Nicotine receptor partial agonists for smoking cessation (Review)

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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). Varenicline was developed as a nicotine receptor partial agonist from cytisine, a drug widely used in central and eastern Europe for smoking cessation. The first trial reports of varenicline were released in 2006, and further trials have now been published or are currently underway.

Objectives

The primary objective of this review is to assess the efficacy and tolerability of nicotine receptor partial agonists, including varenicline and cytisine, for smoking cessation.

Search strategy

We searched the Cochrane Tobacco Addiction Group's specialised register for trials, using the terms ('varenicline' or 'cytisine' or 'Tabex' or 'nicotine receptor partial agonist') and 'smoking' in the title or abstract, or as keywords. We also searched MEDLINE, EMBASE, PsycINFO and CINAHL using MeSH terms and free text, and we contacted authors of trial reports for additional information where necessary. The latest search was in September 2010.

Selection criteria

We included randomized 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 randomization procedure, concealment of allocation, and completeness of follow up.

The main outcome measured was abstinence from smoking after at least six months from the beginning of treatment. We used the most rigorous definition of abstinence, and preferred biochemically validated rates where they were reported. Where appropriate we performed meta-analysis to produce a risk ratio, using the Mantel-Haenszel fixed-effect model.

Main results

We found 11 trials of varenicline compared with placebo for smoking cessation; three of these included a bupropion experimental arm. We also found one relapse prevention trial, comparing varenicline with placebo, and two open-label trials comparing varenicline with nicotine replacement therapy (NRT). We also include one trial in which all the participants were given varenicline, but received behavioural support either online or by phone calls, or by both methods. This trial is not included in the analyses, but contributes to the data on safety and tolerability. The included studies covered >10,300 participants, 6892 of whom used varenicline. We identified one trial of cytisine (Tabex) for inclusion.

The pooled risk ratio (RR) (10 trials, 4443 people, excluding one trial evaluating long term safety) for continuous abstinence at six months or longer for varenicline at standard dosage versus placebo was 2.31 (95% confidence interval [CI] 2.01 to 2.66). Varenicline at lower or variable doses was also shown to be effective, with an RR of 2.09 (95% CI 1.56 to 2.78; 4 trials, 1272 people). The pooled RR for varenicline versus bupropion at one year was 1.52 (95% CI 1.22 to 1.88; 3 trials, 1622 people). The RR for varenicline versus NRT for point prevalence abstinence at 24 weeks was 1.13 (95% CI 0.94 to 1.35; 2 trials, 778 people). The two 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 main adverse effect of varenicline was nausea, which was mostly at mild to moderate levels and usually subsided over time. Post-marketing safety data raised questions about a possible association between varenicline and depressed mood, agitation, and suicidal behaviour or ideation. The labelling of varenicline was amended in 2008, and the manufacturers produced a Medication Guide. Thus far, surveillance reports and secondary analyses of trial data lend little support to a causal relationship.

The one cytisine trial included in this review found that more participants taking cytisine stopped smoking compared with placebo at two-year follow up, with an RR of 1.61 (95% CI 1.24 to 2.08).

Authors' conclusions

Varenicline at standard dose increased the chances of successful long-term smoking cessation between two- and threefold 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. Two open-label trials of varenicline versus NRT suggested a modest benefit of varenicline but confidence intervals did not rule out equivalence. Limited evidence suggests that varenicline may have a role to play in relapse prevention. The main adverse effect of varenicline is nausea, but mostly at mild to moderate levels and tending to subside over time. Possible links with serious adverse events, including depressed mood, agitation and suicidal thoughts, have been reported but are so far not substantiated.

There is a need for further independent community-based trials of varenicline, to test its efficacy and safety in smokers with varying co-morbidities and risk patterns. There is a need for further trials of the efficacy of treatment extended beyond 12 weeks. Cytisine may also increase the chances of quitting, but the evidence at present is inconclusive.

PLAIN LANGUAGE SUMMARY

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

When people stop smoking they experience cravings to smoke and unpleasant mood changes. Nicotine receptor partial agonists such as varenicline aim to reduce withdrawal symptoms and smoking satisfaction. We found 11 randomized controlled trials of varenicline compared with placebo. Three of these trials also included a direct comparison with bupropion. One other trial tested varenicline against placebo, as maintenance therapy for those who had recently quit with varenicline. Two further trials compared varenicline with nicotine patches. One trial gave varenicline to all participants, but varied the delivery of behavioural support. This trial is not included in the analyses, but contributes to the data on safety and tolerability. From these data, varenicline at standard dose increased the chances of quitting more than two-fold compared with placebo. Low-dose varenicline 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. The two trials with nicotine patches did not show a clear benefit of varenicline over the patches. The main side effect of varenicline was nausea, but this was mostly at mild or moderate levels and usually subsided over time. After the licensing phase, there were concerns that varenicline may be linked with depressed mood, agitation or suicidal thinking and behaviour in some smokers. Surveillance studies and further analyses of the trial data have not so far found strong support for this association.

The evidence on cytisine is limited at present, and no firm conclusions can yet be drawn about its effectiveness as an aid to quitting.

BACKGROUND

Smoking is the main preventable cause worldwide of morbidity and premature death. At current rates of smoking, about half of all smokers in the USA and the UK will die prematurely of tobacco-related diseases (DOH 1998; Fiore 2004). 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).

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, which had been shown to be an effective partial agonist for $\alpha 4\beta 2$ receptors (Papke 1994; Slater 2003). Cytisine was developed as a treatment for tobacco dependence in Bulgaria in the 1960s, and is still commercially available in some eastern and central European countries and through internet sales, under the trade name of Tabex (Foulds 2004). Its manufacturers, Sopharma Pharmaceuticals, developed their phytoproduct from the plant Cytisus Laburnum L. (Golden Rain).

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). The relationship between the binding affinity and the functional potency of varenicline at different receptors is still being explored, and more research is needed to establish the precise mechanism of varenicline for smoking cessation (Balfour 2006).

Studies of cytisine have been conducted in Bulgaria, Germany, Russia and Poland, and a Warsaw-based randomized controlled trial is underway. Multicentre trials of varenicline are currently underway or in the preliminary report stage in the USA, Canada, Europe, Australia, Taiwan and South Korea. In addition to placebo-controlled trials, one trial includes direct comparison with NRT. There are also studies underway in special groups, including patients with cardiovascular disease and chronic obstructive pulmonary disease.

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).

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

Types of interventions

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

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 ('varenicline' or 'cytisine' or 'Tabex' or 'nicotine receptor partial agonist') and 'smoking' in the title or abstract, or as keywords. This register has been developed from electronic searching of MEDLINE, EMBASE, PsycINFO and Web of Science, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. We also searched MEDLINE, EMBASE, CINAHL and PsycINFO, using the major MESH terms 'Nicotinic-Agonists' and 'Receptors, Nicotinic'.
We have also searched UK and US online clinical trials registers for ongoing and recently completed trials.
We contacted the authors of ongoing studies of varenicline and cytisine where necessary.
Most recent searches were conducted in September 2010.

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 (LS) checked them. Any discrepancies were resolved by mutual consent, or by recourse to the Co-ordinating Editor. 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 randomization procedure and allocation concealment, as described in the Cochrane Handbook (Higgins 2008). 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 randomization and allocation, and blinding of trialists, participants and assessors
- Demographic characteristics of participants (e.g. average age, sex, average cigs/day)
- Intervention and control description (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

Quit rates are calculated based on the numbers of people randomized to an intervention, and excluding any deaths or untraceable moves, in accordance with the proposed 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.

Although our original review reported the findings as odds ratios, for greater clarity we now present them as risk ratios. Where appropriate, we have conducted meta-analyses of the included studies, using the Mantel-Haenszel risk ratio and a fixed-effect method, 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.
We include in this review the Tobacco Addiction Group glossary of tobacco-specific terms (Appendix 1).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
We found sixteen trials which met our inclusion criteria. Eleven double-blinded randomized controlled trials evaluated varenicline for smoking cessation (Gonzales 2006; Jorenby 2006; Nakamura 2007; Niaura 2008; Nides 2006; Oncken 2006; Rigotti 2010; Tashkin 2010; Tsai 2007; Wang 2009; Williams 2007). Two open-label randomized trials (Aubin 2008; Tsukahara 2010) compared varenicline with nicotine replacement therapy (NRT), but without a placebo arm. One trial evaluated varenicline as an aid to relapse prevention (Tonstad 2006). One trial gave varenicline to all the participants, but delivered behavioural support either online or by phone calls, or by both methods (Swan 2010); data for this trial are not included in any meta-analyses, but contribute to the evaluation of safety and tolerability. One early smoking cessation trial (Scharfenberg 1971) evaluated cytisine (Tabex). Full details of each trial are given in the Characteristics of included studies table.
Thirteen trials compared the experimental drug with a placebo. Gonzales 2006, Jorenby 2006 and Nides 2006 also included an additional experimental arm, comparing bupropion with varenicline and with placebo. Nakamura 2007, Nides 2006 and Oncken 2006 were phase 2 trials, designed to compare the effects of different dose regimens on cessation, tolerability and safety. Niaura 2008

encouraged participants to modify their own dosing regimen, to reduce the incidence of adverse events. Nakamura 2007 evaluated varenicline use in Japanese smokers, the majority of whom were highly addicted, and Tsai 2007 and Wang 2009 in other Asian populations of smokers. Rigotti 2010 tested the safety and efficacy of varenicline in patients with cardiovascular disease, and Tashkin 2010 in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD). Tonstad 2006 assessed varenicline compared with placebo as an aid to maintaining abstinence. Williams 2007 was primarily a safety trial of the long-term use of varenicline (52 weeks), but reported point prevalence abstinence as a secondary outcome. Scharfenberg 1971 compared cytisine with placebo in German smokers.

The varenicline/placebo trials included in our meta-analyses were multi-centre studies; Gonzales 2006 (19 sites), Jorenby 2006 (14 sites), Niaura 2008 (five sites), Nides 2006 (seven sites) and Oncken 2006 (10 sites) were all set in the USA; Williams 2007 (nine sites) was set in the USA and Australia, Nakamura 2007 (19 sites) in Japan, Tsai 2007 (10 sites) in Taiwan and South Korea, and Wang 2009 (15 sites) in China, Singapore and Thailand. Tonstad 2006 (24 sites), Rigotti 2010 (39 sites) and Tashkin 2010 (27 sites) were variously set in the USA, Canada and Europe. For the open-label varenicline/NRT trials, Aubin 2008 (24 sites) was set in the USA and four European countries, and Tsukahara 2010 in Japan. Swan 2010, testing delivery of behavioural support to varenicline users, was set in the USA. The cytisine trial (Scharfenberg 1971) was set in a smoking cessation clinic in what was then East Germany.

The varenicline cessation trials treatment phase lasted for six weeks (Nides 2006),12 weeks (Gonzales 2006; Jorenby 2006; Nakamura 2007; Niaura 2008; Oncken 2006; Rigotti 2010; Swan 2010; Tashkin 2010; Tsai 2007; Wang 2009) or 52+ weeks (Williams 2007). Tonstad 2006 used a 12-week regimen in an open-label trial, but then randomized successful quitters to an additional 12-week relapse prevention phase of varenicline or placebo. All used a regimen of 1 mg tablets of varenicline or 150 mg tablets of bupropion, taken twice a day, with Nakamura 2007, Nides 2006 and Oncken 2006 also testing different permutations of dosage and titration. Niaura 2008 encouraged participants to take between one and four 0.5 mg tablets per day, to achieve optimal balance between efficacy and adverse events. Aubin 2008 compared the standard 12-week regimen of varenicline with 10 weeks of nicotine patch use, while Tsukahara 2010 assigned a 12-week regimen to the varenicline arm and an eight-week regimen to the NRT arm. In addition, all the varenicline trials provided brief counselling support (up to 10 minutes per session) throughout the treatment phase, and during follow-up clinic visits and phone calls to week 52. The cytisine trial used 1.5 mg Tabex® tablets over a 20-day treatment period.

Follow up for the varenicline cessation trials was at 12, 24 and 52 weeks, and for the cytisine trial at four weeks, six months and two years. The varenicline/NRT trials followed up for 24 weeks (Tsukahara 2010) and for 52 weeks (Aubin 2008). The relapse prevention trial (Tonstad 2006) reported abstinence at 24 and 52 weeks.

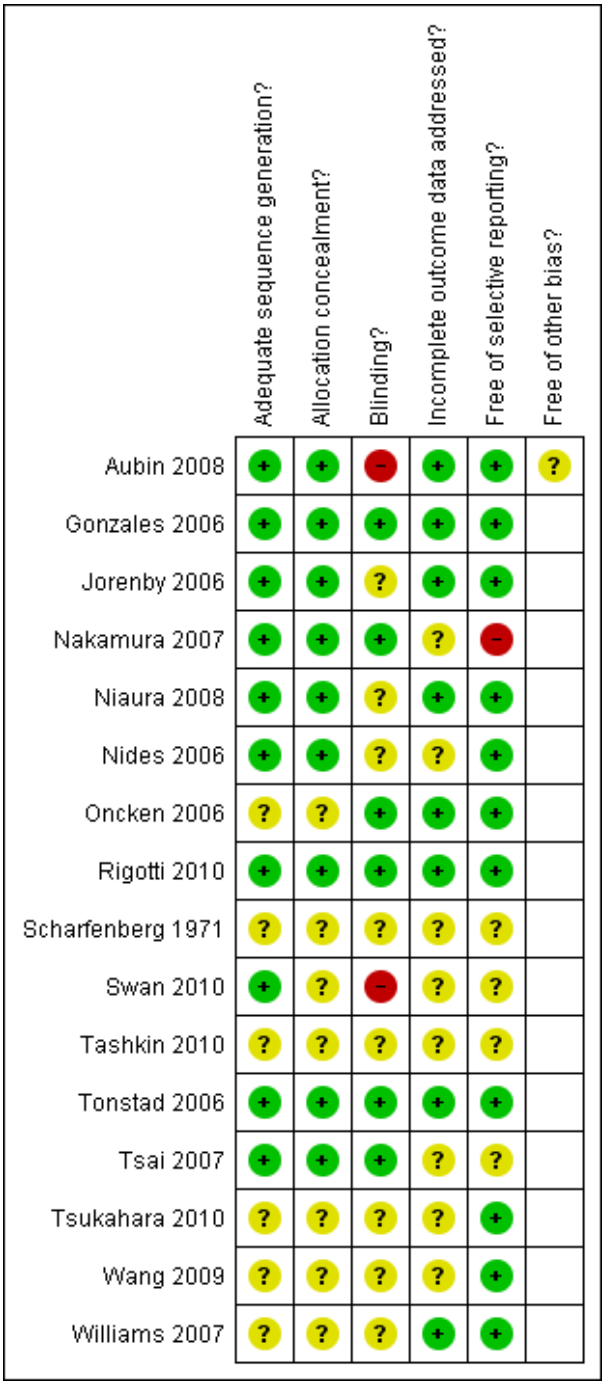
Risk of bias in included studies

Of the fifteen varenicline trials, ten reported randomization and allocation procedures in sufficient detail to be assessed as at minimal risk in their attempts to control selection bias. Oncken 2006, Tashkin 2010, Tsukahara 2010, Wang 2009 and Williams 2007 gave insufficient information for this to be confirmed. A sensitivity analysis removing these trial made little difference to the findings. The cytisine trial gave no details about randomization or allocation procedures, and was therefore rated as unclear. Aubin 2008 was an unblinded open-label trial, which may have led to the differential drop-out rates after randomization, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group. Tsukahara 2010, the other unblinded open-label trial of varenicline versus nicotine patch, suffered minor but equal losses (2/16 from each group), which may reflect the relatively rare prior use of NRT among Japanese smokers, i.e. 1 to 3% compared with 46 to 49% in Western countries. None of the trials reported any assessment of the integrity of the double-blinding procedure. For the relapse prevention trial (Tonstad 2006), the integrity of the double-blind phase may be questionable, since all randomized participants had successfully used varenicline during the open-label phase.

