]
Nides 2006	2/127	0/127		0.3 %	5.00 [0.24, 103.12]
Oncken 2006	9/259	1/129		0.8 %	4.48 [0.57, 35.00]
Rennard 2012	6/493	1/166		0.9 %	2.02 [0.25, 16.66]
Rigotti 2010	23/353	21/354		12.4 %	1.10 [0.62, 1.95]
Steinberg 2011	6/40	5/39		3.0 %	1.17 [0.39, 3.52]
Tashkin 2011	7/248	11/253		6.5 %	0.65 [0.26, 1.65]
Tonstad 2006	10/603	5/607		3.0 %	2.01 [0.69, 5.86]
Tsai 2007	3/126	3/124		1.8 %	0.98 [0.20, 4.78]
Wang 2009	0/165	2/168		1.5 %	0.20 [0.01, 4.21]
Williams 2007	15/251	3/126		2.4 %	2.51 [0.74, 8.51]

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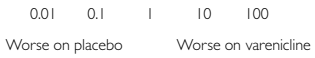
Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Williams 2012	6/85	4/43		3.1 %	0.76 [0.23, 2.55]
Total (95% CI)	**7904**	**7096**		**100.0 %**	**1.25 [1.02, 1.52]**

Total events: 225 (Varenicline), 163 (Placebo)
Heterogeneity: Chi^2 = 18.97, df = 25 (P = 0.80); I^2 =0.0%
Test for overall effect: Z = 2.16 (P = 0.030)
Test for subgroup differences: Not applicable



Analysis 11.3. Comparison 11 Serious adverse events, Outcome 3 Neuropsychiatric SAEs (not deaths).

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 11 Serious adverse events

Outcome: 3 Neuropsychiatric SAEs (not deaths)

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	2/256	4/269		7.8 %	0.53 [0.10, 2.84]
Bolliger 2011	4/394	0/199		1.3 %	4.56 [0.25, 84.22]
Carson 2014	5/119	3/117		6.1 %	1.64 [0.40, 6.70]
Chengappa 2014	2/31	0/29		1.0 %	4.69 [0.23, 93.70]
Eisenberg 2016	1/151	0/151		1.0 %	3.00 [0.12, 73.06]
Evins 2014 (1)	2/40	5/47		9.2 %	0.47 [0.10, 2.29]
Gonzales 2006	0/352	1/344		3.0 %	0.33 [0.01, 7.97]
Jorenby 2006	2/344	0/341		1.0 %	4.96 [0.24, 102.86]
Nahvi 2014a (2)	18/57	25/55		51.1 %	0.69 [0.43, 1.12]
Nakamura 2007	0/155	0/154			Not estimable
Niaura 2008	0/160	0/160			Not estimable
Nides 2006	0/127	0/127			Not estimable

(*Continued* . . .)

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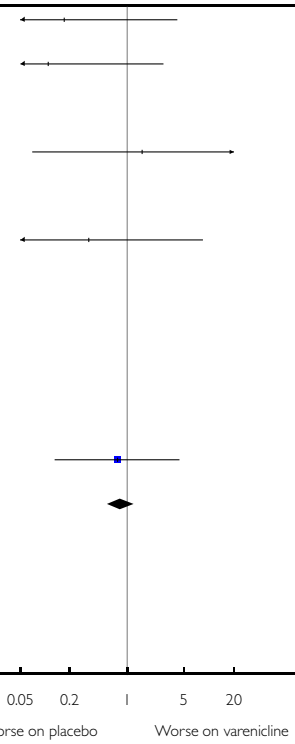
Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Oncken 2006	0/259	1/129		4.0 %	0.17 [0.01, 4.06]
Rennard 2012	0/493	1/166		4.5 %	0.11 [0.00, 2.75]
Rigotti 2010	0/353	0/354			Not estimable
Stein 2013	2/111	0/33		1.5 %	1.52 [0.07, 30.86]
Steinberg 2011	0/40	0/39			Not estimable
Tashkin 2011	0/248	1/253		3.0 %	0.34 [0.01, 8.31]
Tonstad 2011	0/603	0/607			Not estimable
Tsai 2007	0/126	0/124			Not estimable
Wang 2009	0/165	0/168			Not estimable
Williams 2007	0/251	0/126			Not estimable
Williams 2012	3/85	2/43		5.3 %	0.76 [0.13, 4.37]
Total (95% CI)	**4920**	**4035**		**100.0 %**	**0.82 [0.57, 1.19]**

Total events: 41 (Varenicline), 43 (Placebo)

Heterogeneity: Chi^2 = 9.98, df = 13 (P = 0.70); I^2 =0.0%

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable



(1) maintenance phase (12 - 40 wks post-quit) in pts with schizophrenia, schizoaffective or bipolar disorder

