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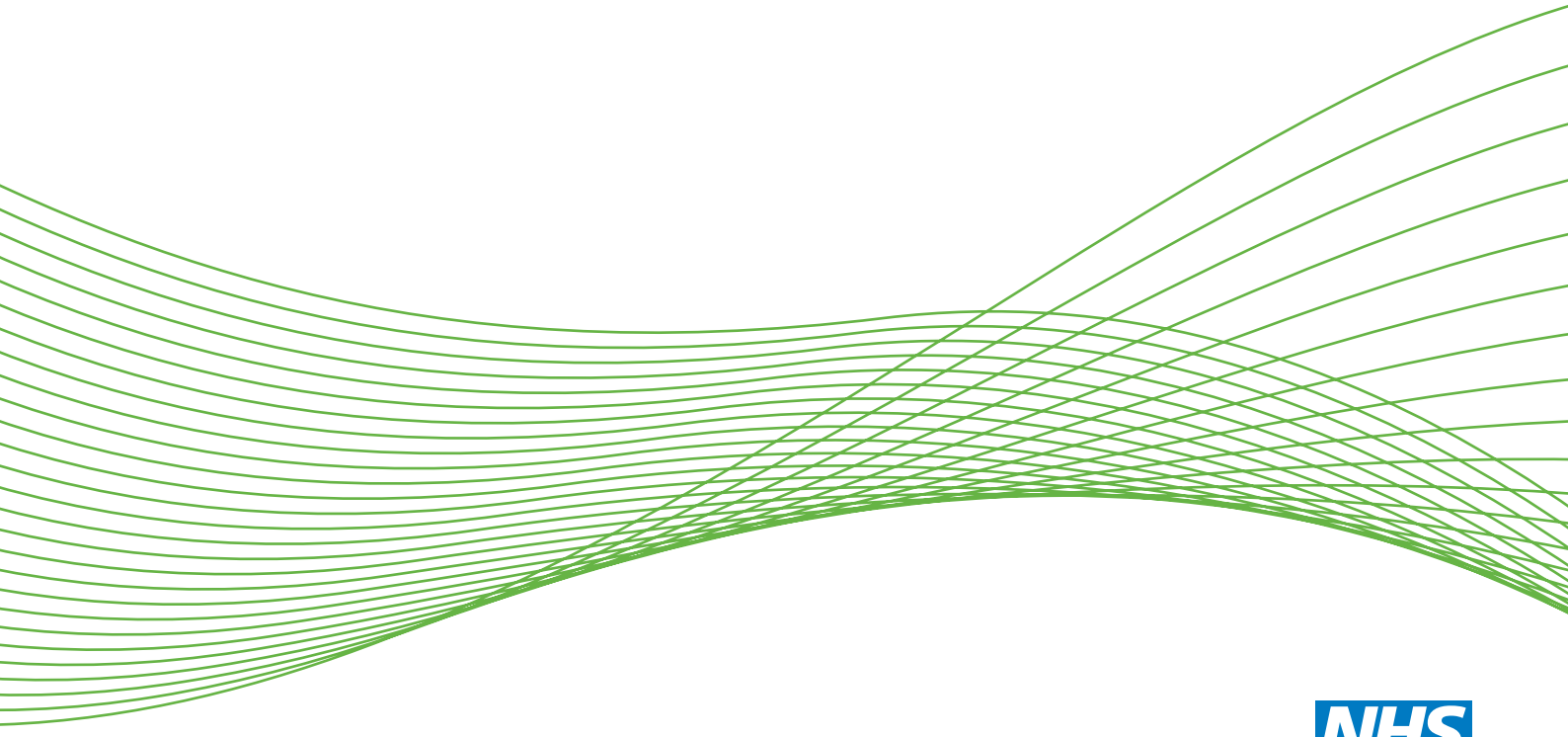

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Joanna Leaviss,* William Sullivan, Shijie Ren, Emma Everson-Hock, Matt Stevenson, John W Stevens, Mark Strong and Anna Cantrell