All the varenicline trials except for Williams 2007 defined their abstinence outcome as 'continuous', and all the varenicline trial outcomes were biochemically verified by expired carbon monoxide (CO) levels of 10 or fewer parts per million. However, Tsukahara 2010 biochemically confirmed abstinence only at 12 weeks, and relied upon telephoned self-report at 24 weeks. 'Continuous abstinence' as defined in these trials excluded the first eight weeks of treatment, and could more accurately be termed 'prolonged abstinence' (Hughes 2003). It was measured at 9 to12, and 9 to 24 weeks, and at 9 to 52 weeks in all except for Tsai 2007, Tsukahara 2010 and Wang 2009. Apart from these three trials which terminated at 24 weeks, and Tonstad 2006, whose participants were all by definition quitters at 12 weeks, all the varenicline trials reported CO-verified seven-day point prevalence abstinence at 12, 24 and 52 weeks. The cytisine trial used self-reported unverified abstinence at four weeks, six months and two years.

Figure 1 presents a summary of the risk of bias assessments for the included studies.

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.



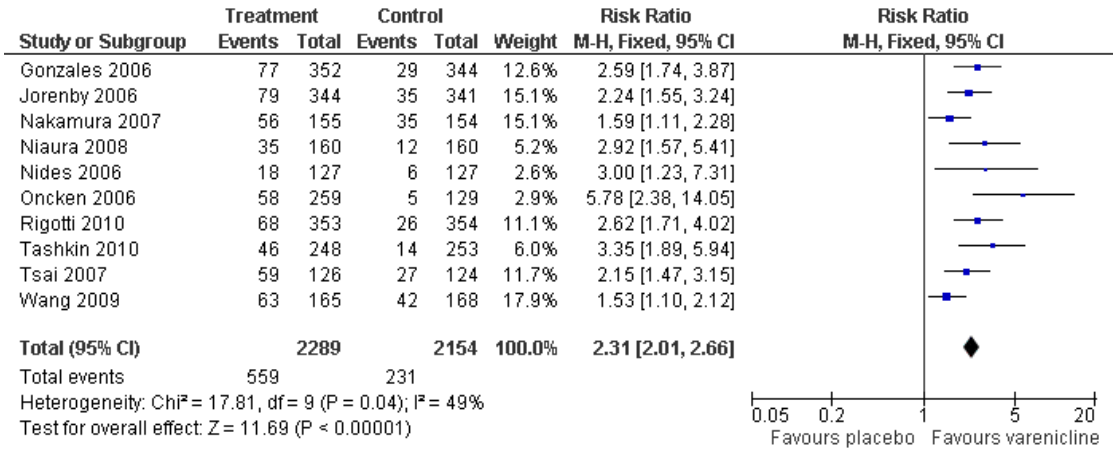
Effects of interventions

Varenicline

The evidence base includes methodologically sound clinical trials, involving more than 10,300 participants, 6892 of whom received varenicline (see Appendix 2). All 11 trials which compared varenicline with placebo for smoking cessation found statistically significant results in favour of the intervention at all of the selected endpoints. 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 eventually 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. We have not included Williams 2007 in the primary meta-analysis, since participants had remained on treatment or placebo up to and beyond the 52-week assessment, and were assessed for point prevalence rather than continuous abstinence. Analyses which included the Williams 2007 outcomes also demonstrated significantly increased heterogeneity.

The pooled risk ratio [RR] for validated continuous abstinence six months or more from the start of the intervention (longest follow up), based on ten cessation trials (excluding the Williams trial) of varenicline versus placebo at standard dose, (Gonzales 2006; Jorenby 2006; Nakamura 2007; Niaura 2008; Nides 2006; Oncken 2006; Rigotti 2010; Tashkin 2010; Tsai 2007; Wang 2009) is 2.31 (95% confidence interval [CI] 2.01 to 2.66; Analysis 1.1; Figure 2). This is similar to the RRs for continuous abstinence at end-of-treatment (2.57, 95% CI 2.33 to 2.84; Analysis 1.2) and at 24 weeks (2.42, 95% CI 2.13 to 2.75; Analysis 1.3). The long-term safety trial (Williams 2007) found a significant effect of varenicline over placebo throughout the 52-week assessment period, with a 53-week follow-up RR for seven-day point prevalence abstinence of 4.91 (95% CI 2.56 to 9.42; Analysis 1.4).

Figure 2. Forest plot of comparison 1: Varenicline (1.0mg 2/d) vs placebo, outcome: 1.1 Continuous abstinence at longest follow up (24+ weeks)



Four trials evaluated lower doses of varenicline, in an attempt to balance efficacy against minimization of adverse events. Three of the trials tested fixed but reduced regimens: Nides 2006 0.3 mg or 1.0 mg daily, Oncken 2006 0.5 mg twice daily titrated and untitrated, and Nakamura 2007 0.25 and 0.5 mg twice daily. Our meta-analysis includes the 1.0 mg daily or 0.5 mg twice daily regimens, rather than the lowest dose options. Niaura 2008 allowed participants to regulate their own consumption of 0.5 mg tablets at between one and four a day, and reported the mean modal dose to be 1.35 mg a day for the varenicline group and 1.63 mg a day for the placebo group. Varenicline at lower doses maintained a clear benefit over placebo, but with too high a level of heterogeneity (68%) to estimate a pooled effect size (Analysis 2.1). A direct comparison between standard and the next lowest dose of varenicline (excluding Niaura 2008) indicates a benefit for the standard regimen, with an RR of 1.25 (95% CI 1.00 to 1.55; Analysis 2.2). However, this enhancement of cessation rates is counterbalanced

clinically by the reduction in adverse events conferred by the lower dose.

Losses to follow up were highest in the placebo groups across most of the included studies, and lowest in the varenicline groups, with the exception of Nakamura 2007 (see Analysis 10.1). Retention rates were atypically high in the Asian trials, at 83% and 86% in the two Japanese studies (Nakamura 2007; Tsukahara 2010), 95% in the South Korean/Taiwanese study (Tsai 2007) and 96% in the Chinese/Singaporean/Thai study (Wang 2009). This may be associated with the relatively high proportion of participants making their first ever quit attempt, i.e. 36% in Nakamura 2007, 51% in Tsai 2007, and 59% in Wang 2009, compared with around 10% in the non-Asian trials.Three studies demonstrated statistically significantly different losses (Jorenby 2006; Oncken 2006; Tonstad 2006). The most extreme difference was in Oncken 2006, between the placebo group, with only 31% followed up at one year, compared with 58% in the combined 1.0 mg treatment group. Since people who are unsuccessful in their quit attempt are more likely to drop out, higher loss to follow-up in a placebo group is not unexpected if the treatment aids abstinence, and is unlikely to indicate bias. However we conducted a sensitivity analysis to test the effect of including all randomized participants in the treatment groups (ITT analysis) versus only those who had follow-up data in the control groups (per protocol analysis). This has the effect of maintaining a conservative quit rate in the treatment group, but a more optimistic one in the control group. The RR on this basis remained statistically significant, at 1.67 (95% CI 1.45 to 1.92; Analysis 11.1). It should be emphasised that this sensitivity analysis makes relatively extreme assumptions about differential distribution of missing data in treatment and control groups. These assumptions inevitably reduce the risk ratio.

Three of the varenicline trials also compared the intervention drug with bupropion. The pooled RR for the three trials at 12 months was 1.52 (95% CI 1.22 to 1.88; Analysis 3.1). We conducted a sensitivity analysis to test the effect of excluding Nides 2006, which had included previous users of bupropion, but the RR remained statistically significant, at 1.46 (95% CI 1.17 to 1.83). The implications of this finding are considered in the Discussion section below.

Two open-label randomized trials compared varenicline with nicotine patch, but Tsukahara 2010 was too small to contribute usefully to the pooled estimate for point prevalence abstinence at 24 weeks, (RR 1.13, 95% CI 0.94 to 1.35; Analysis 4.1), so this reflects the results of Aubin 2008, a larger and more rigorous trial. At 52 weeks Aubin 2008 reported a larger benefit for varenicline over nicotine patch that almost reached statistical significance (RR 1.29, 95% CI 0.99 to 1.67; *analysis not shown*) for biochemically confirmed continuous abstinence.

Tonstad 2006, randomizing successful quitters to a further 12 weeks of varenicline or placebo for relapse prevention, found a significant effect of varenicline on validated continuous abstinence ('not even a puff') at 52 weeks, with an RR of 1.19 (95% CI 1.03 to 1.36; Analysis 5.1). The RR at the end of the double-blind treatment phase (24 weeks) was 1.42 (95% CI 1.29 to 1.56; Analysis 5.2).

Cytisine

The only cytisine (Tabex) trial which met our inclusion criteria (Scharfenberg 1971) detected a benefit of cytisine compared with placebo at two-year follow up (RR 1.61, 95% CI 1.24 to 2.08; Analysis 6.1). The RR for this trial at six months was 1.91 (95% CI 1.53 to 2.37; *analysis not shown*). Abstinence was self-reported and not biochemically verified.

Adverse events:

The predominant adverse event for varenicline was nausea, reported at around 27% in Tashkin 2010, 29% in Gonzales 2006 and Jorenby 2006, 37% in Aubin 2008, 40% in Williams 2007, and 44% in Tsai 2007, with attributable discontinuation rates from 0.6% to 7.6%. 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. 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.

Meta-analyses of the four main adverse events in the varenicline versus placebo groups yielded RRs of 3.19 (95% CI 2.78 to 3.67) for nausea (Analysis 7.1), 1.55 (95% CI 1.33 to 1.82) for insomnia (Analysis 7.2), 3.04 (95% CI 2.35 to 3.94) for abnormal dreams (Analysis 7.3), and 1.18 (95% CI 1.01 to 1.39) for headache (Analysis 7.4). All differences were statistically significant. Numbers and percentages of participants suffering the most frequently reported adverse events across all comparisons are tabulated in Analysis 8.

Adverse events were monitored weekly during treatment from weeks one to seven (Gonzales 2006; Jorenby 2006; Nides 2006; Oncken 2006), or weekly throughout 12 weeks of treatment (Aubin 2008; Nakamura 2007; Niaura 2008; Rigotti 2010; Tashkin 2010; Tsai 2007; Wang 2009). 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. Apart from Nakamura 2007, which reported any occurrence, 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. There were no treatment-related deaths in any of the intervention groups during treatment or follow-up phases. Non-fatal serious adverse events (SAEs) occurred in 14 of the trials. A serious adverse event may be defined as any untoward medical occurrence that resulted in death; was life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability or incapacity; or resulted in a congenital anomaly or birth defect (Nakamura 2007). Gonzales 2006 reported 14 SAEs (four in the varenicline group, one of which may have been attributable to study medication, and three in the bupropion group, one of which may have been attributable to study medication); Jorenby 2006 reported 12 in treatment and five in follow-up phases for the intervention groups (one event in the varenicline group and one in the bupropion group attributed to study medication). Nakamura 2007 reported 10 SAEs across the three varenicline groups (two of them possibly treatment-related), compared with three in the placebo group. Niaura 2008 reported no SAES in either group during treatment, but three in the varenicline group in the 30 days post-treatment; none were considered to be treatment-related. Nides 2006 noted one SAE in the varenicline groups and four in the bupropion group which may have been linked to study medication. Oncken 2006 reported nine SAEs in the varenicline groups during treatment phase, and two in follow-up phase. Rigotti 2010 reported similar rates of SAE in both groups, but with no further details. Tashkin 2010 reported that SAEs were "infrequent" and not thought to be associated with the medication. Tsai 2007 reported three SAEs in each of the groups, one of which in the varenicline group was deemed to be possibly related to the medication. Wang 2009 reported three SAEs in the placebo group and 12 (in eight participants) in the varenicline group. Williams 2007 reported 18 SAEs (15 in the varenicline group and three in the control group, with four consequent discontinuations), one of which was attributed by the investigator to the study medication.

Tonstad 2006 reported 20 non-fatal SAEs during the open-label phase, followed by ten in the double-blind varenicline group and five in the double-blind placebo group. Swan 2010, with all 1202 participants using varenicline, reported nine SAEs, all deemed unrelated to treatment. Aubin 2008 reported ten SAEs during treatment phase (two in the varenicline group and eight in the nicotine patch group), and three during the follow-up phase (two in the varenicline group); two were attributed to treatment. Tsukahara 2010 and Scharfenberg 1971 gave no information about the incidence of SAEs in either group. Details of the SAEs among the included studies are given in Analysis 9.1.