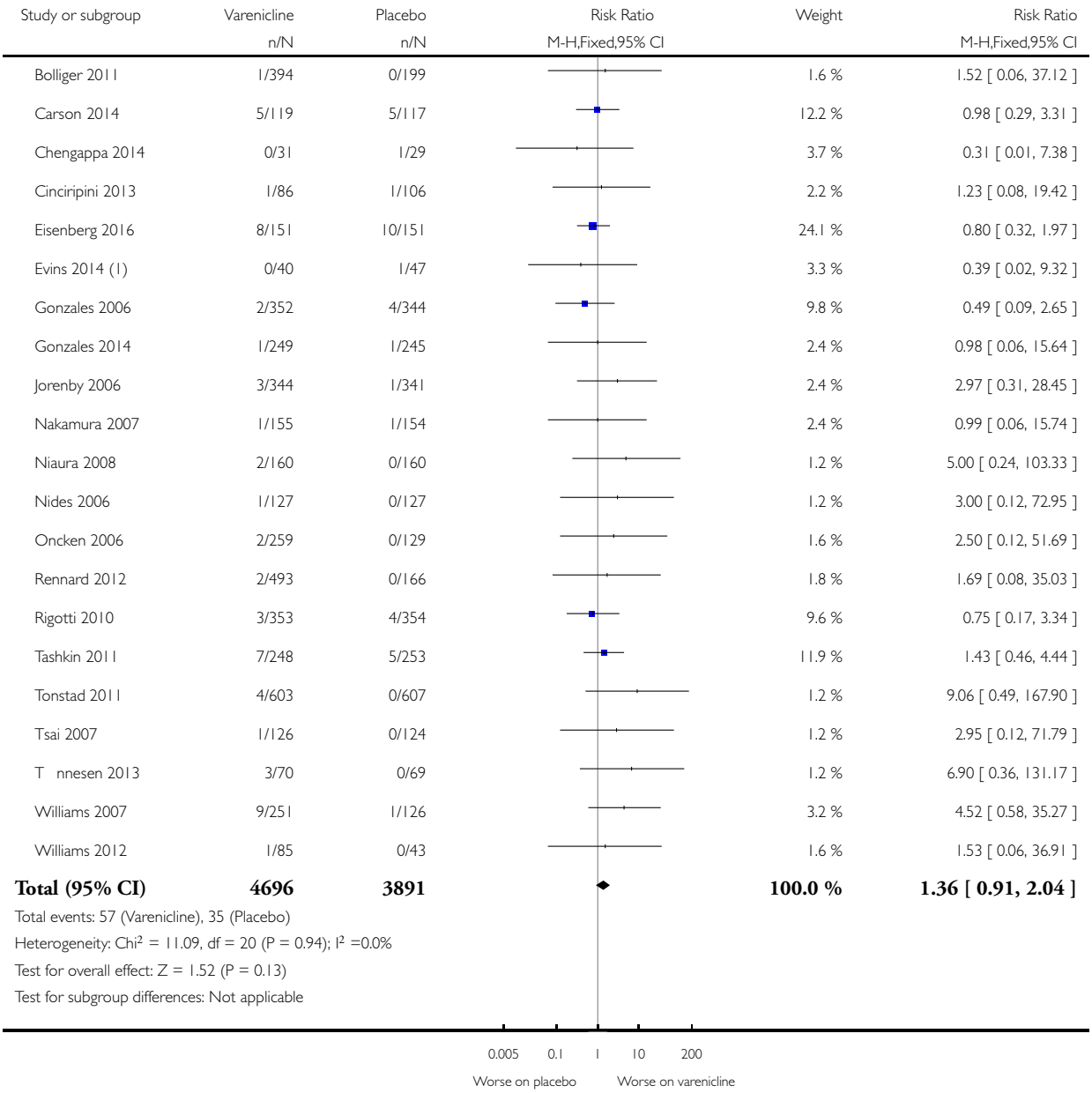
(2) in methadone-maintained patients

Analysis 11.4. Comparison 11 Serious adverse events, Outcome 4 Cardiac SAEs, including deaths.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 11 Serious adverse events

Outcome: 4 Cardiac SAEs, including deaths



(1) maintenance phase (12 - 40 wks post-quit)

Analysis 12.1. Comparison 12 Losses to follow-up, Outcome 1 Participants remaining at end of varenicline trials.

Participants remaining at end of varenicline trials

Study	**Placebo [%]**	**Varenicline [%]**	**Bupropion [%]**	**NRT [%]**	**Chi² and P value**
Anthenelli 2013	179/269 (66.5%)	175/256 (68.4)			0.20, P = 0.66
Aubin 2008		247/378 (65.3)		230/379 (60.7)	1.76, P = 0.18
Baker 2016		389/424 (91.7)		Patch: 226/241 (93.8) C-NRT: 408/421 (96.9)	10.42, P = 0.005**
Bolliger 2011	156/199 (78.4)	336/394 (85.3)			4.44, P = 0.04*
Carson 2014	160/196 (81.6)	165/196 (84.2)			0.45, P = 0.50
Chengappa 2014	20/29 (69.0)	24/31 (77.4)			0.55, P = 0.46
Cinciripini 2013	76/106 (71.7)	65/86 (75.6)	73/102 (71.6)		0.37, P = 0.54
De Dios 2012	7/11 (63.6)	7/10 (70.0)		9/11 (81.8)	0.10, P = 0.76
EAGLES 2016	1552/2035 (76.3)	1598/2037 (78.4)	1586/2034 (80.0)	1557/2038 (76.4)	4.24, P = 0.24
Ebbert 2015	516/750 (68.8)	559/760 (73.6)			4.16, P = 0.04*
Eisenberg 2016	112/151 (74.2)	118/151 (78.1)			0.66, P = 0.42
Evins 2014	33/40 (82.5)	26/47 (55.3)			7.31, P = 0.007**
Gonzales 2006	187/344 (54.4)	213/352 (60.5)	184/329 (55.9)		2.90, P = 0.23
Gonzales 2014	144/247 (58.8)	169/251 (67.9)			4.35, P = 0.04
Hajek 2015	60/100 (60.0)	66/100 (66.0)			0.77, P = 0.38
Heydari 2012	91/91 (100.0)	89/89 (100.0)		92/92 (100.0)	0, P = 1
Jorenby 2006	204/341 (59.8)	240/344 (69.8)	221/342 (64.6)		7.42, P = 0.02*
Nahvi 2014a	43/55 (78.2)	49/57 (86.0)			1.16, P = 0.28
Nakamura 2007	132/154 (85.7)	124/155 (79.5)			1.78, P = 0.18
NCT00828113	20/51 (39.2)	20/50 (40.0)			0.01, P = 0.94

Participants remaining at end of varenicline trials (*Continued*)

NCT01347112	12/16 (75.0)	5/17 (29.4)			10.24, P = 0.001**
Niaura 2008	89/160 (55.6)	100/160 (62.5)			1.56, P = 0.21
Nides 2006	68/127 (53.5)	77/127 (60.6)	68/128 (53.1)		1.83, P = 0.40
Oncken 2006	40/129 (31.0)	146/253 (57.7)			24.38, P < 0.001**
Rennard 2012	132/166 (79.5)	432/493 (87.6)			6.62, P = 0.01*
Rigotti 2010	289/359 (80.5)	302/355 (85.1)			2.61, P = 0.11
Stein 2013	35/45 (77.8)	115/137 (83.9)		107/133 (80.5)	1.05, P = 0.59
Steinberg 2011	21/39 (53.8)	22/40 (55.0)			0.01, P = 0.92
Tashkin 2011	157/254 (61.8)	176/250 (70.4)			4.14, P = 0.04*
Tonstad 2006	463/607 (76.3)	494/603 (81.9)			5.83, P = 0.02*
Tsai 2007	117/124 (94.4)	120/126 (95.2)			0.10, P = 0.75
Tsukahara 2010		14/16 (87.5)		14/16 (87.5)	0, P = 1
Tønnesen 2013	54/69 (78.3)	61/70 (87.1)			1.92, P = 0.17
Walker 2014		473/655 (72.2) [cytisine]		482/655 (73.6)	0.31, P = 0.58
Wang 2009	161/168 (95.8)	158/165 (95.8)			0.001, P = 0.97
Westergaard 2015	14/26 (53.8%)	19/26 (73.1%)			2.07, P = 0.15
Williams 2007	59/126 (46.8)	135/251 (53.8)			1.63, P = 0.20
Williams 2012	40/43 (93.0)	75/85 (88.2)			0.72, P = 0.40
Wong 2012	119/135 (88.1)	134/151 (88.7)			0.02, P = 0.88

Analysis 13.1. Comparison 13 Sensitivity analysis, Outcome 1 ITT treatment vs per protocol control.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 13 Sensitivity analysis