School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

*Corresponding author

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Abstract

What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation

Joanna Leaviss,* William Sullivan, Shijie Ren, Emma Everson-Hock, Matt Stevenson, John W Stevens, Mark Strong and Anna Cantrell

School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK

*Corresponding author

Background: Tobacco smoking is one of the leading causes of deaths worldwide. Nearly one-fifth of adults in the UK regularly smoke cigarettes. The ill-health associated with smoking costs the NHS over £3B every year. A number of pharmacological interventions are available that can help people to quit smoking. These include nicotinic receptor partial agonists such as varenicline or cytisine. Varenicline is a synthetic product licensed for use in the UK, while cytisine is derived naturally from the seeds of the plant *Cytisus laborinum* L. (golden rain acacia).

Objectives: To review the evidence on the clinical effectiveness and safety of cytisine from smoking cessation compared with varenicline; to develop an economic model to estimate the cost-effectiveness of cytisine and varenicline; and to provide recommendations based on value of information analyses as to whether or not a head-to-head trial of cytisine and varenicline would represent effective use of resources.

Data sources: Efficacy and adverse events data were sourced from a recent Cochrane review. These data were supplemented with an updated search of twelve electronic databases, including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library, for the period from December 2011 to January 2013. The review included randomised controlled trials (RCTs) of adult smokers attempting to quit using varenicline or cytisine. Further interventions were considered (placebo, nicotine replacement therapy, bupropion) to allow an indirect comparison between varenicline and cytisine. The primary outcome was abstinence at a minimum of 6 months' follow-up. Secondary outcomes were common adverse events such as abnormal dreams, headache, nausea, insomnia and serious adverse events.

Review methods: A systematic review and network meta-analysis of the clinical evidence was undertaken. A random-effects model was used to allow for heterogeneity between studies. The economic model structure was based on a published model. Probabilistic sensitivity analyses were undertaken to estimate the treatment expected to be most cost-effective given current information. Formal expected value of perfect information, perfect partial information and of sample information were performed.

Results: Twenty-three (RCTs) were included in the systematic review, comprising a total of 10,610 participants. Twenty-one trials of varenicline of differing dosing schedules and two trials of cytisine at standard dose met the inclusion criteria. No head-to-head trials comparing varenicline with cytisine were identified. The methodological quality of the studies was judged to be moderate to good. Cytisine was more efficacious than placebo [hazard ratio (HR) 4.27, 95% credible interval (CrI) 2.05 to 10.05], as was standard-dose varenicline (HR 2.58, 95% CrI 2.16 to 3.15). Standard-dose varenicline treatment was associated with significantly higher rates of headache, insomnia and nausea than placebo; there was no significant difference in the rates of abnormal dreams. There were no significant differences in the rates of

headache or nausea between cytisine and placebo; data were identified for neither abnormal dreams nor insomnia. Using expected values, cytisine is anticipated to dominate varenicline, in that it produces more quality-adjusted life-years at a lower associated cost. This occurred in approximately 90% of the scenarios performed. However, owing to the large number of people who wish to quit smoking (estimated to be 3 million over a 10-year period), the implications of making an incorrect decision is large. The expected value of sample information indicated that conducting a head-to-head trial of cytisine and varenicline was worthwhile, and that 1000 smokers per arm was an appropriate number to recruit.

Conclusions: On the basis of the evidence included in this review, varenicline and cytisine are both effective interventions to aid smoking cessation when compared with placebo. Cytisine is estimated to be both more clinically effective and cost-effective than varenicline. However, there is uncertainty in the decision, and a head-to-head trial of cytisine and varenicline would appear to be an effective use of resources.

Study registration: The study was registered as PROSPERO CRD42012003455.

Funding details: The National Institute for Health Research Health Technology Assessment programme.

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Glossary

All definitions are taken from Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012;**4**:CD006103.

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 and continuous/sustained abstinence.