Varenicline was judged on the evidence of the trials so far to be safe and well tolerated at all the tested dosages and over all the tested time periods. However, post-marketing surveillance has raised new concerns, which are considered in the Discussion section.

DISCUSSION

Varenicline

The evidence from the trials conducted so far indicates that varenicline increases the chances of successful smoking cessation. Sensitivity analyses demonstrate a slight downward trend in the relative risks at three months (2.57), six months (2.42) and twelve months (2.31), suggesting a marginal convergence in abstinence rates between treatment and control groups once the treatment phase was complete. However, the confidence intervals for all three estimates overlap, weakening the evidence for this possible trend. Even at longest follow up, varenicline sustains a more than two-fold advantage over control groups receiving placebo treatment.

In three of the trials, varenicline was shown to increase the probability of quitting more than bupropion. The efficacy of bupropion is fully addressed in another Cochrane review (Hughes 2007), but we briefly discuss it here because of some unexpected findings in these trials. Because bupropion has been shown to be less effective in smokers who have used it before (Gonzales 2001), two of the trials (Gonzales 2006; Jorenby 2006) excluded participants with any prior use of that drug. Both trials demonstrated a significant benefit of bupropion over placebo at three, six and twelve months (pooled ORs of 1.97, 1.91 and 1.76 respectively). Nides 2006 excluded smokers who had used bupropion within the previous 12 months, but otherwise included former users, yielding a rate of previous usage across the five groups of between 13 and 20.6%. Although the results of this trial showed bupropion doubling the chances of quitting compared with placebo at 12 weeks, at later endpoints (24 and 52 weeks) it failed to demonstrate significant separation from placebo. It is possible that the inclusion of some smokers who had already failed to quit using bupropion contributed to this. However, this remains speculative, and the study was in any event not powered to detect a difference between bupropion and placebo at these time points.

There is limited direct evidence comparing varenicline with NRT, but there have been a small number of studies directly comparing bupropion with NRT (Hughes 2007). These show some heterogeneity but tend to favour bupropion. This would imply that if varenicline is more efficacious than bupropion it is probably also more efficacious than NRT, which is consistent with the direction of effect found in Aubin 2008.

The number needed to treat to benefit (NNTb) to achieve each additional successful quitter 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. For a typical clinical trial with behavioural support quit rate of 7.5% the NNTb for varenicline is 10 (95% CI 8 to 13). For comparison we can estimate NNTbs from recent meta-analyses of nicotine replacement therapy (NRT) (RR 1.58, 95% CI 1.50 to 1.66, Stead 2008) and bupropion (RR 1.69 95% CI 1.53 to 1.85, Hughes 2007), 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 27), and the NNTb for bupropion is 20 (95% CI 16 to 26). Compared with the varenicline studies, the meta-analyses for NRT and bupropion include some pragmatic trials conducted after the initial licensing trials. The estimates of the treatment effect were usually lower in these trials, reducing the cumulative risk ratio.

The one relapse prevention trial conducted so far (Tonstad 2006) found a benefit of varenicline over placebo which persisted through 12 months' follow up. Although the authors refer to it as a trial of maintenance therapy, the findings are derived and presented as a comparison of two different treatment protocols, testing standard therapy against extended therapy. If we consider the data strictly in terms of relapse prevention, the odds ratio for the double-blind treatment phase (weeks 13 to 24) is 0.41 (95% CI 0.33 to 0.52), strongly favouring the extended treatment group. However, during the following 12-week phase (weeks 25 to 36), when both groups had entered the no-treatment phase, the relapse rate OR is 2.27 (95% CI 1.55 to 3.33) in favour of the placebo group, meaning that a significantly higher proportion of the extended treatment group were relapsing. During the final follow-up phase (weeks 37 to 52) the relapse rate OR is 1.11 (95% CI 0.68 to 1.81), which, although no longer statistically significant, suggests that a slightly higher proportion of the extended treatment group continued to relapse. Although the two groups did not converge during the study follow-up period, the pattern of sustained cessation while on treatment followed by rapid relapse suggests that further trials over longer follow-up periods are needed to determine whether extended treatment leads to higher long-term cessation rates.

Stapleton 2008, a non-randomized uncontrolled evaluation study comparing varenicline with NRT in a regular smoking cessation clinic, included smokers with concurrent mental illness (112/412), a group that is routinely excluded from clinical trials. Because the final assessment was at four weeks after quit date, the study was not eligible for inclusion in our meta-analyses. However, the results for those receiving psychiatric treatment were reassuring, with no evidence of harm from using varenicline, and with similar four-week abstinence rates to the rest of the cohort (71.7% versus 72.1%). The study demonstrated an overall benefit of varenicline over NRT (OR 1.70, 95% CI 1.09 to 2.67).

A number of reviews and evaluations of varenicline have been published since 2006, including Keating 2006; Wu 2006; Glover 2007; Kerr 2007; Lam 2007; Reus 2007; Fagerström 2008; Hays 2008; Cahill 2009; Jimenez-Ruiz 2009. Only the Wu systematic review included meta-analyses.

Cytisine

There is a lack of well-designed randomized controlled trials of cytisine for smoking cessation. Much of the existing research was conducted during the 1960s and 1970s, as non-randomized or observational studies without long-term follow up. A recent systematic review (Etter 2006; Etter 2007; Etter 2008) of controlled studies of cytisine, with a meta-analysis of three trials, found a pooled odds ratio at three to six months of 1.83 (95% CI 1.12 to 2.99) in favour of cytisine over placebo, but studies were generally inadequately reported and of poor quality. Many of the cytisine studies excluded from this review are discussed and evaluated in the Etter review. A UK-Polish randomized controlled trial of Tabex (TASC 2007) is currently underway, and we plan to include its findings in future updates of this review.

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 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; 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.

Full details of the comparative incidence of craving and withdrawal symptoms are shown in Appendix 3.

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 randomized 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 great an inference from the difference in rates between the two phases of the study.

Post-marketing surveillance raised new 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, and a Medication Guide produced by Pfizer Inc. Subsequent studies have found little evidence to support the possible association. A recent review of the ten trials completed up to the end of 2008 (Tonstad 2010) found no significant excess incidence of psychiatric 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). 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 are broadly reassuring that the absolute incidence is low.

The cytisine trial (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.

All the varenicline trials reported in this review, apart from Swan 2010 and Tsukahara 2010, were funded and managed by Pfizer Inc, the manufacturers of varenicline. Evidence from recent 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 (Bekelman 2003; Bhandari 2004; Lexchin 2003). We hope that future updates of this review will include additional findings from community-based independently conducted randomized controlled trials.

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.

- Two open-label trials of varenicline versus nicotine replacement therapy suggest a modest benefit for varenicline, but are inconclusive.

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

- The main adverse effect of varenicline was nausea, but mostly at mild to moderate levels and tending to subside over time.

- Causal links with serious adverse events, including depressed mood, agitation and suicidal thoughts, have not been conclusively established. Further monitoring and analyses of safety data may clarify any possible associations.

Implications for research

- There is a need for more independent community-based trials of varenicline, to test its efficacy and safety in smokers with varying co-morbidities and risk patterns, in real-world settings.

- Further trials comparing the long-term success of extended treatment with standard 12-week treatment are needed.

- Well-designed and -conducted trials of cytisine are needed, to test the findings from earlier and poorer quality trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aubin 2008

Methods	Medication: VARENICLINE / NRT OPEN LABEL Country: Belgium, France, Netherlands, UK, USA Setting: 24 research centres Randomization by central computer-generated sequence. Analysis: Power calculation (90%, alpha=.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 >45.5kg, BMI 15-38, smoking >=15 CPD. Varenicline arm 378, NRT arm 379. Mean age 42.9, 49.2% male, 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 x2/day for 12 wks, titrated 1st wk. 2. Nicotine patch (21mg wks 2-6, 14mg wks 7-9, 7mg 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<=10ppm. Drop-outs 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.
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 randomized [378/379], which tips the RR into statistical significance. Not included in main MA, as no placebo group.

Risk of bias

Item	Authors' judgement	Description

Aubin 2008 (*Continued*)

Adequate sequence generation?	Yes	"Using a central computer-generated sequence"
Allocation concealment?	Yes	Central allocation
Blinding? All outcomes	No	"using an open-label design"
Incomplete outcome data addressed? All outcomes	Yes	"Missing CO data were assumed to be <10ppm provided other conditions were met", i.e. no NRT other than prescribed patches. Missing=negative assumption reduced successes by 1 in each group.
Free of selective reporting?	Yes	All predicted outcomes fully reported, + analysis by country and treatment centre
Free of other bias?	Unclear	Different duration of regimens, but effect sizes similar in last 4 wks of each course+

Gonzales 2006

Methods	Medication: VARENICLINE Country: USA Setting: 19 research centres Study Design: Double-blind placebo-controlled parallel-group RCT. Randomization by computer-generated lists stratified by centre, block allocation in groups of 6 Analysis: Power calculation (90%, alpha=.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% male, 79% white, mean age 42.4, mean CPD 21, mean Fagerström 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 1mg x2/day. 2. Bupropion 150mg x2/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.

Gonzales 2006 (*Continued*)

Outcomes	Primary outcome: Continuous validated abstinence at 9-12 wks. Secondary outcomes: Continuous abstinence at 9-24 wks and 9-52 weeks; 7-day PP abstinence 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<=10ppm. Drop-outs 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.
Notes	This trial had the same aims and study design as Jorenby 2006. The trial was funded by Pfizer Inc.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"predefined ... computer-generated randomization sequence", 1:1:1, using block size of 6, stratified by centre.
Allocation concealment?	Yes	Central allocation
Blinding? All outcomes	Yes	"Participants and investigators were blinded to drug treatment assignments[, and] ... were not encouraged to guess their treatment assignment".
Incomplete outcome data addressed? All outcomes	Yes	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.
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Jorenby 2006

Methods	Medication: VARENICLINE Country: USA Setting: 14 research centres Study Design: Double-blind placebo-controlled RCT. Randomization by computer-generated lists stratified by centre. Analysis: Power calculation (90%, alpha=.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% male, 84% white, mean age 43.3, mean CPD 22, mean Fagerström 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 1mg x2/day. 2. Bupropion 150mg 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: Continuous validated abstinence at 9-12 wks. Secondary outcomes: Continuous abstinence at 9-24 wks and 9-52 wks; 7-day PP abstinence 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<=10ppm. Drop-outs 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.
Notes	This trial had the same aims and study design as Gonzalez 2006. The trial was funded by Pfizer Inc.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer-generated list"
Allocation concealment?	Yes	"completed centrally ... and sites used an electronic system to assign participants to treatment"
Blinding? All outcomes	Unclear	"in a double-blind manner"

Incomplete outcome data addressed? All outcomes	Yes	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.
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Nakamura 2007

Methods	Medication:VARENICLINE Country: Japan Setting: 19 study sites Aim: To test efficacy, safety and tolerability of 3 doses of varenicline over 12 wks. Study Design: Double-blind, placebo-controlled, parallel group RCT. Randomization was by computer-generated random number lists. Analysis: Power calculation (90%, alpha=.05) for 0.5 or 1.0mg 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 >=10cpd. Allocated to varenicline 0.25mg BID (153), 0.5mg BID (156), 1.0mg BID (156) or placebo BID (154). One participant withdrew before treatment, and is excluded from ITT denominator. One 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% male, mean age 39.8, mean CPD 24, mean Fagerström 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 0.25mg x 2/day 2. Varenicline 0.50mg x 2/day 3. Varenicline 1.00mg 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: Continuous validated abstinence at 9-12 wks. Secondary outcomes: Continuous abstinence at 9-24 wks and 9-52 wks; 7-day PP abstinence at wks 2, 12, 24 and 52. Validation was by expired CO<=10ppm. Other outcomes: Withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events.

Nakamura 2007 (*Continued*)

	Drop-outs 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).
Notes	Trial was funded by Pfizer Inc. New for 2008 update

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer-generated list of random numbers"
Allocation concealment?	Yes	"randomized to 1 of the 4 treatment groups ina 1:1:1:1 ratio using a central procedure"
Blinding? All outcomes	Yes	"double-blinding of subjects and investigators was maintained throughout the study".
Incomplete outcome data addressed? All outcomes	Unclear	No comment on level or handling of missing data
Free of selective reporting?	No	CARs for all participants reported, but demographics, withdrawal and craving measures, and PPA for nicotine-dependent group only.

Niaura 2008

Methods	Medication: VARENICLINE Country: USA Setting: 5 research centres Study Design: Double-blind placebo-controlled RCT. Randomization by computer-generated permuted blocks lists Analysis: Power calculation (90%, alpha=.05); ITT denominators and logistic regression analysis (step-down procedure)
Participants	320 healthy adult volunteers, aged 18-65, smoking >=10cpd. Allocated to varenicline (160), or placebo (160). 52% M, 91% white, mean age 42, mean CPD 22, mean Fagerström 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 bid. 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<=10ppm. 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. Drop-outs 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.
Notes	The trial was funded by Pfizer Inc. New for 2010 update

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"randomly permuted blocks and a pseudo-random number generator"
Allocation concealment?	Yes	"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? All outcomes	Unclear	"double-blind" but no further information
Incomplete outcome data addressed? All outcomes	Yes	Missing data imputed if prior and subsequent abstinence confirmed, otherwise assumed still smoking
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Nides 2006

Methods	Medication: VARENICLINE Country: USA Setting: 7 research centres Aim: To test efficacy, tolerability and safety of 3 doses of varenicline over 6 wks. Study Design: Phase 2 double-blind placebo-controlled RCT. Randomization by computer-generated lists using randomly permuted blocks and pseudo-random number generator. Medication assigned in numerical order of acceptance to study. Analysis: Power calculation (80%, two-tailed, alpha=.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 10cpd on average. 48% male, 87% white, av age 42, av CPD 20, mean Fagerström 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 0.3mg 1/d for 6w, + 1wk placebo 2. varenicline tartrate 1.0mg 1/d for 6w, + 1wk placebo 3. varenicline tartrate 1.0mg 2/d for 6w, + 1wk placebo 4. bupropion 150mg 2/d (titrated in wk 1) for 7 wks 5. placebo tablets 2/d for 7 wks All groups received self-help booklet *Clearing the Air* at baseline, + brief (≤10mins) 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<=10ppm. Trial report ITT analysis based on numbers treated (N=626); for consistency our MA used numbers randomized (N=638). Attrition was 30% during treatment period, 25% of follow-up consenters lost during follow-up phase.
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 randomized in our MA. The trial was funded by Pfizer Inc.