Outcome: 1 ITT treatment vs per protocol control

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	52/254	28/179		4.0 %	1.31 [0.86, 1.99]
Bolliger 2011	155/394	26/198		4.2 %	3.00 [2.05, 4.37]
Carson 2014	61/190	42/160		5.6 %	1.22 [0.88, 1.70]
Chengappa 2014	6/31	2/20		0.3 %	1.94 [0.43, 8.66]
Cinciripini 2013	24/86	15/76		1.9 %	1.41 [0.80, 2.49]
De Dios 2012	3/10	0/7		0.1 %	5.09 [0.30, 85.39]
EAGLES 2016	444/2037	191/1552		26.4 %	1.77 [1.51, 2.07]
Ebbert 2015	182/760	45/516		6.5 %	2.75 [2.02, 3.73]
Eisenberg 2016	53/148	39/112		5.4 %	1.03 [0.74, 1.43]
Evins 2014	16/40	5/26		0.7 %	2.08 [0.87, 4.99]
Gonzales 2006	77/352	29/187		4.6 %	1.41 [0.96, 2.08]
Gonzales 2014	50/249	8/144		1.2 %	3.61 [1.76, 7.41]
Heydari 2012 (1)	29/89	6/91		0.7 %	4.94 [2.16, 11.32]
Jorenby 2006	79/344	35/204		5.4 %	1.34 [0.94, 1.92]
Nahvi 2014a	3/37	0/43		0.1 %	8.11 [0.43, 151.98]
Nakamura 2007	56/155	35/132		4.6 %	1.36 [0.96, 1.94]
NCT00828113	10/50	11/34		1.6 %	0.62 [0.30, 1.29]
NCT01347112	4/16	0/5		0.1 %	3.18 [0.20, 50.67]
Niaura 2008	35/160	12/155		1.5 %	2.83 [1.52, 5.24]
Nides 2006	18/127	6/68		1.0 %	1.61 [0.67, 3.86]
Oncken 2006	58/259	5/40		1.1 %	1.79 [0.77, 4.19]
Rennard 2012	171/493	21/132		4.0 %	2.18 [1.45, 3.29]
Rigotti 2010	68/355	26/289		3.5 %	2.13 [1.39, 3.25]
Stein 2013	2/137	0/35		0.1 %	1.30 [0.06, 26.57]
Tashkin 2011	46/248	14/157		2.1 %	2.08 [1.18, 3.66]
Tsai 2007	59/126	27/117		3.4 %	2.03 [1.39, 2.97]

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wang 2009	63/165	42/161		5.2 %	1.46 [1.06, 2.02]
Wong 2012	55/151	34/119		4.6 %	1.27 [0.90, 1.82]
Total (95% CI)	**7463**	**4959**		**100.0 %**	**1.79 [1.65, 1.94]**

Total events: 1879 (Treatment), 704 (Control)
Heterogeneity: Chi^2 = 68.07, df = 27 (P = 0.00002); I^2 =60%
Test for overall effect: Z = 14.40 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) per protocol and ITT denominators identical (no losses to follow-up reported)

Analysis 13.2. Comparison 13 Sensitivity analysis, Outcome 2 Continuous abstinence at 9 - 12 weeks.

Review: Nicotine receptor partial agonists for smoking cessation
Comparison: 13 Sensitivity analysis
Outcome: 2 Continuous abstinence at 9 - 12 weeks

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	92/256	42/269		4.0 %	2.30 [1.67, 3.18]
Bolliger 2011	209/390	37/199		4.8 %	2.88 [2.12, 3.91]
Carson 2014	95/190	71/194		6.9 %	1.37 [1.08, 1.73]
Chengappa 2014	15/31	3/29		0.3 %	4.68 [1.51, 14.50]
Cinciripini 2013	37/86	18/106		1.6 %	2.53 [1.56, 4.12]
De Dios 2012 (1)	3/10	0/11		0.0 %	7.64 [0.44, 131.75]
EAGLES 2016	682/2037	254/2035		25.1 %	2.68 [2.35, 3.06]
Eisenberg 2016	67/151	45/151		4.4 %	1.49 [1.10, 2.02]
Gonzales 2006	155/352	61/344		6.1 %	2.48 [1.92, 3.21]
Gonzales 2014	112/249	29/245		2.9 %	3.80 [2.63, 5.49]
Hajek 2015	26/100	23/100		2.3 %	1.13 [0.69, 1.84]
Jorenby 2006	151/344	60/341		6.0 %	2.49 [1.93, 3.23]

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nakamura 2007	104/155	60/154		5.9 %	1.72 [1.37, 2.16]
NCT01347112	6/16	1/17		0.1 %	6.38 [0.86, 47.29]
Niaura 2008	63/160	18/160		1.8 %	3.50 [2.17, 5.63]
Nides 2006	36/127	13/127		1.3 %	2.77 [1.54, 4.97]
Oncken 2006	128/259	15/129		2.0 %	4.25 [2.60, 6.95]
Rennard 2012	262/493	32/166		4.7 %	2.76 [2.00, 3.80]
Rigotti 2010	167/353	26/354		2.6 %	6.44 [4.38, 9.48]
Steinberg 2011	12/40	13/39		1.3 %	0.90 [0.47, 1.72]
Tashkin 2011	105/248	22/253		2.2 %	4.87 [3.18, 7.45]
Tsai 2007	75/126	40/124		4.0 %	1.85 [1.38, 2.47]
Wang 2009	83/165	53/168		5.2 %	1.59 [1.22, 2.09]
Wong 2012 (2)	71/151	43/135		4.5 %	1.48 [1.09, 1.99]
Total (95% CI)	**6489**	**5850**		**100.0 %**	**2.49 [2.33, 2.65]**

Total events: 2756 (Treatment), 979 (Control)

Heterogeneity: Chi^2 = 142.05, df = 23 (P<0.00001); I^2 =84%

Test for overall effect: Z = 27.82 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) 7-day PPA result

(2) 7-day PPA at 12 wks

Analysis 13.3. Comparison 13 Sensitivity analysis, Outcome 3 Continuous abstinence at 24 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 13 Sensitivity analysis