Biochemical verification Also called biochemical validation or biochemical confirmation. Biochemical verification is 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. The trade names are Zyban® (GlaxoSmithKline, UK) and Wellbutrin XL® (GlaxoSmithKline, UK) when prescribed as an antidepressant.

Carbon monoxide 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.

Efficacy Also called treatment effect or effect size. The difference in outcome between the experimental and control groups.

Nicotine An alkaloid derived from tobacco, responsible for the psychoactive and additive effects of smoking.

Nicotine replacement therapy 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.

Pharmacotherapy A treatment using pharmaceutical drugs, e.g. nicotine replacement therapy, bupropion.

Point prevalence abstinence 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 2 weeks), to allow for slips/lapses during the first few days when the effect of treatment may still be emerging.

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.

List of abbreviations

A&E	accident and emergency
BENESCO	Benefits of Smoking Cessation on Outcomes
b.i.d.	bis in die (twice a day)
BNF	*British National Formulary*
CAR	continuous abstinence rate
CHD	coronary heart disease
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CrI	credible interval
EVPI	expected value of perfect information
EVPPI	expected value of partial perfect information
EVSI	expected value of sample information
FDA	US Food and Drug Administration
HR	hazard ratio
INB	incremental net benefit
LY	life-year
NICE	National Institute for Health and Care Excellence
NRT	nicotine replacement therapy
PPA	point prevalence abstinence
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
q.d.	quaque die (every day)
RCT	randomised control trial
SAE	serious adverse event
SD	standard deviation
STA	single technology appraisal

Scientific summary

Background

Tobacco smoking is one of the leading causes of preventable deaths worldwide. Nearly one-fifth of adults in the UK regularly smoke cigarettes. The ill-health associated with smoking costs the NHS over £3B every year. Stopping smoking is difficult; however, it can significantly reduce the risk of smoking-related illnesses such as heart disease and cancer. A number of interventions are available that can help people to quit smoking. These include nicotinic receptor partial agonists such as varenicline or cytisine. Varenicline is a synthetic product licensed for use in the UK as an aid to smoking cessation. Cytisine is a naturally occurring product, derived from the seeds of the plant *Cytisus laborinum* L. (golden rain acacia), which is not currently licensed for use in the UK, although it has been available as an aid to smoking cessation in a number of Eastern European countries for over 40 years. Reviews of these interventions have shown them to be more effective in helping people to quit smoking than placebo. Concerns over the safety of varenicline have been raised; however, reviews have produced inconsistent findings. To date there have been no head-to-head trials comparing the clinical effectiveness of varenicline and cytisine. Consequently, there remain outstanding questions regarding which of the two drugs shows greater clinical efficacy. In addition, although cytisine is reported to be cheaper than varenicline, it is unclear which of the two drugs is the most cost-effective.

Objectives

The main research question addressed by this assessment is 'What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation?' The specific objectives of the assessment are:

- to review the evidence on the clinical effectiveness and safety of cytisine for smoking cessation compared with varenicline
- to develop an economic model to estimate the cost-effectiveness of cytisine and varenicline within the context of NHS smoking cessation services
- to provide recommendations based on value of information analyses whether or not a head-to-head trial of cytisine and varenicline would represent effective use of resources and, if so, the recommended number of smokers in each arm.

Methods

Clinical effectiveness methods

The inclusion criteria for the review were as follows:

- Population: adult smokers.
- Interventions and comparators: cytisine, in any formulation, or varenicline, in any formulation. In the anticipated absence of data from head-to-head studies of cytisine and varenicline, any other comparators [e.g. placebo, nicotine replacement therapy (NRT), bupropion] were considered that would allow an indirect comparison to be made.
- Outcomes: the primary outcome was abstinence at a minimum follow-up of 6 months. Secondary outcomes were common adverse events, namely abnormal dreams, headache, and nausea and insomnia.
- Study design: randomised controlled trials (RCTs).