Risk of bias

Item	Authors' judgement	Description

Nides 2006 (*Continued*)

Adequate sequence generation?	Yes	"computer-generated using a method of randomly permuted blocks and a pseudo-random number generator"
Allocation concealment?	Yes	"assigned ... medication to subjects in numerical order of acceptance into the study"
Blinding? All outcomes	Unclear	"double-blind", "to preserve treatment blinding"
Incomplete outcome data addressed? All outcomes	Unclear	No information
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Oncken 2006

Methods	Medication: VARENICLINE Country: USA Setting: 10 research centres Aim: To evaluate efficacy and safety of 4 varenicline dose regimens Study Design: Phase 2 double-blind placebo-controlled RCT. Method of randomization not stated Analysis: Power calculation (90%, two-tailed, alpha=.05); Logistic regression with treatment and centre as independent variables. Likelihood ratio chi-square statistic.
Participants	647 healthy volunteer smokers, aged 18-65, smoking at least 10cpd. 49.5% male, 80% white, av CPD 21, mean Fagerström 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. 0.5mg nontitrated (2/d for 12 wks) 2. 0.5mg titrated (wk1 1/d, wks 2-12 2/d) 3. 1.0mg nontitrated (2/d for 12 wks) 4. 1.0mg titrated (0.5mg 1/d for 3 days, 0.5mg 2/d for 4 days, 1.0mg 2/d wks 2-12) 5. placebo tablets 2/d 12 wks All groups received self-help booklet at baseline, + brief (≤10mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3d 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.

Oncken 2006 (*Continued*)

	Other outcomes: weight change; craving and withdrawal changes using MNWS and mCEQ; adverse events Validation was by expired CO<=10ppm Cessation analyses were ITT (all participants randomized), 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.
Notes	For cessation analyses, titrated and nontitrated results were reported separately and pooled. 24wk continuous cessation data supplied by authors. The trial was funded by Pfizer Inc.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	"Eligible subjects were randomly assigned to 1 of 5 groups"
Blinding? All outcomes	Yes	"Subjects and investigators were blinded to the study drug treatment [, and] were not encouraged to guess their treatment assignment"
Incomplete outcome data addressed? All outcomes	Yes	Missing COs or visits OK if confirmed abstinent before and after missed measure.
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Rigotti 2010

Methods	Medication: VARENICLINE Country: 15 countries in Europe, Asia, Americas Setting: 39 research centres Aim: To evaluate efficacy and safety of varenicline in patients with stable CVD 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 10cpd, with stable CVD and motivated to quit. 79% male, 80% white, mean CPD 22, mean Fagerström 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/d for 12 wks, preceded by 1wk titrated dose. 2. Placebo tablets as above. Both groups received brief (≤10mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3d 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: Continuous verified 4-wk abstinence at wks 9-12. Secondary outcomes: Continuous verified abstinence 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<=10ppm Cessation analyses were ITT (all participants randomized 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% in 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.
Notes	The study was funded by Pfizer Inc New for 2010 update

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	"The study sponsor conducted the randomization centrally using a computer-generated list that prespecified the order of treatment allocation"
Allocation concealment?	Yes	See above
Blinding? All outcomes	Yes	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 addressed? All outcomes	Yes	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.

Rigotti 2010 (*Continued*)

Free of selective reporting?	Yes	All expected and predicted outcomes covered

Scharfenberg 1971

Methods	Medication: CYTISINE [TABEX] Country: East Germany Setting: smoking cessation clinic, Magdeburg, July-December 1967 Study Design: double-blind placebo-controlled randomized trial; no details of randomization or allocation methods, other than smokers being given 'a numbered pouch'. 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 <10cpd, 42.4% 10-20cpd, 48.9% 21-30 CPD, 5.2%>30cpd. 40.4% had smoked >20yrs. 40.6% had tried to quit at least once before. Randomized to cytisine (607) or placebo (607). Exclusion criteria not stated (214 volunteers excluded at initial screening)
Interventions	1. 20-day course of cytisine. 1.5mg 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.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	not stated
Allocation concealment?	Unclear	"a numbered pouch"
Blinding? All outcomes	Unclear	not stated
Incomplete outcome data addressed? All outcomes	Unclear	not stated
Free of selective reporting?	Unclear	not stated

Swan 2010

Methods	Medication: VARENICLINE Country: USA Setting: HMO (Group Health), Seattle WA Study Design: RCT. Randomization by automated algorithm Analysis: Power calculation (80%); Intention-to-treat denominators and logistic regression analysis for relationship of mode of counselling to smoking outcomes.
Participants	Recruitment and intervention conducted via phone and mail, by Free & Clear. 1202 adults ($\geq$ 18 yrs), smoked 10+ CPD, with phone and internet access. Randomized to web-based counselling = 401, proactive telephone-based counselling [PTC] = 402, or a combination of both = 399. 33% M, mean age 47, mean CPD 19.6, 90% W.
Interventions	All participants received 12 wk course of varenicline (1mgx2/day, titrated 1st wk). All received 5-10 min orientation call, printed Quit Guides and access to a free support line for ad hoc calls. No non-treatment control group. 1. Web-based counselling: Access to an online programme with standardized content and interactive tools, including a quit plan, an online library, quit calendar, cost calculator, progress tracker, email links to friends and family and discussion forums. 2. Proactive telephone-based counselling: Free & Clear Quit for Life program. Up to 5 one-to-one phone sessions initiated by F&C counsellor. Offered practical expert help for problem-solving and coping, timed for convenience and at relapse-sensitive stages. Used MI techniques. 3. Combination: Proactive calls + web access; counsellor could view info entered online. Participants encouraged to use website for additional info and social support, and to track CPD. Counsellors could view quit status, last log-in and last use of discussion forum.
Outcomes	Primary outcome: Self-reported PPA at 3m and 6m. Other outcomes: adverse events, serious adverse events [SAEs], levels of treatment compliance. Validation: none Drop-outs: 23.7% at 3m, 25.8% at 6m, equally distributed across all arms. 64% were no longer taking varenicline at 3m, but no between-group diffs in non-compliance or reasons for stopping.
Notes	Not included in MAs, as no placebo group and all pts took varenicline. Study was funded by National Cancer Institute. New for 2010 update.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Group assignment was randomly allocated using an automated algorithm built into the study database"

Swan 2010 (*Continued*)

Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	"Participants and study staff were not blinded to treatment assignment"
Incomplete outcome data addressed? All outcomes	Unclear	Not stated
Free of selective reporting?	Unclear	All expected and predicted outcomes covered

Tashkin 2010

Methods	Medication: VARENICLINE Country: USA (17 centres), Spain (3 centres), France (4 centres), Italy (3 centres) Setting: 27 research centres. 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%)); Intention-to-treat 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% male, mean age 57, CPD 24-25, Fagerström 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 2/d for 12 wks, preceded by 1wk titrated dose. 2. Placebo tablets as above. Both groups received SC educational booklet, + brief (≤10mins) counselling at weekly clinic visits throughout treatment phase, and phone call 3d 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: Continuous verified 4-wk abstinence at wks 9-12. Secondary outcomes: Continuous verified abstinence at wks 9-52 and 9-24; 7-day PPA at wks 12, 24 and 52. Other outcomes: Adverse events; serious adverse events; wight change, Validation was by expired CO<=10ppm Cessation analyses were ITT (all participants randomized), 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.

Tashkin 2010 (*Continued*)

Notes	The study was funded by Pfizer Inc. New for 2010 update	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"participants were randomized"
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	"double blind" but details not stated
Incomplete outcome data addressed? All outcomes	Unclear	Not stated
Free of selective reporting?	Unclear	All expected and predicted outcomes covered

Tonstad 2006

Methods	Medication: VARENICLINE Country: USA (6 centres) and 'international' (18 centres, across Canada, Czech Republic, Denmark, Norway, Sweden, UK*) Setting: 24 research centres Study Design: Double-blind placebo-controlled RCT. Randomization by computer-generated lists stratified by centre, x4 random block design Analysis: Power calculation (80%, alpha=.05); Intention-to-treat 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, randomized to varenicline (603) or placebo (607) for a further 12 wks. 49% male, 97% white, mean age 45, BMI <15 or >38 or weight <45.5 kg, mean CPD 21, mean Fagerström 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 1mg x2/day for 11 wks after 1wk 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

Tonstad 2006 (*Continued*)

Outcomes	Primary outcome: Relapse prevention: maintenance of continuous validated abstinence at 24 wks Secondary outcome: Continuous validated abstinence at wk 52; 7-day PP abstinence at wks 24 and 52. Two 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<=10ppm. Drop-outs 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.
Notes	* additional information supplied by author. The trial was funded by Pfizer Inc.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer-generated randomization sequence (stratified by center with a block size of 4)"
Allocation concealment?	Yes	"a single, centralised [system]"
Blinding? All outcomes	Yes	"double-blind treatment phase"; "participant blinding was maintained during this [non-treatment follow-up] phase"
Incomplete outcome data addressed? All outcomes	Yes	Missing COs were considered abstinent if other criteria OK; at wk 52 all criteria had to be met.
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Tsai 2007

Methods	Medication: VARENICLINE Country: Taiwan and Korea Setting: 5 sites in each country Study Design: Double-blind placebo-controlled RCT. Randomization by randomly permutated blocks (block=4), via internet- and phone-based assignment centre. Analysis: Power calculation (>=90%, alpha=.05); ITT denominators and logistic regression model including treatment and centre.
Participants	250 healthy adult volunteers, motivated to quit, aged 18 to 75; allocated to varenicline (126), or placebo (124). 89% male, mean age 40.3, BMI <15 or >38 or weight <45.5 kg, mean CPD 24, mean Fagerström score 5.1. Treatment groups were comparable at baseline.

Tsai 2007 (*Continued*)

	Exclusion criteria: Standard pharmacotherapy trial criteria.
Interventions	1. Varenicline 1.0mg 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: Continuous validated abstinence at 9-12 wks. Secondary outcomes: Continuous abstinence at 9-24 wks; 7-day PP abstinence at wks 12 and 24. Validation was by expired CO<=10ppm. Other outcomes: Withdrawal symptoms (using MNWS, QSU-brief and mCEQ), adverse events. Drop-outs 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.
Notes	Trial was funded by Pfizer Inc. New for 2008 update

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"randomly permuted blocks" (block size= 4)
Allocation concealment?	Yes	web- and telephone-based assignment
Blinding? All outcomes	Yes	Subjects, investigators, study staff and sponsor personnel
Incomplete outcome data addressed? All outcomes	Unclear	No information, but very high compliance rates
Free of selective reporting?	Unclear	All expected and predicted outcomes covered

Tsukahara 2010

Methods	Medication: VARENICLINE/NRT OPEN LABEL Country: Japan Setting: Cessation clinic in Fukuoka University Hospital Study Design: Randomized controlled open label trial. The VN-SEESAW Study. Randomization by computer, allocating men: women 3:1 to reflect Japanese smoking prevalence (M: 40%, F: 12%).
Participants	32 adult smokers, motivated to quit, allocated to varenicline (16) or Nicotine patch (16). 75% male, 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 2/day for 12 wks, following 1wk 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. Drop-outs 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.
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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"by computer"
Allocation concealment?	Unclear	not stated
Blinding? All outcomes	Unclear	not stated
Incomplete outcome data addressed? All outcomes	Unclear	not stated

Tsukahara 2010 (*Continued*)

Free of selective reporting?	Yes	All expected and predicted outcomes covered

Wang 2009

Methods	Medication: VARENICLINE Country: China (10 sites), Singapore (3 sites), Thailand (2 sites) Study Design: Double-blind placebo-controlled RCT. Randomization not reported in detail. Analysis: Power calculation (>=90%, alpha=.05); ITT denominators and logistic regression model including treatment with site, country, Fagerström score, CPD and time to first cigarette. No interactions found.
Participants	333 healthy adult volunteers, aged 18 to 75; allocated to varenicline (165), or placebo (168). 97% male, mean age 39, BMI >15 and <38 or weight >45.5 kg, mean CPD 20, mean Fagerström 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 1.0mg 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 ($\leq$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. Drop-outs 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.
Notes	The trial was funded by Pfizer Inc. New for 2010 update.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	"eligible subjects were randomized in a 1:1 ratio"
Allocation concealment?	Unclear	See above

Wang 2009 (*Continued*)

Blinding? All outcomes	Unclear	"double-blind", but no further information
Incomplete outcome data addressed? All outcomes	Unclear	No information, but very high compliance rates
Free of selective reporting?	Yes	All expected and predicted outcomes covered

Williams 2007

Methods	Medication: VARENICLINE Country: USA and Australia Setting: Nine research centres (8 USA, 1 Aus) Study Design: Double-blind placebo-controlled RCT. Randomization 2:1 varenicline: placebo, method not stated Analysis: ITT (all who took at least one dose of medication)
Participants	377 adult smokers, aged 18-75, smoking at least 10cpd. 49.9% male, 88.6% white, av CPD at baseline 23, mean Fagerström 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 x2/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-randomization). 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<=10ppm). Other outcomes: Weight change; changes in vital signs Attrition was 46.2% in varenicline group, 53.2% in control group by end of study.
Notes	This was a safety study, with cessation rates collected as a secondary outcome. The trial was funded and conducted by Pfizer Inc. In first version of this review, this trial appeared as Reeves 2006 (unpublished data).
Risk of bias	

Williams 2007 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	No information reported
Allocation concealment?	Unclear	No information reported
Blinding? All outcomes	Unclear	No information reported
Incomplete outcome data addressed? All outcomes	Yes	Missing CO and/or visit taken as smokers
Free of selective reporting?	Yes	Primary outcome was safety, so minimal cessation data

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
ITT: intention-to-treat
MA: meta-analysis
mCEQ: Modified Cigarette Evaluation Questionnaire
MNWS: Minnesota Nicotine Withdrawal Scale
PPA: point-prevalence abstinence
QSU-brief: Brief Questionnaire of Smoking Urges
RCT: randomized controlled trial
SAE: serious adverse event
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	Thirty-nine smokers randomized 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.
Ebbert 2009a	Open-label, single arm Phase II study, for safety and efficacy of varenicline plus bupropion.