Outcome: 3 Continuous abstinence at 24 weeks

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Anthenelli 2013	64/256	33/269		4.0 %	2.04 [1.39, 2.99]
Bolliger 2011	155/394	26/199		4.3 %	3.01 [2.06, 4.40]
Carson 2014	78/191	54/194		6.6 %	1.47 [1.10, 1.95]
Chengappa 2014	6/31	2/29		0.3 %	2.81 [0.61, 12.81]
Cinciripini 2013	24/86	15/106		1.7 %	1.97 [1.11, 3.52]
De Dios 2012 (1)	3/10	0/11		0.1 %	7.64 [0.44, 131.75]
EAGLES 2016	444/2037	191/2035		23.6 %	2.32 [1.98, 2.72]
Ebbert 2015	244/760	52/750		6.5 %	4.63 [3.49, 6.14]
Eisenberg 2016	54/151	39/151		4.8 %	1.38 [0.98, 1.95]
Gonzales 2006	104/352	36/344		4.5 %	2.82 [1.99, 4.00]
Gonzales 2014	72/249	19/245		2.4 %	3.73 [2.32, 5.99]
Heydari 2012	52/89	12/91		1.5 %	4.43 [2.54, 7.72]
Jorenby 2006	102/344	45/341		5.6 %	2.25 [1.64, 3.09]
Nakamura 2007	63/155	44/154		5.5 %	1.42 [1.04, 1.95]
NCT01347112	4/16	0/17		0.1 %	9.53 [0.55, 164.01]
Niaura 2008	44/160	14/160		1.7 %	3.14 [1.80, 5.50]
Nides 2006	26/127	9/127		1.1 %	2.89 [1.41, 5.92]
Oncken 2006	75/259	7/129		1.2 %	5.34 [2.53, 11.24]
Rennard 2012	171/493	21/166		3.9 %	2.74 [1.81, 4.16]
Rigotti 2010	100/353	34/354		4.2 %	2.95 [2.06, 4.23]
Stein 2013	2/137	0/45		0.1 %	1.67 [0.08, 34.08]
Steinberg 2011	8/40	11/39		1.4 %	0.71 [0.32, 1.57]
Tashkin 2011	64/248	18/253		2.2 %	3.63 [2.22, 5.94]
Tsai 2007	59/126	27/124		3.4 %	2.15 [1.47, 3.15]
Wang 2009	63/165	42/168		5.1 %	1.53 [1.10, 2.12]
Wong 2012 (2)	54/151	35/135		4.6 %	1.38 [0.97, 1.97]

(*Continued* . . .)

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	**7380**	**6636**		**100.0 %**	**2.44 [2.26, 2.63]**
Total events: 2135 (Treatment), 786 (Control)					
Heterogeneity: Chi^2 = 103.35, df = 25 (P<0.00001); I^2 =76%					
Test for overall effect: Z = 23.28 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) 7-day PPA result

(2) 7-day PPA at 6m

APPENDICES

Appendix 1. Glossary of tobacco-related terms

Term	Definition
Abstinence	A period of being quit, i.e. stopping the use of cigarettes or other tobacco products. May be defined in various ways; see also: point prevalence abstinence; prolonged abstinence; continuous/sustained abstinence
Biochemical verification	Also called 'biochemical validation' or 'biochemical confirmation': A procedure for checking a tobacco user's report that he or she has not smoked or used tobacco. It can be measured by testing levels of nicotine or cotinine or other chemicals in blood, urine, or saliva, or by measuring levels of carbon monoxide in exhaled breath or in blood
Bupropion	A pharmaceutical drug originally developed as an antidepressant, but now also licensed for smoking cessation; trade names Zyban, Wellbutrin (when prescribed as an antidepressant)
Carbon monoxide (CO)	A colourless, odourless highly poisonous gas found in tobacco smoke and in the lungs of people who have recently smoked, or (in smaller amounts) in people who have been exposed to tobacco smoke. May be used for biochemical verification of abstinence
Cessation	Also called 'quitting' The goal of treatment to help people achieve abstinence from smoking or other tobacco use, also used to describe the process of changing the behaviour

(*Continued*)

Continuous abstinence	Also called 'sustained abstinence' A measure of cessation often used in clinical trials involving avoidance of all tobacco use since the quit day until the time the assessment is made. The definition occasionally allows for lapses. This is the most rigorous measure of abstinence
'Cold Turkey'	Quitting abruptly, and/or quitting without behavioural or pharmaceutical support
Craving	A very intense urge or desire [to smoke]. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614
Dopamine	A neurotransmitter in the brain which regulates mood, attention, pleasure, reward, motivation and movement
Efficacy	Also called 'treatment effect' or 'effect size': The difference in outcome between the experimental and control groups
Harm reduction	Strategies to reduce harm caused by continued tobacco/nicotine use, such as reducing the number of cigarettes smoked, or switching to different brands or products, e.g. potentially reduced exposure products (PREPs), smokeless tobacco
Lapse/slip	Terms sometimes used for a return to tobacco use after a period of abstinence. A lapse or slip might be defined as a puff or two on a cigarette. This may proceed to relapse, or abstinence may be regained. Some definitions of continuous, sustained or prolonged abstinence require complete abstinence, but some allow for a limited number or duration of slips. People who lapse are very likely to relapse, but some treatments may have their effect by helping people recover from a lapse
nAChR	[neural nicotinic acetylcholine receptors]: Areas in the brain which are thought to respond to nicotine, forming the basis of nicotine addiction by stimulating the overflow of dopamine
Nicotine	An alkaloid derived from tobacco, responsible for the psychoactive and addictive effects of smoking
Nicotine Replacement Therapy (NRT)	A smoking cessation treatment in which nicotine from tobacco is replaced for a limited period by pharmaceutical nicotine. This reduces the craving and withdrawal experienced during the initial period of abstinence while users are learning to be tobacco-free. The nicotine dose can be taken through the skin, using patches, by inhaling a spray, or by mouth using gum or lozenges
Outcome	Often used to describe the result being measured in trials that is of relevance to the review. For example smoking cessation is the outcome used in reviews of ways to help smokers quit. The exact outcome in terms of the definition of abstinence and the length of time that has elapsed since the quit attempt was made may vary from trial to trial
Pharmacotherapy	A treatment using pharmaceutical drugs, e.g. NRT, bupropion

(*Continued*)

Point prevalence abstinence (PPA)	A measure of cessation based on behaviour at a particular point in time, or during a relatively brief specified period, e.g. 24 hours, 7 days. It may include a mixture of recent and long-term quitters. cf. prolonged abstinence, continuous abstinence
Prolonged abstinence	A measure of cessation which typically allows a 'grace period' following the quit date (usually of about two weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging. See: Hughes et al 'Measures of abstinence in clinical trials: issues and recommendations'; Nicotine & Tobacco Research, 2003: 5 (1); 13-25
Relapse	A return to regular smoking after a period of abstinence
Secondhand smoke	Also called passive smoking or environmental tobacco smoke [ETS] A mixture of smoke exhaled by smokers and smoke released from smouldering cigarettes, cigars, pipes, bidis, etc. The smoke mixture contains gases and particulates, including nicotine, carcinogens and toxins
Self efficacy	The belief that one will be able to change one's behaviour, e.g. to quit smoking
SPC [Summary of Product Characteristics]	Advice from the manufacturers of a drug, agreed with the relevant licensing authority, to enable health professionals to prescribe and use the treatment safely and effectively
Tapering	A gradual decrease in dose at the end of treatment, as an alternative to abruptly stopping treatment
Titration	A technique of dosing at low levels at the beginning of treatment, and gradually increasing to full dose over a few days, to allow the body to get used to the drug. It is designed to limit side effects
Withdrawal	A variety of behavioural, affective, cognitive and physiological symptoms, usually transient, which occur after use of an addictive drug is reduced or stopped. See: Shiffman et al 'Recommendations for the assessment of tobacco craving and withdrawal in smoking cessation trials' Nicotine & Tobacco Research 2004: 6(4): 599-614