A recent good-quality Cochrane review of nicotinic receptor partial agonists was identified. Data for efficacy and adverse events from this review were used to evaluate the clinical effectiveness and cost-effectiveness of cytisine and varenicline. In addition, a comprehensive search was undertaken in order to update the data in this review and use both sets of data to inform, where appropriate, indirect comparisons between the two interventions. The updated search was conducted across 12 electronic databases, including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature and The Cochrane Library, for the period from December 2011 to January 2013. Bibliographies of any newly identified trials were hand searched to identify any further trials. Two reviewers sifted potentially relevant studies independently and inclusion decisions were agreed among the broader research team with reference to the project's clinical experts. The methodological quality of the newly included studies was assessed using the Cochrane risk of bias tool. The results of included studies were synthesised using both narrative and statistical methods.

Methods of data synthesis

Abstinence data and adverse events data were synthesised using a network meta-analysis. The analysis combined evidence across studies in which there was at least one treatment in a study that was common to at least one other study. A random (treatment)-effects model was used to allow for heterogeneity in treatment effects between studies.

Cost-effectiveness methods

As detailed in the protocol, the model structure was based on the Benefits of Smoking Cessation on Outcomes model. The economic analysis was focused on a population of smokers in England and Wales aged 18 years or older who are motivated to quit smoking. It evaluated the cost of the standard doses of both cytisine and varenicline, and was modelled on a hypothetical cohort of 10,000 smokers, with each smoker assumed to make a single quit attempt, assisted by either varenicline or cytisine.

Results

Results of clinical effectiveness review

Twenty studies from the existing Cochrane review were included in the review and a further three studies were identified by the updated search. The studies comprised 10,610 participants. Twenty-one of the studies evaluated varenicline, with the remaining two studies evaluating cytisine. Comparators included placebo, NRT and bupropion. Overall, the quality of the studies was good, with no studies judged to be at high risk of bias.

As no head-to-head trials comparing cytisine with varenicline were identified, indirect comparisons were made using network meta-analyses. These showed that cytisine produced the greatest effect on abstinence than placebo and had the highest probability of being the most effective intervention.

Standard-dose varenicline treatment was associated with significantly higher rates of headache, insomnia and nausea than placebo; there was no significant difference in the rates of abnormal dreams. There were no significant differences in rates of headache or nausea between cytisine and placebo; data were not identified for abnormal dreams or insomnia.

Results of cost-effectiveness analyses

Outputs from the economic model estimated that cytisine treatment would produce more mean life-years and quality of life-adjusted years, and lower mean lifetime costs, than varenicline treatment and is, therefore, expected to dominate over varenicline. The economic analysis is driven by the relative effectiveness of cytisine and varenicline. The treatment that generates the greatest number of quitters will have the best long-term health outcomes, as smoking cessation produces reduced costs associated with longer-term conditions associated with smoking. Based on the current available data, if treatment costs were equal for cytisine and varenicline, there is a greater probability that cytisine will be the optimal choice. However, there is uncertainty in this decision and, owing to the very large numbers of smokers receiving NHS treatment for smoking cessation each year (around 800,000 individuals), the value of further information on the relative effectiveness of both treatments is high.

Expected value of sample information analyses indicated that a RCT with 1000 smokers per arm comparing cytisine with varenicline would represent efficient use of scarce resources and would allow more robust conclusions to be made regarding the relative efficacies of the two treatments.

Discussion

Previous systematic reviews of varenicline and cytisine have produced findings consistent with this review. Varenicline has been shown to increase smoking cessation by around twofold, and reviews of cytisine show modest efficacy rates compared with placebo, although it is acknowledged that only two high-quality trials of cytisine with a minimum of 6 months of follow-up have been conducted to date, and that absolute quit rates are low. Trials in real-world settings such as pre-operative surgeries or using participants with underlying medical conditions have shown the efficacy of varenicline to be stable. No such trials of cytisine that study subpopulations have been conducted to date.