(*Continued*)

Ebbert 2009b	Cohort analysis of 104 pts on varenicline+NRT and 135 pts treated prior to release of varenicline (93% used NRT).
Ebbert 2010	Pilot study of varenicline for smokeless tobacco users. 12-wk outcome (EoT) reported, not long-term post-treatment.
Faessel 2009	Outcomes were safety, tolerability and pharmacokinetics, not smoking cessation.
Granatowicz 1976	Polish uncontrolled study of 1968 smokers, 71% taking cytisine, followed for 6m.
Kempe 1967	Bulgarian 1965 observational uncontrolled study of 30 male smokers given Tabex for 25 days and followed up for 6m.
Maliszewski 1972	Polish uncontrolled study of 14 smokers on a 25 day course of 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.
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.
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 Tabex. Follow up was 60 days.
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.
Paun 1968	Bulgarian controlled trial of Tabex (366 smokers) vs placebo (239 smokers) but followed only for 8 wks. Observational study of 230 Tabex-users followed for 26 wks, but no comparator group.
Pfizer 2006	Phase II flexible-dosing trial of 312 participants. Treatment lasted 12 weeks, and cessation outcomes reported for continuous abstinence through weeks 9-12.
Schmidt 1974	Non-randomized trial of 16 smoking cessation preparations, including Tabex (200 smokers); participants allocated to treatment 'by chance', and followed up over 3m. Placebo group not directly matched to Tabex group.
Sicras-Minar 2010	Multicentre observational non-randomized non-controlled study.
Stapleton 2008	Non-randomized 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.
Zatonski 2006	Polish uncontrolled observational study of 342 smokers; at 12 months 13.8% abstinent.

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

NCT00155298

Trial name or title	A 12-week double-blind, placebo controlled, multicenter study with varenicline tartrate 1mg BID for smoking cessation
Methods	Randomized double-blind controlled trial
Participants	250 smokers (>=10 CPD)
Interventions	12 weeks varenicline 1mg BID vs placebo
Outcomes	Continuous abstinence at 6 months
Starting date	March 2005
Contact information	Fei-Ran Guo
Notes	

NCT00492349

Trial name or title	Varenicline adjunctive treatment in schizophrenia
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	60 smokers with schizophrenia
Interventions	7 weeks varenicline 0.5mg qd vs placebo
Outcomes	BPRS, SANS, SDS, neurocognitive and biomarkers, Quality of life, addiction scales, MCCB
Starting date	May 2007
Contact information	L Elliot Hong
Notes	

NCT00502216

Trial name or title	Naltrexone and varenicline: weight gain and tolerability in cigarette smokers
Methods	Randomized double-bind controlled trial
Participants	44 adult smokers
Interventions	12 weeks open-label varenicline 1mg bid + naltrexone 25mg or placebo

NCT00502216 (*Continued*)

Outcomes	Weight gain in treatment completers, abstainers, + efficacy and tolerability
Starting date	July 2007
Contact information	Benjamin Toll
Notes	

NCT00507728

Trial name or title	Pharmacogentics, emotional reactivity and smoking
Methods	Randomized double-blind placebo-controlled trial
Participants	375 smokers attempting to quit using varenicline, bupropion or placebo
Interventions	Drug regimen + counselling
Outcomes	Patient emotional reactivity during smoking cessation
Starting date	December 2005
Contact information	Paul Cinciripini
Notes	

NCT00523445

Trial name or title	The effects of varenicline on cognitive function in patients with schizophrenia
Methods	Randomized double-blind placebo-controlled trial
Participants	120 smokers with schizophrenia
Interventions	Antipsychotic medication, + 8 weeks varenicline 1.0mg bid or placebo
Outcomes	Effects on cognitive dysfunction, + abstinence at 8 weeks
Starting date	September 2007
Contact information	J-C Shim
Notes	

NCT00525837

Trial name or title	Study of mood effects of varenicline (Chantix) in depressed outpatient smokers
Methods	Open-label uncontrolled single group
Participants	15 depressed outpatient smokers
Interventions	Varenicline 6-8 wks
Outcomes	Improvement of symptoms (depression, anhedonia), tolerability, tobacco use
Starting date	September 2007
Contact information	NS Philip
Notes	

NCT00548470

Trial name or title	Varenicline effects in schizophrenic smokers
Methods	Open-label uncontrolled before-and-after study
Participants	20 inpatients with schizophrenia, in a hospital with a smoking ban
Interventions	8 weeks varenicline 1-3mg a day
Outcomes	Self-reported and verified abstinence at end of treatment, + neuropsychological symptoms
Starting date	June 2007
Contact information	RC Smith
Notes	

NCT00554840

Trial name or title	Comparison of varenicline and placebo for smoking cessation in schizophrenia
Methods	Randomized double-blind placebo-controlled trial
Participants	44 smokers with schizophrenia
Interventions	12 weeks varenicline 1.0mg bid/placebo
Outcomes	PPA at 12 weeks, neuropsychiatric symptoms
Starting date	November 2007

NCT00554840 (*Continued*)

Contact information	E Weiner
Notes	

NCT00571805

Trial name or title	Placebo-controlled study of varenicline effects on nicotine withdrawal followed by a test of smoking topography, reward, and reinforcement
Methods	Randomized double-blind placebo-controlled trial
Participants	40 smokers
Interventions	Varenicline 1.0mg/bid vs placebo
Outcomes	Lab-based smoking reward, + 1-wk abstinence craving
Starting date	September 2007
Contact information	Richard Reid
Notes	

NCT00580853

Trial name or title	The effect of varenicline (Chantix) and bupropion (Zyban) on smoking lapse behavior
Methods	Randomized 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	

NCT00594204

Trial name or title	A 12-week double-blind, randomized, placebo-controlled, multi-center study with follow up evaluating the efficacy and safety of varenicline tartrate 1mg bid for smoking cessation
Methods	Randomized double-blind placebo-controlled trial
Participants	593 adult smokers in Latin America, Africa and the Middle East
Interventions	12 weeks varenicline 1mg bid
Outcomes	CAR wks 9-12, wks 9-24
Starting date	April 2008
Contact information	Pfizer
Notes	

NCT00595868

Trial name or title	Efficacy of varenicline in ambivalent smokers
Methods	Randomized double-blind placebo-controlled trial
Participants	220 smokers not motivated to quit but thinking about whether to make a quit attempt
Interventions	8 weeks varenicline 1mg bid vs placebo
Outcomes	Number of quit attempts
Starting date	January 2008
Contact information	John Hughes
Notes	

NCT00596882

Trial name or title	Message priming and enrolment in, and response to, a smoking cessation program: a pilot study
Methods	Randomized open-label trial
Participants	100 smokers
Interventions	Messages, genetic info + messages; all participants get varenicline
Outcomes	Attendance, enrolment, 7-day PPA, cigarette consumption

NCT00596882 (*Continued*)

Starting date	February 2008
Contact information	R Schnoll
Notes	

NCT00621777

Trial name or title	A study of varenicline for prevention of relapse to smoking in patients with schizophrenia
Methods	Randomized double-blind placebo-controlled trial
Participants	274 smokers with schizophrenia or schizoaffective disorder
Interventions	12 weeks open-label varenicline, + 40 weeks randomized to varenicline or placebo
Outcomes	7-day PPA at wk 53 (12 wks cessation treatment + 40 weeks relapse prevention treatment), safety/efficacy
Starting date	February 2008
Contact information	AE Evins
Notes	

NCT00644969

Trial name or title	Smoking cessation study for patients with schizophrenia or schizoaffective disorder
Methods	Randomized double-blind placebo-controlled trial
Participants	120 smokers with schizophrenia or schizoaffective disorder, randomized 2:1 intervention:control
Interventions	12 weeks varenicline 1.0mg bid/placebo
Outcomes	Safety, 7-day PPA, reduction at wks 12 and 24
Starting date	May 2008
Contact information	Pfizer Inc
Notes	

NCT00691483

Trial name or title	A phase 4, prospective, multi-national, randomized, double-blind, placebo-controlled study to evaluate smoking cessation with varenicline tartrate compared with placebo in the setting of patient self-selected (flexible) quit date
Methods	Randomized triple-blind placebo-controlled trial
Participants	659 adult smokers
Interventions	Varenicline 1.0mg/bid for 12 wks vs placebo
Outcomes	CAR at wks 9-12
Starting date	September 2008
Contact information	Pfizer Inc
Notes	

NCT00727103

Trial name or title	Varenicline treatment in alcohol and nicotine dependent patients with schizophrenia
Methods	Randomized triple-blind placebo-controlled trial
Participants	30 adult smokers with alcohol dependence
Interventions	Varenicline 1.0mg bid vs placebo for 8 weeks
Outcomes	alcohol use and smoking cessation at EoT
Starting date	July 2008
Contact information	ZS Meszaros
Notes	

NCT00756275

Trial name or title	Varenicline and motivational advice for smokers with SUD
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	274 adult smokers with substance use disorder
Interventions	Varenicline vs NRT patches for 12 weeks, plus motivational advice
Outcomes	7-day PPA at 3, 6 and 12m

NCT00756275 (*Continued*)

Starting date	January 2009
Contact information	Damaris J Rohsenow
Notes	

NCT00789074

Trial name or title	Effects of an extended period of varenicline use prior to quitting smoking on post-quitting urges to smoke
Methods	Randomized triple-blind placebo-controlled trial
Participants	101 adult smokers
Interventions	4 weeks pre-quit varenicline vs 3 weeks placebo + 1 week varenicline
Outcomes	Ratings of urges to smoke at 1 day and 7days post-quit
Starting date	July 2009
Contact information	Peter Hajek
Notes	

NCT00790569

Trial name or title	Varenicline versus nicotine replacement for methadone-maintained smokers
Methods	Randomized double-blind placebo-controlled trial
Participants	602 adult smokers
Interventions	Varenicline, NRT or placebo for up to 6m
Outcomes	Smoking cessation
Starting date	September 2008
Contact information	M Stein
Notes	

NCT00794573

Trial name or title	Evaluation of varenicline (Champix) in smoking cessation for patients post-acute coronary syndrome (EVITA) trial
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	300 smokers with recent heart attack
Interventions	Varenicline 1.0mg bid vs placebo for 12 weeks
Outcomes	Amoking cessation at 24 wks
Starting date	September 2009
Contact information	MJ Eisenberg
Notes	

NCT00802919

Trial name or title	Varenicline for cognitive deficits and cigarette smoking in schizophrenia
Methods	Randomized double-blind placebo-controlled trial
Participants	60 adult smokers with schizophrenia
Interventions	Varenicline 1-2mg/day vs placebo
Outcomes	Cotinine-verified cessation, + MATRICS, PANNS, Hamilton Depression Scale
Starting date	September 2008
Contact information	RC Smith
Notes	

NCT00828113

Trial name or title	Long-term (52 wks) varenicline treatment for smoking cessation
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	100 adult smokers
Interventions	All get 13 weeks varenicline, then half continue and half switch to placebo, until week 52
Outcomes	Biochemically confirmed abstinence (at ? timepoint)

NCT00828113 (*Continued*)

Starting date	January 2009
Contact information	DE Jorenby
Notes	

NCT00835900

Trial name or title	Extended varenicline for smoking cessation: A pilot study
Methods	Randomized triple-blind placebo-controlled trial
Participants	60 adult smokers
Interventions	Varenicline vs placebo, variable dosing schedule
Outcomes	Smoking cessation at EoT, + craving, changes in smoking behaviour, smoking satisfaction and withdrawal
Starting date	March 2009
Contact information	MC Mahoney
Notes	

NCT00860028

Trial name or title	Varenicline for smoking cessation in heavy drinking smokers
Methods	Randomized triple-blind placebo-controlled trial
Participants	30 heavy drinking smokers
Interventions	3 wks pre-quit varenicline + 5 wks varenicline vs 3 wks pre-quit placebo + 5 wks varenicline
Outcomes	CAR wks 5-8
Starting date	October 2008
Contact information	SS O'Malley
Notes	

NCT00894166

Trial name or title	Evaluation of a tailored smoking cessation treatment algorithm based on initial treatment response and genotype
Methods	Randomized triple-blind placebo-controlled trial
Participants	530 adult smokers
Interventions	NRT, bupropion and varenicline combinations
Outcomes	CAR at wks 8-11
Starting date	May 2009
Contact information	JE Rose
Notes	

NCT00906386

Trial name or title	Methadone maintenance treatment and smoking cessation (MMTASC)
Methods	Randomized double-blind placebo-controlled trial
Participants	112 smokers on methadone maintenance for opioid dependence
Interventions	Varenciline 1.0mg/bid 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	Randomized quadruple-blind placebo-controlled trial
Participants	254 smokers diagnosed with HIV infection
Interventions	Varenicline 1.0mg/bid vs placebo for 12 weeks
Outcomes	CAR for wks 9-48

NCT00918307 (*Continued*)

Starting date	October 2009
Contact information	Patrick Mercie
Notes	

NCT00931021

Trial name or title	Smoking cessation treatment for head and neck cancer patients
Methods	Randomized open-label trial
Participants	30 smokers diagnosed with head and neck cancer
Interventions	Varenicline 1.0mg bid vs 21mg nicotine patch for 8 weeks
Outcomes	CAR at wks 5-8
Starting date	July 2009
Contact information	Bnejamin Toll
Notes	

NCT00935818

Trial name or title	Varenicline and bupropion for smoking cessation (CHANBAN)
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	450 adult smokers
Interventions	Varenicline + bupropion vs varenicline + placebo for 12 wks
Outcomes	CAR and PPA at 12 wks
Starting date	September 2009
Contact information	Jon O Ebbert
Notes	

NCT00937508

Trial name or title	Smoking cessation in preadmission clinic. The use of a teachable moment
Methods	Randomized quadruple-blind placebo-controlled trial
Participants	290 smokers, preop surgical patients
Interventions	Pre- and post-op counselling + varenicline vs Pre- and post-op counselling + placebo
Outcomes	Abstinence or reduction at 26 and 52 wks
Starting date	June 2008
Contact information	Frances Chung
Notes	

NCT00943618

Trial name or title	Effectiveness of varenicline vs. varenicline plus bupropion or placebo for smoking cessation
Methods	Randomized 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	