Appendix 2. Participant numbers in varenicline trials

Study	*Varenicline*	*Placebo*	*Bupropion*	*NRT*	*TOTAL*
Anthenelli 2013	256	269			525
Aubin 2008	378			379	757
Baker 2016	424			662	

(*Continued*)

Bolliger 2011	394	199			593
Carson 2014	196	196			392
Chengappa 2014	31	29			60
Cinciripini 2013	86	106	102		294
De Dios 2012	10	11		11	32
EAGLES 2016	Psych 1032 Non-psych 1005	Psych 1026 Non-psych 1009	Psych 1033 Non-psych 1001	Psych 1025 Non-psych 1013	4116 4028
Ebbert 2015	760	750			1510
Eisenberg 2016	151	151			302
Evins 2014	40	47			87
Gonzales 2006	352	344	329		1025
Gonzales 2014	249	245			494
Hajek 2015	100	100			200
Heydari 2012	89	91		92	272
Jorenby 2006	344	341	342		1027
Nahvi 2014a	57	55			112
Nides 2006	128 (0.3 x 1) 128 (1.0 x 1) 127 (1.0 x 2)*	127	128		638
NCT00828113	50 (Extended) 51 (Standard)				101
NCT01347112	16	17			33
Oncken 2006	129 (0.5NT) 130 (0.5T) 129 (1.0NT)* 130 (1.0T)*	129			647
Williams 2012	85	43			128
Rennard 2012	493	166			659

(*Continued*)

Stein 2013	137	45		133	315
Tønnesen 2013	70	69			139
Tonstad 2006	1927 Phase 1 [603] Phase 2*	[607] Phase 2			1927
Nakamura 2007	153 (0.25x2) 156 (0.5x2) 156 (1.0x2)*	154			619
Tsai 2007	126	124			250
Williams 2007	251	126			377
Niaura 2008	160	160			320
Wang 2009	165	168			333
Rigotti 2010	355	359			714
Rose 2013	112			114	226
Steinberg 2011	40	39			79
Tsukahara 2010	16			16	32
Tashkin 2011	250	254			504
Westergaard 2015	26	25			52
Wong 2012	151	135			286
TOTALS	**11,801** * used in primary MA	**7109**	**2935**	**3445**	**25,290**

Appendix 3. Measures of craving, withdrawal and reinforcement

Study	MNWS or WSWS	QSU-B Total Craving score	mCEQ (for smokers)
Carson 2014 (wk 1) 1.0 mg bid vs placebo	At week 1, Likert scale: Craving: V: 3.36; placebo: 4.45 Anxiety: V: 3.19; placebo: 4.25 Confidence: V: 7.95; placebo:		

(*Continued*)

	7.02 Motivation: V: 8.22; placebo: 7.50		
Gonzales 2006 (wks 1 - 7) 1.0 mg bid vs placebo	Urge to smoke: -0.54 (P < .001) ES: -0.57*N Negative affect: -0.19 (P < .001) ES: -0.30 Restlessness: -0.14 (P < .01) ES: -0.16 Increased appetite: +0.12 (P = .04) ES: 0.15 Insomnia: +0.05 (P = .36) ES: 0.06	-0.45 (1.69 V, 2.13 P); P < 0.001; ES: -0.33	Baseline to wk 1: diff in changes between V&P: Smoking satisfaction: -0.60 (P < .001) ES: -0.47 Psych Reward: -0.50 (P < .001) ES: -0.37 Enjoy resp tract: -0.34 (P < .001) ES: -0.21 Craving reduction: -0.52 (P < .001) ES: -0.33 Aversion: -0.18 (P = .053) ES: -0.19
Jorenby 2006 (wks 1 - 7) 1.0 mg bid vs placebo	Diff in mean change in: Urge to smoke: -0.48 (P < .001) Negative affect: -0.13 (P = 0.001) Restlessness:-0.10(P = 0.05) Increased appetite: +0.07 (P = 0.22) Insomnia: +0.10 (P = 0.07)	-0.44 ; (P < .001) [Factor 1 (pleasure) -0.56; (P < .001) Factor 2 (negative affect relief) -0.27 (P < .001)]	Baseline to wk 1: diff in changes between V&P: Smoking satisfaction: -0.44 (P < .001) Psych Reward: -0.32 (P < .001) Enjoy resp tract: -0.22 (P = 0.01) Craving reduction: -0.25 (P = 0.04) Aversion: 0 (P = 0.96)
Nides 2006 (wks 1 - 7) 1.0 mg bid vs placebo	Diff in mean change in: Urge to smoke: wk 1 -1.14; wk 2 -1.19; wk 3 -1.57; wk 4 -1.81; wk 5 -1.88; wk 6 -2.04; wk 7 -1.61(P < .001 for wks 1 - 6, P < .01 wk 7)	Total score: wk 1 -7.00; wk 2 -10.71; wk 3 -12.72; wk 4 -14.08; wk 5 -13.24; wk 6 -14.94; wk 7 -14.38 (wks 1, 3, 5 P < .001, wks 2, 4, 6, 7 P < .01)	Baseline to wk 1: diff in changes between V&P: Smoking satisfaction: -1.62 Psych Reward: -0.35 Enjoy resp tract: -0.29 Craving reduction: -0.13 Aversion:-0.79
Oncken 2006 (MNWS: wks 1 - 12; mCEQ wks 1 - 7) 1.0 mg bid vs placebo	Diff in mean change in Urge to Smoke score (extrapolated from graph): Wk 7: -0.2, Wk 12 -0.5; (P < .001 for both)		Baseline to wk 7: diff in changes between V&P: (extrapolated from graph) Smoking satisfaction: -1.3 (P < 0.01) Psych reward: -2.2 (P < 0.001) Enjoy resp tract: -0.6 (P < 0.001)

(*Continued*)