NCT00944554

Trial name or title	Relapse prevention with varenicline
Methods	Randomized triple-blind placebo-controlled trial
Participants	120 adult smokers
Interventions	Varenicline vs placebo for 5 weeks
Outcomes	Volunteers to relapse and time to relapse
Starting date	October 2008

NCT00944554 (*Continued*)

Contact information	ML Stitzer
Notes	

NCT00948649

Trial name or title	Effects of Chantix for relapse prevention on smoking cessation
Methods	Randomized triple-blind crossover study
Participants	62 adult smokers
Interventions	21 day course of varenicline vs placebo, including 3-day abstinence
Outcomes	Days of abstinence following programmed lapse
Starting date	September 2006
Contact information	Caryn Lerman
Notes	

NCT00959972

Trial name or title	Varenicline versus transdermal nicotine patch for smoking cessation in patients with coronary heart disease
Methods	Randomized 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	

NCT00977249

Trial name or title	Varenicline for long-term NRT users
Methods	Randomized placebo-controlled quadruple-blind trial
Participants	100-200 ex-smoking long-term users of NRT
Interventions	Varenicline 1.0mg bid vs placebo for 12 weeks
Outcomes	7-day PPA at 12 weeks, not smoking or on NRT
Starting date	September 2009
Contact information	Philip Tønneson
Notes	

NCT01010204

Trial name or title	Varenicline treatment for smoking cessation in patients with bipolar disorder (BEST)
Methods	Randomized placebo-controlled quadruple-blind trial
Participants	80 smokers with bipolar disorder
Interventions	Varenicline 1.0mg bid vs placebo for 12 weeks
Outcomes	Smoking cessation at 24 weeks
Starting date	January 2010
Contact information	KN Roy Chengappa
Notes	

NCT01027754

Trial name or title	Smoking cessation treatment for methadone maintenance patients
Methods	Randomized placebo-controlled quadruple-blind trial
Participants	134 smokers in methadone treatment for substance abuse
Interventions	Varenciline 1.0mg bid vs placebo for 12 weeks
Outcomes	Cotinine-verified PPA at 12 weeks
Starting date	August 2009

NCT01027754 (*Continued*)

Contact information	Shadi Nahvi
Notes	

NCT01067612

Trial name or title	Extended treatment for smoking cessation
Methods	Randomized 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	

NCT01078298

Trial name or title	Safety and efficacy of varenicline for smokers with depression
Methods	Randomized placebo-controlled double-blind trial
Participants	500 adult smokers diagnosed with depression
Interventions	Varenicline 1.0mg bid vs placebo for 12 weeks
Outcomes	CAR for wks 9-12, + PPA at 52 wks
Starting date	March 2010
Contact information	Pfizer Inc
Notes	

NCT01093937

Trial name or title	Varenicline for smoking cessation/reduction in patients with bipolar disorder
Methods	Randomized placebo-controlled quadruple-blind trial
Participants	30 adult smokers with bipolar disorder
Interventions	Varenicline flexible dosing (0.5 to 2.0mg/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	

NCT01111149

Trial name or title	Varenicline and smoking cessation in schizophrenia (VSCS)
Methods	Randomized double-blind factorial trial
Participants	60 smokers with schizophrenia
Interventions	12 weeks of Varenicline vs bupropion vs placebo.
Outcomes	Cotinine-confirmed abstinence at 12 weeks
Starting date	December 2009
Contact information	S Hossein Fatemi
Notes	

NCT01141855

Trial name or title	Smoking Termination Opportunity for inPatients (STOP trial)
Methods	Randomized single-blind controlled trial
Participants	392 adult smokers
Interventions	Varenicline + counselling vs counselling alone for 12 weeks
Outcomes	Smoking abstinence at 12 months
Starting date	May 2008

NCT01141855 (*Continued*)

Contact information	Brian J Smith
Notes	

NCT01170338

Trial name or title	Safety and efficacy of varenicline in patients with acute coronary syndrome
Methods	Randomized 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	

TASC 2007

Trial name or title	Tabex for Smoking Cessation (TASC) Trial
Methods	Randomized double-blind placebo-controlled trial
Participants	740 Polish smokers
Interventions	25 days cytisine vs placebo
Outcomes	Continuous abstinence at 12 months & safety
Starting date	January 2007
Contact information	West R
Notes	

DATA AND ANALYSES

Comparison 1. Varenicline (1.0mg 2/d) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous abstinence at longest follow up (24+ weeks)	10	4443	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [2.01, 2.66]
2 Abstinence at 9-12 weeks	10	4454	Risk Ratio (M-H, Fixed, 95% CI)	2.57 [2.33, 2.84]
3 Abstinence at 9-24 weeks	10	4452	Risk Ratio (M-H, Fixed, 95% CI)	2.42 [2.13, 2.75]
4 Abstinence for long-term (52 weeks) use of varenicline	1	377	Risk Ratio (M-H, Fixed, 95% CI)	4.91 [2.56, 9.42]

Comparison 2. Low-dose varenicline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Low dose varenicline vs placebo at 52 weeks	4	1272	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.56, 2.78]
2 Standard dose vs low dose varenicline at 52 weeks	3	1083	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.55]

Comparison 3. Varenicline vs bupropion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Continuous abstinence at 52 weeks	3	1622	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [1.22, 1.88]

Comparison 4. Varenicline vs NRT (open-label)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Point prevalence abstinence at 24 weeks	2	778	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.94, 1.35]

Comparison 5. Varenicline as maintenance therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abstinence at 52 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Abstinence at 24 weeks (end of double-blind phase)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 6. Cytisine vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Point prevalence abstinence at 2 years	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

Comparison 7. Adverse event meta-analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	11	4782	Risk Ratio (M-H, Fixed, 95% CI)	3.19 [2.78, 3.67]
2 Insomnia	10	4472	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [1.33, 1.82]
3 Abnormal dreams	8	3827	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [2.35, 3.94]
4 Headache	9	4155	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [1.01, 1.39]

Comparison 8. Most frequent adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea			Other data	No numeric data
2 Insomnia			Other data	No numeric data
3 Abnormal dreams			Other data	No numeric data
4 Headache			Other data	No numeric data

Comparison 9. Serious Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 [*= possibly or probably attributed to study medication]			Other data	No numeric data

Comparison 10. Losses to follow up

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

Comparison 11. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 ITT treatment vs per protocol control	10	3801	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [1.45, 1.92]

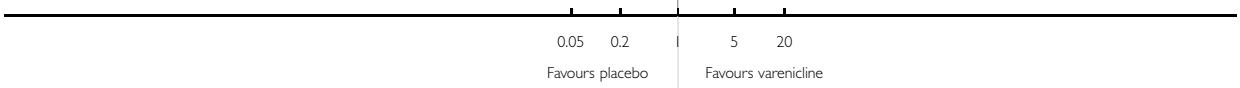
Analysis 1.1. Comparison 1 Varenicline (1.0mg 2/d) vs placebo, Outcome 1 Continuous abstinence at longest follow up (24+ weeks).

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Varenicline (1.0mg 2/d) vs placebo

Outcome: 1 Continuous abstinence at longest follow up (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
Gonzales 2006	77/352	29/344		12.6 %	2.59 [1.74, 3.87]
Jorenby 2006	79/344	35/341		15.1 %	2.24 [1.55, 3.24]
Nakamura 2007	56/155	35/154		15.1 %	1.59 [1.11, 2.28]
Niaura 2008	35/160	12/160		5.2 %	2.92 [1.57, 5.41]
Nides 2006	18/127	6/127		2.6 %	3.00 [1.23, 7.31]
Oncken 2006	58/259	5/129		2.9 %	5.78 [2.38, 14.05]
Rigotti 2010	68/353	26/354		11.1 %	2.62 [1.71, 4.02]
Tashkin 2010	46/248	14/253		6.0 %	3.35 [1.89, 5.94]
Tsai 2007	59/126	27/124		11.7 %	2.15 [1.47, 3.15]
Wang 2009	63/165	42/168		17.9 %	1.53 [1.10, 2.12]
Total (95% CI)	**2289**	**2154**		**100.0 %**	**2.31 [2.01, 2.66]**
Total events: 559 (Treatment), 231 (Control)					
Heterogeneity: Chi^2 = 17.81, df = 9 (P = 0.04); I^2 =49%					
Test for overall effect: Z = 11.69 (P < 0.00001)					



Analysis 1.2. Comparison 1 Varenicline (1.0mg 2/d) vs placebo, Outcome 2 Abstinence at 9-12 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Varenicline (1.0mg 2/d) vs placebo

Outcome: 2 Abstinence at 9-12 weeks

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Jorenby 2006	151/344	60/341		15.2 %	2.49 [1.93, 3.23]
Nides 2006	36/127	13/127		3.3 %	2.77 [1.54, 4.97]
Gonzales 2006	155/352	61/344		15.5 %	2.48 [1.92, 3.21]
Oncken 2006	128/259	15/129		5.0 %	4.25 [2.60, 6.95]
Tsai 2007	75/126	40/124		10.1 %	1.85 [1.38, 2.47]
Nakamura 2007	104/156	60/154		15.2 %	1.71 [1.36, 2.15]
Niaura 2008	63/160	18/160		4.5 %	3.50 [2.17, 5.63]
Wang 2009	83/165	53/168		13.2 %	1.59 [1.22, 2.09]
Rigotti 2010	167/355	50/359		12.5 %	3.38 [2.55, 4.47]
Tashkin 2010	105/250	22/254		5.5 %	4.85 [3.17, 7.42]
Total (95% CI)	**2294**	**2160**		**100.0 %**	**2.57 [2.33, 2.84]**

Total events: 1067 (Varenicline), 392 (Placebo)

Heterogeneity: Chi^2 = 47.44, df = 9 (P<0.00001); I^2 =81%

Test for overall effect: Z = 18.61 (P < 0.00001)

Analysis 1.3. Comparison 1 Varenicline (1.0mg 2/d) vs placebo, Outcome 3 Abstinence at 9-24 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Varenicline (1.0mg 2/d) vs placebo

Outcome: 3 Abstinence at 9-24 weeks

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gonzales 2006	104/352	36/344		13.1 %	2.82 [1.99, 4.00]
Jorenby 2006	102/344	45/341		16.2 %	2.25 [1.64, 3.09]
Oncken 2006	75/259	7/129		3.4 %	5.34 [2.53, 11.24]
Nides 2006	26/127	9/127		3.2 %	2.89 [1.41, 5.92]
Tsai 2007	59/126	27/124		9.8 %	2.15 [1.47, 3.15]
Nakamura 2007	63/156	44/154		15.9 %	1.41 [1.03, 1.94]
Niaura 2008	44/160	14/160		5.0 %	3.14 [1.80, 5.50]
Wang 2009	63/165	42/168		14.9 %	1.53 [1.10, 2.12]
Tashkin 2010	64/250	18/254		6.4 %	3.61 [2.21, 5.91]
Rigotti 2010	100/353	34/359		12.1 %	2.99 [2.09, 4.29]
Total (95% CI)	**2292**	**2160**		**100.0 %**	**2.42 [2.13, 2.75]**

Total events: 700 (Varenicline), 276 (Placebo)

Heterogeneity: Chi^2 = 29.50, df = 9 (P = 0.00053); I^2 =69%

Test for overall effect: Z = 13.71 (P < 0.00001)

Analysis 1.4. Comparison 1 Varenicline (1.0mg 2/d) vs placebo, Outcome 4 Abstinence for long-term (52 weeks) use of varenicline.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 1 Varenicline (1.0mg 2/d) vs placebo

Outcome: 4 Abstinence for long-term (52 weeks) use 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
Williams 2007	88/251	9/126		100.0 %	4.91 [2.56, 9.42]
Total (95% CI)	**251**	**126**		**100.0 %**	**4.91 [2.56, 9.42]**
Total events: 88 (varenicline), 9 (placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.78 (P < 0.00001)					

Analysis 2.1. Comparison 2 Low-dose varenicline, Outcome 1 Low dose varenicline vs placebo at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 2 Low-dose varenicline

Outcome: 1 Low dose varenicline vs placebo at 52 weeks

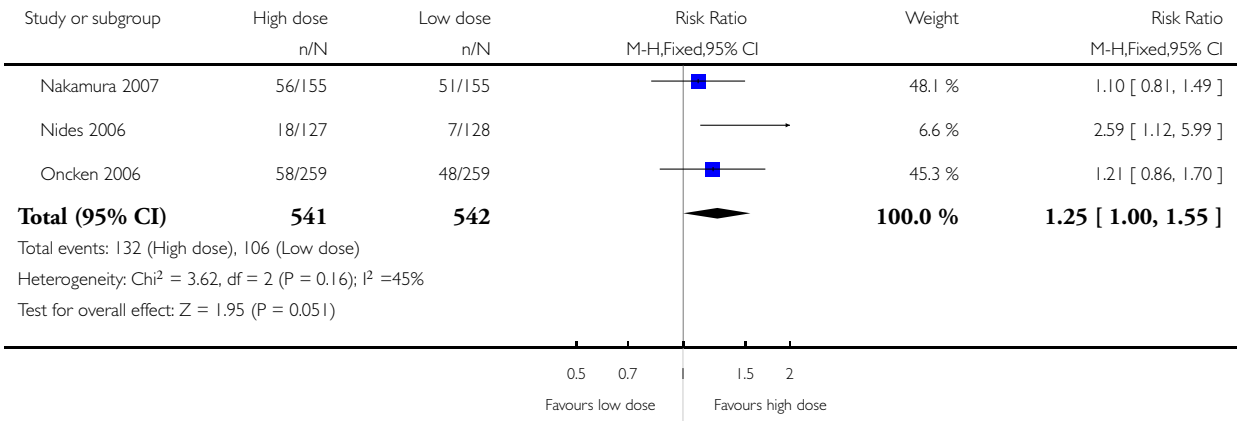
Study or subgroup	varenicline n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nakamura 2007	51/155	35/154		58.7 %	1.45 [1.00, 2.09]
Niaura 2008	35/160	12/160		20.1 %	2.92 [1.57, 5.41]
Nides 2006	7/128	6/127		10.1 %	1.16 [0.40, 3.35]
Oncken 2006	48/259	5/129		11.2 %	4.78 [1.95, 11.72]
Total (95% CI)	**702**	**570**		**100.0 %**	**2.09 [1.56, 2.78]**
Total events: 141 (varenicline), 58 (placebo)					
Heterogeneity: Chi^2 = 9.38, df = 3 (P = 0.02); I^2 =68%					
Test for overall effect: Z = 4.99 (P < 0.00001)					

Analysis 2.2. Comparison 2 Low-dose varenicline, Outcome 2 Standard dose vs low dose varenicline at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 2 Low-dose varenicline

Outcome: 2 Standard dose vs low dose varenicline at 52 weeks

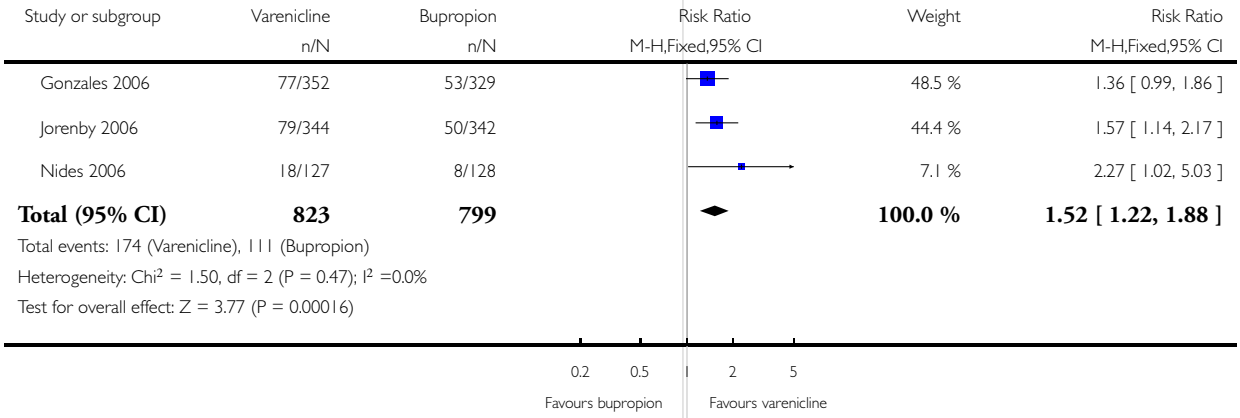


Analysis 3.1. Comparison 3 Varenicline vs bupropion, Outcome 1 Continuous abstinence at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 3 Varenicline vs bupropion

Outcome: 1 Continuous abstinence at 52 weeks



Analysis 4.1. Comparison 4 Varenicline vs NRT (open-label), Outcome 1 Point prevalence abstinence at 24 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 4 Varenicline vs NRT (open-label)

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	145/376	126/370		94.8 %	1.13 [0.94, 1.37]
Tsukahara 2010	7/16	7/16		5.2 %	1.00 [0.46, 2.19]
Total (95% CI)	**392**	**386**		**100.0 %**	**1.13 [0.94, 1.35]**

Total events: 152 (varenicline), 133 (NRT)

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0.0\%$

Test for overall effect: Z = 1.25 (P = 0.21)

Analysis 5.1. Comparison 5 Varenicline as maintenance therapy, Outcome 1 Abstinence at 52 weeks.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 5 Varenicline as maintenance therapy

Outcome: 1 Abstinence at 52 weeks

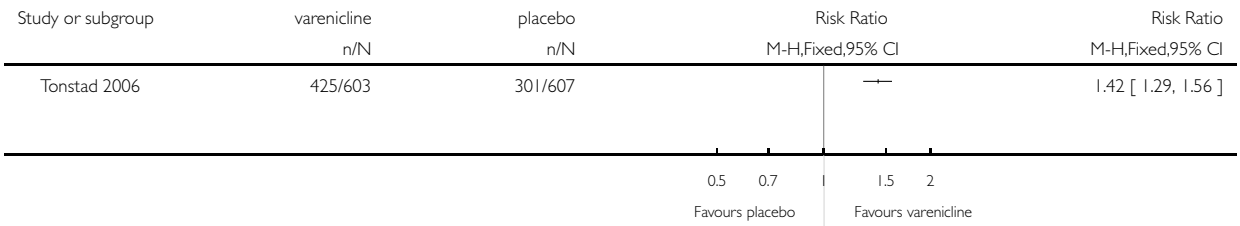
Study or subgroup	varenicline n/N	placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Tonstad 2006	263/601	224/607		1.19 [1.03, 1.36]

Analysis 5.2. Comparison 5 Varenicline as maintenance therapy, Outcome 2 Abstinence at 24 weeks (end of double-blind phase).

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 5 Varenicline as maintenance therapy

Outcome: 2 Abstinence at 24 weeks (end of double-blind phase)

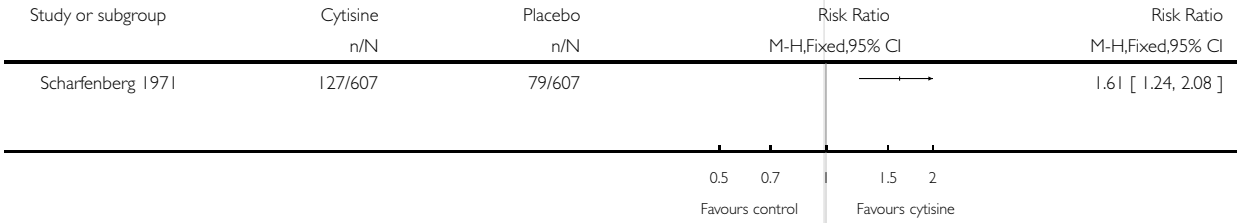


Analysis 6.1. Comparison 6 Cytisine vs placebo, Outcome 1 Point prevalence abstinence at 2 years.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 6 Cytisine vs placebo

Outcome: 1 Point prevalence abstinence at 2 years



Analysis 7.1. Comparison 7 Adverse event meta-analyses, Outcome 1 Nausea.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Adverse event meta-analyses

Outcome: 1 Nausea

Study or subgroup	Varenicline n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gonzales 2006	98/349	29/344		12.9 %	3.33 [2.26, 4.90]
Jorenby 2006	101/343	33/340		14.6 %	3.03 [2.11, 4.36]
Nakamura 2007	38/156	12/154		5.3 %	3.13 [1.70, 5.75]
Niaura 2008	21/157	8/155		3.5 %	2.59 [1.18, 5.67]
Nides 2006	65/125	23/123		10.2 %	2.78 [1.85, 4.17]
Oncken 2006	97/253	18/121		10.7 %	2.58 [1.64, 4.06]
Rigotti 2010	104/353	30/350		13.3 %	3.44 [2.35, 5.02]
Tashkin 2010	67/248	20/251		8.7 %	3.39 [2.12, 5.41]
Tsai 2007	55/126	14/124		6.2 %	3.87 [2.27, 6.58]
Wang 2009	48/165	20/168		8.7 %	2.44 [1.52, 3.93]
Williams 2007	101/251	10/126		5.9 %	5.07 [2.75, 9.36]
Total (95% CI)	**2526**	**2256**		**100.0 %**	**3.19 [2.78, 3.67]**

Total events: 795 (Varenicline), 217 (Placebo)

Heterogeneity: Chi^2 = 5.80, df = 10 (P = 0.83); I^2 =0.0%

Test for overall effect: Z = 16.29 (P < 0.00001)

Analysis 7.2. Comparison 7 Adverse event meta-analyses, Outcome 2 Insomnia.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 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
Gonzales 2006	49/349	44/344		19.6 %	1.10 [0.75, 1.60]
Jorenby 2006	49/343	42/340		18.7 %	1.16 [0.79, 1.70]
Niaura 2008	34/157	17/155		7.6 %	1.97 [1.15, 3.38]
Nides 2006	44/125	27/123		12.1 %	1.60 [1.06, 2.41]
Oncken 2006	75/253	14/121		8.4 %	2.56 [1.51, 4.34]
Rigotti 2010	42/353	23/350		10.2 %	1.81 [1.11, 2.94]
Tashkin 2010	24/248	15/251		6.6 %	1.62 [0.87, 3.01]
Tsai 2007	19/126	17/124		7.6 %	1.10 [0.60, 2.02]
Wang 2009	10/165	5/168		2.2 %	2.04 [0.71, 5.83]
Williams 2007	48/251	12/126		7.1 %	2.01 [1.11, 3.64]
Total (95% CI)	**2370**	**2102**		**100.0 %**	**1.55 [1.33, 1.82]**

Total events: 394 (Varenicline), 216 (Placebo)

Heterogeneity: Chi^2 = 12.34, df = 9 (P = 0.19); I^2 =27%

Test for overall effect: Z = 5.47 (P < 0.00001)

Analysis 7.3. Comparison 7 Adverse event meta-analyses, Outcome 3 Abnormal dreams.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 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
Gonzales 2006	36/349	19/344		25.4 %	1.87 [1.09, 3.19]
Jorenby 2006	45/343	12/340		16.0 %	3.72 [2.00, 6.90]
Nides 2006	19/125	10/123		13.4 %	1.87 [0.91, 3.86]
Oncken 2006	46/253	6/121		10.8 %	3.67 [1.61, 8.35]
Rigotti 2010	28/353	6/350		8.0 %	4.63 [1.94, 11.04]
Tashkin 2010	27/248	7/251		9.2 %	3.90 [1.73, 8.80]
Tsai 2007	7/126	1/124		1.3 %	6.89 [0.86, 55.17]
Williams 2007	57/251	9/126		15.9 %	3.18 [1.63, 6.21]
Total (95% CI)	**2048**	**1779**		**100.0 %**	**3.04 [2.35, 3.94]**

Total events: 265 (Varenicline), 70 (Placebo)

Heterogeneity: $Chi^2 = 7.39$, df = 7 (P = 0.39); $I^2 = 5\%$

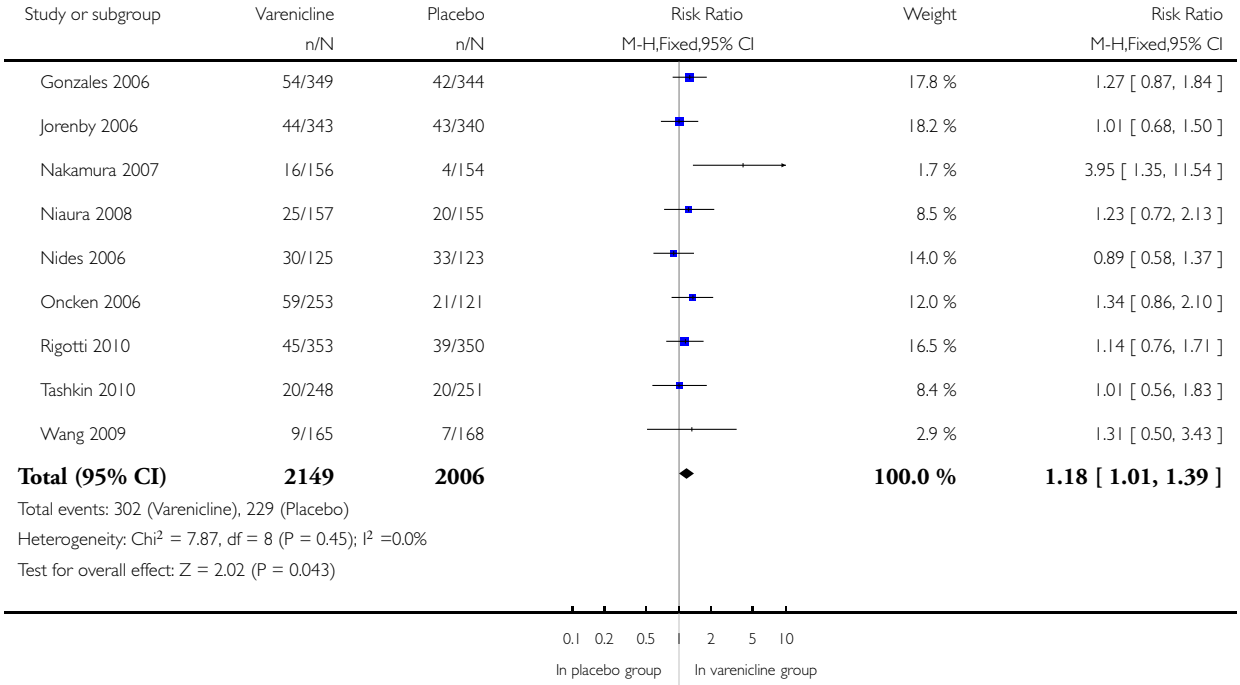
Test for overall effect: Z = 8.44 (P < 0.00001)

Analysis 7.4. Comparison 7 Adverse event meta-analyses, Outcome 4 Headache.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 7 Adverse event meta-analyses

Outcome: 4 Headache



Analysis 8.1. Comparison 8 Most frequent adverse effects, Outcome 1 Nausea.

Nausea

Study	Placebo n/N (%)	Varenicline n/N (%)	Bupropion n/N (%)	NRT n/N(%)
Aubin 2008		140/376 (37.2)		36/370 (9.7)
Gonzales 2006	29/344 (8.4)	98/349 (28.1)	41/329 (12.5)	
Jorenby 2006	33/340 (9.7)	101/343 (29.4)	25/340 (7.4)	
Nakamura 2007	12/154 (7.8)	38/156 (24.4)		
Niaura 2008	8/155 (5.2)	21/157 (13.4)		
Nides 2006	23/123 (18.7)	0.3mgx1: 22/126 (17.5) 1.0mgx1: 47/126 (37.3) 1.0mg bid: 65/125 (52.0)	27/126 (21.4)	

Nausea (*Continued*)

Oncken 2006	18/121 (14.9)	97/253 (38.3) [45/129 (34.9) titrated 52/124 (41.9) non-titrated]		
Rigotti 2010	30/350 (8.6)	104/353 (29.5)		
Swan 2010	N/A	323/917 (35.2)		
Tashkin 2010	20/251 (8.0)	67/248 (27.0)		
Tsai 2007	14/124 (11.3)	55/126 (43.7)		
Tsukahara 2010		4/14 (28.6)		0.0
Wang 2009	20/168 [11.9]	48/165 [29.1]		
Williams 2007	10/126 (7.9)	101/251 (40.2)		

Analysis 8.2. Comparison 8 Most frequent adverse effects, Outcome 2 Insomnia.