Tonstad 2006 1.0 mg bid vs placebo	Diff in mean change in Urge to Smoke score (extrapolated from graph): All participants: Wk 13: -0.35, Wk 25 -0.25; Abstainers only: Wk 13: -0.30, Wk 25 +0.02		
Tsai 2007 (wks 1 - 6) 1.0 mg bid vs placebo	Diff in mean change in Urge to Smoke: Wks 1 - 6: -0.40 (P < 0.001)	Mean total score, wks 1 - 6: -0.39 (P < 0.001)	Mean diff wks 1 - 6: V vs P: Smoking satisfaction: -0.39 (P < 0.008)
Nakamura 2007 (wks 1 - 7) 1.0 mg bid vs placebo (Nicotine-dependent group only)	Diff in mean change in: Urge to Smoke score: -0.51 (P < 0.001) Negative Affect score: -0.28 (P < 0.001) Restlessness score: -0.38 (P < 0.001) Appetite+ score: -0.09 (P = 0.481) Insomnia score: 0.56 (P = 0.380)	Mean total score: -0.51 (P < 0.001) Factor 1 [pleasure] mean diff: -0.60 (P < 0.001) Factor 2 [negative affect] mean diff: -0.38 (P < 0.001)	Mean diff wks 1 - 7: V vs P: Smoking satisfaction: -0.74 (P < 0.001) Psych reward: -0.53 (P < 0.001) Enjoy resp tract: -1.00 (P < 0.001) Craving reduction: -0.45 (P < 0.001) Aversion:-0.38 (P < 0.0007)
Steinberg 2011 1.0 mg bid vs placebo	At 4 wks, Varenicline group had score of -1.45, placebo +0.11		
Aubin 2008 (wks 1 - 7) 1.0 mg bid **vs NRT**	Diff in mean change in: Urge to Smoke score: -0.32 (P < 0.001); E.S. -0.37 Negative Affect score: -0.16 (P < 0.001); E.S. -0.21 Restlessness score: -0.20 (P < 0.001); E.S. -0.21 Appetite + score: 0.09 (P = 0.116); E.S. 0.12 Insomnia score: -0.07 (P = 0.207); E.S. -0.07		Mean diff wks 1 - 7: V vs NRT: Smoking satisfaction: -0.54 (P < 0.001); E.S. -0.43 Psych reward: -0.32 (P = 0.001) E.S. -0.26 Enjoy resp tract: -0.39 (P < 0.001); E.S. -0.25 Craving reduction: -0.52 (P < 0.001); E.S. -0.32 Aversion: -0.07 (P = 0.436); E.S. 0.08
Niaura 2008 1 - 4 x 0.5 mg *ad lib*	Diff in Urge to smoke, all pts: Wk 1: -0.4; Wk 2: -0.4; Wk 3 -0.6; Wk 4 -0.5; Wk 5 -0.6; Wk		Diff in changes between V&P: Smoking satisfaction: Enjoy resp tract: Wk 1 -0.1; Wk

(*Continued*)

	6 -0.5; Wk 7 -0.4; Wk 12 -0.6 Diff in withdrawal, all pts: Wk 1: -0.4; Wk 2: -0.7; Wk 3 -0.7; Wk 4 -1.1; Wk 5 -0.3; Wk 6 -0.4; Wk 7 -0.2; Wk 12 -0.9		2 -0.3; Wk 3 -0.4; Wk 4 -0.5; Wk 5 -0.5; Wk 6 -0.5; Wk 7 -0.4
Tsukahara 2010 1.0 mg bid **vs NRT**	Diff in withdrawal score (all symptoms), V vs NRT: Wk 2 2.36; Wk 4 0.64; Wk 8 0.78; Wk 12 0.08		
Cinciripini 2013			Significantly higher reward score (3.8) in placebo relapsers than in varenicline relapsers (2.7; P = 0.01) (extrapolated from graph)
Evins 2014	WSWS measured over 12 wks open-label varenicline: Total score: Baseline:59.9 - wk 12: 50.77 Urge to smoke: Baseline: 11.85 - wk12: 8.2 Irritability: Baseline: 5.62 - wk 12: 4.46 Depression: Baseline: 6.61 - wk 12: 5.8 Increased appetite: Baseline: 11.79 - wk 12: 11.88 Difficulty concentrating: Baseline: 5.86 - wk 12: 5.15 Insomnia: Baseline: 8.52 - wk 12: 8.25 Anxiety: Baseline: 8.84 - wk 12: 7.04		
Tønnesen 2013	For V vs placebo at 12 wks: Craving: -0.26 for V (P < 0.0001) Appetite: -0.14 for V (P = 0.001) Total symptoms score: -0.16 (P = 0.002)		
Hajek 2015	Smoking enjoyment ratings up to TQD: Baseline/pre-randomizarion: V: 2.5, placebo: 2.5 Day 15 (≤ 3 mg/day): V: 1.8, placebo: 2.1		

(*Continued*)

	Day 18 (≤ 4 mg/day): V: 1.7, placebo: 2.1 TQD (day 21; ≤ 5 mg/day): V: 1.6, placebo: 2.0			

Appendix 4. Serious Adverse Events and deaths

Study ID	Period	Placebo	Varenicline	Bupropion	NRT
VARENICLINE trials					
Anthenelli 2013	*During treatment or within 30 days of last dose*	Intentional self injury; Depression with suicidal ideation; Agitation; Depression	Psychotic disorder and depression; Suicidal ideation		
	Post-treatment to week 52	Intentional self injury 2 other SAEs	2 deaths: overdose of clonazepam and morphine sulfate; Accidental fall 3 other SAEs		
Aubin 2008	*During treatment or within 30 days of last dose*		Depression*; Constipation		Bile duct ca, sepsis; Gastrointestinal bleed; MI (2); Chest pain (2); Salivary gland tumour; Aggravation of old knee trauma
			Acute ethanol intoxication; Suicidal ideation*; No deaths reported		Abdominal cyst; No deaths reported
Baker 2016	*Post-treatment to week 52*		Hospitalised due to allergic reaction to varenicline		None reported
Bolliger 2011	*During treatment or within 30 days of last dose*	Thyroid neoplasm; Appendicitis, peritonitis, diverticuli-	Abortion (possibly *); Hypersensitivity;		

(*Continued*)

		tis; No deaths reported	Overdose; Bronchitis and asthma; Nasal septum deviation; Suicidal ideation + depressed mood; Suicidal ideation*; Tachycardia, bradychardia +dyspnoea; Panic attack; Injury; Appendicitis No deaths reported		
Carson 2014	*During treatment*	*(active control: counselling):* Depressive episodes x 2; Agitation; 4 N-STEMI (died); 2 lung ca (died) 1 stroke (died)	Atrial fibrillation; Depressive episodes x 3; Aggression; 1 arrhythmia (died) 1 bradycardia (died) 2 respiratory/ COPD (died) 2 N-STEMI (died)		
	Post-treatment to 52 weeks		Depressive episode		
Chengappa 2014	*During treatment*	Alcohol intoxication; Exacerbation of asthma; Pregnancy;	Exacerbation of anxiety; Rash; Agitation, hostility, alcohol abuse, drug abuse*; Hypoxia, asthma with COPD; Tremulousness, grogginess, left-arm weakness;		
	Post-treatment to 52 weeks	Chest pain, left-hand numbness	Pneuomonia		
Cincripini 2013		Diabetes; Chest pain*	Chest pain; Psychiatric hospitalisation	Bilateral mammoplasty; Facial paralysis; Syncope*	

(*Continued*)