Insomnia

Study	**Placebo n/N (%)**	**Varenicline n/N (%)**	**Bupropion n/N (%)**	**NRT n/N (%)**
Aubin 2008		80/376 (21.3)		71/370 (19.2)
Gonzales 2006	44/344 (12.8)	49/349 (14.0)	72/329 (21.9)	
Jorenby 2006	42/340 (12.4)	49/343 (14.3)	72/340 (21.2)	
Niaura 2008	17/155 (11.0)	34/157 (21.7)		
Nides 2006	27/123 (22.0)	44/125 (35.2)	57/126 (45.2)	
Oncken 2006	14/121 (11.6)	75/253 (29.6) 48/129 (37.2) titrated 27/124 (21.8) non-titrated		
Rigotti 2010	23/350 (6.6)	42/353 (11.9)		
Swan 2010		371/917 (40.5)		
Tashkin 2010	15/251 (6.0)	24/248 (9.7)		
Tsai 2007	17/124 (13.7)	19/126 (15.1)		
Tsukahara 2010		6/14 (42.9)		2/14 (14.3)

Insomnia (*Continued*)

Wang 2009	5/168 [3.0]	10/165 [6.1]		
Williams 2007	12/126 (9.5)	48/251 (19.1)		

Analysis 8.3. Comparison 8 Most frequent adverse effects, Outcome 3 Abnormal dreams.

Abnormal dreams

Study	**Placebo n/N (%)**	**Varenicline n/N (%)**	**Bupropion n/N (%)**	**n/N (%)**
Aubin 2008		44/376 (11.7)		31/370 (8.4)
Gonzales 2006	19/344 (5.5)	36/349 (10.3)	18/329 (5.5)	
Jorenby 2006	12/340 (3.5)	45/343 (13.1)	20/340 (5.9)	
Nides 2006	10/123 (8.1)	19/125 (15.2)	15/126 (11.9)	
Oncken 2006	6/121 (5.0)	46/253 (18.2) 25/129 (19.4) titrated 21/124 (16.9) non-titrated		
Rigotti 2010	6/350 (1.7)	28/353 (7.9)		
Swan 2010		344/917 (37.6)		
Tashkin 2010	7/251 (2.8)	27/248 (10.9)		
Tsai 2007	1/124 (0.8)	7/126 (5.6)		
Williams 2007	9/126 (7.1)	57/251 (22.7)		

Analysis 8.4. Comparison 8 Most frequent adverse effects, Outcome 4 Headache.

Headache

Study	**Placebo n/N (%)**	**Varenicline n/N (%)**	**Bupropion n/N (%)**	**n/N (%)**
Aubin 2008		72/376 (19.1)		36/370 (9.7)
Gonzales 2006	42/344 (12.2)	54/349 (15.5)	47/329 (14.3)	
Jorenby 2006	43/340 (12.6)	44/343 (12.8)	27/340 (7.9)	
Nakamura 2007	4/154 (2.6)	16/156 (10.3)		
Niaura 2008	20/155 (12.9)	25/157 (15.9)		

Headache (*Continued*)

Nides 2006	33/123 (26.8)	30/125 (24.0)	38/126 (30.2)	
Oncken 2006	21/121 (17.4)	59/253 (23.3) 29/129 (22.5) titrated 30/124 (24.2) non-titrated		
Rigotti 2010	39/350 (11.1)	45/353 (12.7)		
Tashkin 2010	20/251 (8.0)	20/248 (8.1)		
Wang 2009	7/168 [4.2]	9/165 [5.5]		

Analysis 9.1. Comparison 9 Serious Adverse Events, Outcome 1 [*= possibly or probably attributed to study medication].

[*= possibly or probably attributed to study medication]

Study	**Placebo**	**Varenicline**	**Bupropion**	**NRT**
Aubin 2008		Depression *; Constipation		Bile duct cancer + sepsis; GI bleeding; MI x 2; salivary gland tumour; chest pain x 2; aggravation of existing knee trauma
Gonzales 2006	lung cancer; acute MI; schizophrenia (acute exacerbation); chest pain; urinary tract infection; atrial fibrillation; underarm chest pain	abdominal pain; atrial fibrillation*; pneumonia; possible stroke	cholecystitis and septic shock; headache; grand mal seizure*	
Jorenby 2006	Five SAEs (no details given in study report)	cancer (lung or brain); 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	

[*= **possibly or probably attributed to study medication**] (*Continued*)

Nakamura 2007	Three SAEs (no further details)	cholecystits * angina pectoris* Eight no further info		
Niaura 2008	None	All in post-treatment 30 days: MyocardiaI Infarct Ventricular fibrillation Spontaneous abortion		
Nides 2006		Transient ischaemic attacks*	Bloody diarrhoea*; syncope*; convulsions* (2 people)	
Oncken 2006	syncope; suicide attempt	*0.5x2 non-tit.*: syncope *0.5x2 tit.*: duodenal ulcer; cholesteatoma; unstable angina; post-RTA seizure. *1.0x2:* paroxysmal supraventricular tachycardia; aseptic meningitis; MS; carcinoid colon cancer.		
Rigotti 2010	21 SAEs (6.0%: no further info). 5 deaths	23 SAEs (6.5%: no further info). 2 deaths		
Scharfenberg 1971	Not reported	Not reported		
Swan 2010	Not applicable	9 SAEs, inc. 2 cardiac deaths and 1 psychiatric hospitalisation		
Tashkin 2010	1 death from amyotrophic lateral sclerosis	Two deaths: Sudden cardiac arrest, post-MI and CABG; 1 RTA		
Tonstad 2006	5 non-fatal SAEs during double-blind phase	Three deaths: 1 post-treatment suicide; 1 complications of lung cancer; 1 back pain + rectal sarcoma. 20 SAEs during open-label phase, and 15 in double-blind phase (10 varenicline and 5 placebo) . No further details given.	20 non-fatal SAEs during open-label phase, and 10 in double-blind phase. Three deaths: 1 post-treatment suicide; 1 complications of lung cancer; 1 back pain + rectal sarcoma. 20 SAEs during open-label phase, and 15 in	

[*= **possibly or probably attributed to study medication**] (*Continued*)

			double-blind phase (10 varenicline and 5 placebo) .	
Tsai 2007	Three traffic accidents	peritonitis/acute appendicitis; acute pyelonephritis; unstable angina *		
Tsukahara 2010		None reported		None reported
Wang 2009	Gingival pain Decreased libido Throat irritation	Upper abdominal pain Nausea Pyrexia Nasopharnygitis Tonsillitis Gout Dizziness Insomnia Abnormal blood tests		
Williams 2007	Three (no details given in study report)	15 SAEs, including bilateral subcapsular cataracts*		

Analysis 10.1. Comparison 10 Losses to follow up, Outcome 1 Participants remaining at end of trial.

Participants remaining at end of trial

Study	**Placebo [%]**	**Varenicline [%]**	**Bupropion [%]**	**NRT [%]**	**X2 and P value**
Aubin 2008		247/378 [65.3]		230/379 [60.7]	1.76, P=0.18
Gonzales 2006	187/344 [54.4]	213/352 [60.5]	184/329 [55.9]		2.90, P=0.23
Jorenby 2006	204/341 [59.8]	240/344 [69.8]	221/342 [64.6]		7.42, P=0.02*
Nakamura 2007	132/154 [85.7]	124/155 (79.5)			1.77, P=0.18
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]			24.32, P=0.0000008**
Rigotti 2010	289/359 [80.5]	302/355 [85.1]			2.61, P=0.106

Participants remaining at end of trial (*Continued*)

Tashkin 2010	157/254 [61.8]	176/250 [70.4]			
Tonstad 2006	463/607 [76.3]	494/603 [81.9]			5.83, P=0.016*
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]	0.00, P=1.00
Wang 2009	161/168 [95.8]	158/165 [95.8]			0.0, P=0.97
Williams 2007	59/126 [46.8]	135/251 [53.8]			1.62, P=0.20

Analysis 11.1. Comparison 11 Sensitivity analysis, Outcome 1 ITT treatment vs per protocol control.

Review: Nicotine receptor partial agonists for smoking cessation

Comparison: 11 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
Nides 2006	18/127	6/68		3.0 %	1.61 [0.67, 3.86]
Oncken 2006	58/259	5/40		3.3 %	1.79 [0.77, 4.19]
Gonzales 2006	77/352	29/187		14.3 %	1.41 [0.96, 2.08]
Jorenby 2006	79/344	35/204		16.6 %	1.34 [0.94, 1.92]
Tsai 2007	59/126	27/117		10.6 %	2.03 [1.39, 2.97]
Nakamura 2007	56/155	35/132		14.3 %	1.36 [0.96, 1.94]
Niaura 2008	35/160	12/155		4.6 %	2.83 [1.52, 5.24]
Wang 2009	63/165	42/161		16.1 %	1.46 [1.06, 2.02]
Tashkin 2010	46/248	14/157		6.5 %	2.08 [1.18, 3.66]
Rigotti 2010	68/355	26/289		10.8 %	2.13 [1.39, 3.25]
Total (95% CI)	**2291**	**1510**		**100.0 %**	**1.67 [1.45, 1.92]**

Total events: 559 (Treatment), 231 (Control)

Heterogeneity: Chi^2 = 9.78, df = 9 (P = 0.37); I^2 =8%

Test for overall effect: Z = 7.28 (P < 0.00001)

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
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.

(*Continued*)

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
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.

(*Continued*)

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*
Gonzales 2006	352	344	329		1025
Jorenby 2006	344	341	342		1027
Nides 2006	128 (0.3x1) 128 (1.0x1) 127 (1.0x2)*	127	128		638
Oncken 2006	129 (0.5NT) 130 (0.5T) 129 (1.0NT)* 130 (1.0T)*	129			647
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
Aubin 2008	378			379	757
Niaura 2008	160	160			320

(*Continued*)

Wang 2009	165	168			333
Rigotti 2010	355	359			714
Swan 2010	1202				1202
Tsukahara 2010	16			16	32
Tashkin 2010	250	254			504
TOTALS	**6892** * used in primary MA	**2286**	**799**	**395**	**10372**

Appendix 3. Measures of craving, withdrawal and reinforcement

Study	MNWS	QSU-B Total Craving score	mCEQ (for smokers)
Gonzales (wks1-7) 1.0mg 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 2.13P); P<0.001; ES: -0.33	Baseline to wk1: 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 (wks1-7) 1.0mg 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 wk1: 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)

(*Continued*)

Nides (wks1-7) 1.0mg bid vs placebo	Diff in mean change in: Urge to smoke: wk1 -1.14; wk2 -1.19; wk3 -1.57; Wk4 -1.81; wk5 -1.88; wk6 -2.04; wk7 -1.61(p<.001 for wks1-6, P<.01 wk7)	Total score: wk1 -7.00; wk2 -10.71; wk3 -12.72; wk4 -14.08; wk5 -13.24; wk6 -14.94; wk7 -14.38 (wks 1,3,5 P<.001, wks 2,4,6,7 P<.01)	Baseline to wk1: 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 (MNWS: wks1-12; mCEQ wks1-7) 1.0mg 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 wk7: 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)
Tonstad 1.0mg bid vs placebo	Diff in mean change in Urge to Smoke score (extrapolated from graph): All participants: Wk13: -0.35, Wk 25 -0.25; Abstainers only: Wk13: -0.30, Wk 25 +0.02		
Tsai (wks1-6) 1.0mg bid vs placebo	Diff in mean change in Urge to Smoke: Wks 1-6: -0.40 (P<0.001)	Mean total score, wks1-6: -0.39 (P<0.001)	Mean diff wks 1-6: V vs P: Smoking satisfaction: -0.39 (P<0.008)
Nakamura (wks1-7) 1.0mg 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)
Aubin (wks1-7) 1.0mg bid **vs NRT**	Diff in mean change in: Urge to Smoke score: -0.32 (P<0.001); E.S. -0.37		Mean diff wks 1-7: V vs NRT: Smoking satisfaction: -0.54 (P<0.001); E.S. -0.43

(*Continued*)

	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		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 2009 1-4 0.5mg *ad lib*	Diff in Urge to smoke, all pts: Wk1: -0.4; Wk 2: -0.4; Wk3 -0.6; Wk4 -0.5; Wk5 -0.6; Wk6 -0.5; Wk7 -0.4; Wk12 -0.6. Diff in withdrawal, all pts: Wk1: -0.4; Wk 2: -0.7; Wk3 -0.7; Wk4 -1.1; Wk5 -0.3; Wk6 -0.4; Wk7 -0.2; Wk12 -0.9.		Diff in changes between V&P: Smoking satisfaction: Enjoy resp tract: Wk1 -0.1; Wk2 -0.3; Wk3 -0.4; Wk4 -0.5; Wk5 -0.5; Wk6 -0.5; Wk7 -0.4;
Tsukahara 2010 1.0mg bid **vs NRT**	Diff in withdrawal score (all symptoms), V vs NRT: Wk2 2.36; Wk4 0.64; Wk 8 0.78; Wk12 0.08		

WHAT'S NEW

Last assessed as up-to-date: 29 October 2010.

Date	Event	Description
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.
8 November 2010	New search has been performed	Six new RCTs added; sources of funding added for all trials. Ongoing trials section expanded.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2007

Date	Event	Description
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 electronic searching, extracted data and drafted the review. LS checked data extraction, and advised on content. TL gave editorial and conceptual support. All authors contributed to text and findings. Jean-Francois Etter supplied bibliographical data and original articles and translations for the cytisine content. Sebastian Straube translated and extracted data from the German language papers.

DECLARATIONS OF INTEREST

None of the authors has any potential conflict of interest to report. Robert West, who is an editor for the Tobacco Addiction Group, 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.

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Internal sources

- Department of Primary Health Care, University of Oxford, UK.
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INDEX TERMS

Medical Subject Headings (MeSH)

Alkaloids [therapeutic use]; Azocines [therapeutic use]; Benzazepines [adverse effects; therapeutic use]; Bupropion [therapeutic use]; Nicotine [antagonists & inhibitors]; Nicotinic Agonists [adverse effects; *therapeutic use]; Quinolizines [therapeutic use]; Quinoxalines [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic; Smoking [*drug therapy]; Smoking Cessation [*methods]

MeSH check words

Humans