EAGLES 2016	*During treatment or within 30 days of last dose* (Detail of SAES given in ClinicalTrials.gov posted results)	16 (non-psych) 25 (psych) 2 deaths (suicide, non-psych; pulmonary embolism, psych)	16 (non-psych) 23 (psych) 2 deaths (heroin OD non-psych; CV event, psych)	19 (non-psych) 29 (psych)	21 (non-psych) 24 (psych)
	> 30 days after last dose	2 deaths (RTA, non-psych; MI, non-psych)		1 death (lung cancer, psych)	3 deaths (prostate cancer, non-psych; oesophageal adenoma, psych; sepsis, psych)
Ebbert 2015	*During treatment or within 30 days of last dose*	10 x suicidal ideation	6 x suicidal ideation		
	Post-treatment to week 52	18 other SAEs	10 other SAEs		
Eisenberg 2016	*Within 30 days of treatment*	3 MIs 5 unstable anginas Ischaemic cardiomyopathy Sick sinus syndrome Ruptured pseudoaneurysm Bowel obstruction COPD Rheumatoid arthritis Road traffic accident Melena Non-cardiac chest pain Allergic reaction	2 deaths (1 cardiac, 1 sudden death undefined) 3 MIs Unstable angina Depression Pulmonary embolism TIA Arrythmia and ICD implant 2 gastric bleeds 2 suspected unstable anginas (ruled out) Peroneal embolus with septic cellulitis Bowel surgery Dehydration Syncope Wound infection		
Evins 2014	*Randomization phase*	Sepsis (died); MI; Depressed mod and discontinuation of meds; Suicidal ideation; Worsened	Pancreatitis; Hyperglycaemia; Depressed mood; Worsened psychotic symptoms		

(*Continued*)

		psychosis; Worsened psychosis and MJ intoxication; Manic symptoms			
Gonzales 2006	*During treatment or within 7 days of last dose*	Lung cancer; Acute MI; Acute exacerbation of schizophrenia; Chest pain (2); UTI Atrial fibrillation	Abdominal pain; Atrial fibrillation*; Pneumonia; Possible stroke	Cholecystitis, septic shock; Headache; Grand mal seizure*	
	Post-treatment to week 52	Mediastinal mass; Fall, fractured elbow, collapsed lung, death unexplained; I death (as above)	Non-cardiac chest pain; Acute appendicitis; No deaths reported	Appendicitis; UTI; No deaths reported	
Gonzales 2014	*During treatment or within 30 days of last dose*	Acute coronary syndrome; Ligament rupture; Hyperventilation; Drug sensitivity	Knee arthroplasty; pyelonephritis; Intervertebral disc protrusion; Ankle fracture; Chest pain*; Drug sensitivity to amoxicillin; Drug sensitivity to hair dye		
	Post-treatment to week 52		Acute on chronic alcoholism (died)		
Jorenby 2006	*During treatment or within 7 days of last dose*	Ruptured ovarian cyst; Ischaemic heart disease; Ruptured appendix; Pneumonia; Allergic reaction	Lung or brain cancer; Acute coronary syndrome; Chest pain; Dehydration, periorbital cellulitis; Acute psychosis, emotional lability; Vertigo, raised BP, chest pain*	Ectopic pregnancy; Angiodoema*; Gunshot wound; Post-op bleeding; Lower Leg pain; Breast cancer (female)	

(*Continued*)

	Post-treatment to week 52	Appendicitis; No deaths reported	Staphylococcal cellulitis; Acute psychosis; No deaths reported	Occlusion coronary artery; Miscarriage; 1 death (RTA)	
Nahvi 2014a	*During treatment*	Chest pain; Alcohol detoxification	Hypoglycaemia; Alcohol and cocaine rehab; Knee replacement		
	Post-treatment to 24 weeks	Total hip relacement	Alcohol rehab, acute cholecystitis; Asthma exacerbation		
Nakamura 2007	*During treatment*	Subarachnoid haemorrhage; Contusion; Foot fracture	*0.25 mg bid:* Gastroenteritis; Cholecystitis*; Gastric cancer; Cholecystitis, peritonitis; Herpes Zoster *0.5mg bid:* Haemorrhoids, intestinal prolapse; Pituitary haemorrhage; *1 mg bid:* Neurosensory deafness; Angina pectoris*, intervertebral disc protrusion, MS; 1 death (RTA)		
NCT00828113	*During treatment*	Road traffic accident			
	More than 30 days after treatment		Bladder surgery		
Niaura 2008	*Post-treatment or within 30 days of last dose*	None reported No deaths reported	MI; Ventricular fibrillation; Spontaneous abortion; No deaths reported		

(*Continued*)

Nides 2006	*During treatment*	None reported No deaths reported	Transient ischaemic attack*, transient loss of vision*; No deaths reported	Syncope, possible seizure*; Grand mal convulsion*; Bloody diarrhoea*; No deaths reported	
Oncken 2006	*During treatment*	Syncope	Syncope; Duodenal ulcer; Cholesteatoma; Generalised tonic-clonic seizure; Unstable angina; Paroxysmal supraventricular tachycardia; Cholelithiasis; Aseptic meningitis; Relapsing MS	None reported	
	Post-treatment	Suicide attempt; No deaths reported	Carcinoid colon cancer; Diabetes (> 30d post-treat); No deaths reported	None reported No deaths reported	
Rennard 2011	*During treatment and within 30 days of last dose*	Suicidal ideation	Intervertebral disc protrusion x 2; Carotid artery stenosis; Syncope; PAOD; Ureteric calculus		
Rigotti 2010	*During treatment*	Atrial fibrillation*; Congestive cardiac failure*; Chest pain*; Acute coronary syndrome*; + 17 others 1 death (unrelated)	Chest pain*; MI*; Gingival bleeding*; CVA*; + 19 others		
	Post-treatment to week 52	4 deaths (unrelated)	2 deaths (unrelated)		
Stein 2013	*During and post-treatment*		Rashes x 2		Heart attack

(*Continued*)

Steinberg 2011	*During and post-treatment to week 24*	5 events (no detail) No deaths	6 events (no detail) No deaths		
Tashkin 2010	*During treatment or within 28 days of last dose*	Bronchitis; CVA; Cholelithiasis; Lung cancer; Pneumonia; Musculoskeletal pain; Acute MI; Appendicitis; COPD; Chest pain; Anxiety	Acute MI; Vocal cord polyp; Hyperkeratosis; Back pain; Angina pectoris; CVA; Cellulitis;		
	Post-treatment	COPD; Pneumonia; Palpitations; Chest pain; 1 death (amyotrophic lateral sclerosis)	L Ventricular dysfunction; Aortic valve stenosis; COPD; Chest pain; Laryngeal cancer; 2 deaths (1 cardiac, I RTA)		
Tønnesen 2013	*Post-treatment*	Rectal cancer with ileostomy, peritonitis; Gall stone; Malignant melanoma; Exacerbation of COPD	Stroke; Severe constipation; Bradycardia; Cardiac arrest; Probable dengue fever		
Tonstad 2006	*Open-label phase (during treatment)*		R Breast indeterminate path; Suicidal ideation; Menorrhagia; Glandular adenocarcinoma; Diminshed vision; Accidental injury; Headache; Abdominal pain*; Acute psychosis*; Acute pancreatitis; Neopharyngeal car-		

(*Continued*)

			cinoma; Raised AST, ALT, LDH, CPK; Grand mal convulsion; Atrial fibrillation; Ureteral stones; Persistent epistaxis; Worsening kidney stones; Loss of teeth, dislocated shoulder		
	Open-label phase (post-treatment)		MI; Miscarriage		
	Double-blind phase (during treatment)	Increased dysmenorrhoea; Appendicitis; Spinal cord compression; Abdominal pain	Injury to tibial artery; Uterine & bladder prolapse, suspected MI; Alcohol poisoning, costal fracture; Transient vision loss*; MI		
	Double-blind phase (post- treatment)	Acute cholecystitis; No deaths reported	Colon cancer; Tumour; Ovarian tumour; Cerebral infarct, deep cerebral vein thrombosis; Supraventricular tachycardia; 3 deaths (unrelated)		
Tsai 2007	*During treatment or within 28 days of last dose*	3 RTAs; No deaths reported	Unstable angina*; Acute pyelonephritis; Peritonitis, acute appendicitis; No deaths reported		
Tsukahara 2010		None reported	None reported		

(*Continued*)

Wang 2009	*During treatment or within 7 days of last dose*	Intestinal ulcer; 1 not described; No deaths reported	None reported No deaths reported		
Williams 2007	*Up to week 52*	Vertebral compression fracture; DVT, pulmonary embolism; Worsening coronary artery disease; No deaths reported	Coronary artery disease; Herniated disc; Bilateral subcapsular cataracts* Chest pain, hypoglycaemia; Sinus bradycardia, hypotension, ventricular bigeminy, coronary angioplasty; Stroke; Cardiac catheterization; Tachycardia; Suspected GI bleed; Saphenous vein occlusion, ischaemia; MI, DVT; Ileus; Chest wall pain; Non-cardiac chest pain, chronic bronchitis, pneumonia, chest pain; Spinal stenosis; No deaths reported		
Williams 2012	*During treatment and within 30 days of last dose*	Hyperglycaemia; Breast cancer; Aggression; Suicidal ideation; No deaths	Chest pain; Convulsion; "Psychiatric symptom"; Suicidal ideation; Suicidal attempt; Asthma; 1 death		
CYTISINE trials					
Scharfenberg 1971	*CYTISINE*	Not reported	Not reported		
Vinnikov 2008	*CYTISINE*	None reported	None reported		

(*Continued*)

Walker 2014			56 events in 45 people (see Table S5 in NEJM supplementary data)		45 events in 39 people (see Table S5 in NEJM supplementary data)
West 2011	*CYTISINE*	COPD (died); Stroke (died); Lung cancer (died)	Stroke; Tracheal cancer; Cardiac arrest (died) ; Lung cancer (died);		
DIANICLINE trial					
Tonstad 2011	*DIANICLINE*	Subileus; Thrombophlebitis; SVT; No deaths reported	Appendicitis; Severe asthma; MI; No deaths reported		

* Possibly, probably or definitely attributable to study medication

Abbreviations: ALT: Alanine transaminase; AST: Aspartate transaminase; BP: blood pressure; COPD: Chronic Obstructive Pulmonary Disease; CPK: Creatine phosphokinase; CVA: cerebrovascular accident; DVT: deep vein thrombosis; LDH: Lactate dehydrogenase; MI: myocardial infarction; MS: Multiple Sclerosis; N/STEMI: non-ST-elevation myocardial infarction; PAOD: peripheral arterial occlusive disease; RTA: road traffic accident; SVT: supraventricular tachycardia; UTI: urinary tract infection

WHAT'S NEW

Last assessed as up-to-date: 12 May 2015.

Date	Event	Description
31 January 2016	New citation required and conclusions have changed	Additional comparisons. Analyses expanded and restructure. SAE information updated
31 January 2016	New search has been performed	39 trials of varenicline now included

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2007

Date	Event	Description
16 May 2013	Amended	Minor change made to labelling on forest plot.
14 March 2012	New citation required and conclusions have changed	Safety profile modified, as new possible cardiovascular and psychiatric adverse events information incorporated. Efficacy findings unchanged but confirmed
14 March 2012	New search has been performed	Seven new included studies (5 varenicline, 1 cytisine, 1 dianicline) and 14 new excluded studies added, plus safety data
13 January 2011	Amended	Vinnikov trial of cytisine added to Studies awaiting Classification, for inclusion in next update
8 November 2010	New search has been performed	Six new RCTs added; sources of funding added for all trials. Ongoing trials section expanded
8 November 2010	New citation required and conclusions have changed	Surveillance data and secondary analyses do not support fears about safety. Efficacy conclusions strengthened but unchanged
17 July 2008	Amended	Date of last search amended (2007 corrected to 2008) ; Source of support added
12 May 2008	New citation required and conclusions have changed	Three new included trials, switch in the MA metric from OR to RR, updated background section and new safety information
15 March 2008	New search has been performed	New search conducted.
30 August 2007	Amended	Converted to new review format.
15 November 2006	New citation required and conclusions have changed	Substantive amendment.

CONTRIBUTIONS OF AUTHORS

KC: Performed clinical trials register searching, extracted data, conducted the analyses and wrote the review.

NL-H: Extracted data, contributed to the writing and updating process.

TF: Conducted the neuropsychiatric adverse event meta-analyses and advised on statistical interpretation.

KT: Contributed data and advice on neuropsychiatric adverse event data.

TL: Gave editorial and conceptual support.

All authors contributed to text and findings, and approved the final version.

DECLARATIONS OF INTEREST

Kate Cahill : None known

Nicola Lindson-Hawley: NLH is a co-applicant on the Preloading Trial, which is funded by the NIHR HTA. The study treatment is nicotine patches which are provided free of charge by GlaxoSmithKline.

Tom Fanshawe: None known

Kyla Thomas: None known

Tim Lancaster: None known

Robert West, who is an editor for the Tobacco Addiction Group, has ruled himself out of participating in the editorial process for this review, as he is a member of the varenicline advisory board for Pfizer Inc.

SOURCES OF SUPPORT

Internal sources

- Department of Primary Care Health Sciences, University of Oxford, UK.
- National School for Health Research School for Primary Care Research, UK.

External sources

- NHS Research and Development Fund, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this 2016 update, we have restructured the analyses to accommodate increasing variation in the settings, populations, comparisons and regimens of trials that have been conducted.

For this 2016 update we include 'Summary of findings' tables for the main comparisons.

INDEX TERMS

Medical Subject Headings (MeSH)

Alkaloids [*therapeutic use]; Azepines [*therapeutic use]; Azocines [therapeutic use]; Benzazepines [*therapeutic use]; Bupropion [therapeutic use]; Counseling [methods]; Heterocyclic Compounds with 4 or More Rings [*therapeutic use]; Nicotine [adverse effects; antagonists & inhibitors]; Nicotinic Agonists [adverse effects; *therapeutic use]; Quinolizines [therapeutic use]; Quinoxalines [*therapeutic use]; Randomized Controlled Trials as Topic; Smoking [drug therapy]; Smoking Cessation [*methods]; Substance Withdrawal Syndrome [prevention & control]; Varenicline

MeSH check words

Humans