The results of the network meta-analysis showed varenicline to be associated with greater risk of some common adverse events than cytisine, although there was no difference in the risk of serious adverse events and data were not available for cytisine for all adverse events. Overall, the safety evidence in the current review was weak and a full safety review was not undertaken. Previous reviews of varenicline for smoking cessation have highlighted potentially serious adverse effects, although the results of these reviews are not consistent. Conflicting findings for cardiovascular events have been reported and reviews of trial data have shown no increased risk of serious adverse neuropsychiatric events. These recent systematic reviews use only trial data, and these may not capture all adverse events owing to strict exclusion criteria. Practitioners should be aware when making treatment decisions for individual smokers that adverse events may be more likely in those with underlying medical conditions. A full safety review of cohort studies for both varenicline and cytisine is recommended.

We believe that this research is the first to explicitly evaluate the benefits associated with undertaking a RCT of cytisine compared with varenicline. Cytisine is currently unlicensed for use in the UK and, therefore, the cost may increase if the manufacturer were to incur costs associated with fulfilling licensing requirements. However, the fundamental conclusion that a head-to-head trial of cytisine compared with varenicline is needed remains unchanged.

Conclusions

On the basis of the evidence included in this review, varenicline and cytisine are both effective interventions to aid smoking cessation when compared with placebo. Cytisine showed the greater expected efficacy and was estimated to be the more cost-effective intervention. However, uncertainty still remains and a head-to-head RCT of 1000 smokers is recommended and estimated to be an efficient use of resources.

Study registration

The study was registered as PROSPERO CRD42012003455.

Funding details

The National Institute for Health Research Health Technology Assessment programme.

Chapter 1 Background

Description of health problem

Tobacco smoking is a major cause of a number of chronic diseases, including heart disease and cancers, and is attributed as the leading cause of preventable deaths worldwide.[1,2] Smoking-related illnesses include every type of cancer except for skin cancer; cardiovascular, respiratory and digestive problems;[3] amputation due to peripheral vascular disease;[4] diabetes; cataracts; and impotence and reproductive problems.[5]

Despite these statistics, nearly one-fifth of adults in the UK are regular cigarette smokers. Although the rate of cigarette smoking has been falling slowly since the mid-1990s, in 2010 the proportion of males over 16 years who were smokers was reported to be 21%.[6] In 2006–7, smoking-related ill-health cost the NHS £3.3B.[7] Stopping smoking is known to reduce the risk of smoking-related disease, but it is challenging. Without smoking cessation aids, only between 2% and 5% of quit attempts are successful.[8,9] Smoking cessation strategies have varied success rates.

Available smoking cessation interventions

Broadly speaking, there are two types of smoking cessation intervention: (1) those designed to prompt quit attempts and (2) those designed to assist with quit attempts. The current review focuses on the latter type. A number of pharmacological interventions exist that aid smoking cessation in terms of assisting quit attempts. These include nicotine replacement therapy (NRT), typical antidepressant medications such as bupropion hydrochloride and nicotinic receptor partial agonists such as varenicline, cytisine and dianicline. Behavioural support interventions have also been developed to assist with quit attempts. Recent Cochrane reviews have demonstrated behavioural support (group, individual and telephone counselling), single-product nicotine replacement therapy and bupropion hydrochloride to demonstrate similar effectiveness as smoking cessation aids.[10–14] Greater effect sizes have been reported for nicotine partial agonists such as varenicline and cytisine.[15]

This review assesses the clinical effectiveness and cost-effectiveness of two nicotinic receptor partial agonists: varenicline and cytisine. Nicotinic receptor partial agonists offer a pharmacological method to aid smoking cessation. Varenicline (Champix or Chantix; Pfizer, UK) and cytisine (Tabex; Sopharma, Bulgaria) are included in this class of drug. These drugs act by relieving craving and withdrawal symptoms, while also blocking the reinforcing effects of nicotine if a cigarette is smoked.[16] Cytisine is a naturally occurring product, extracted from the seeds of the plant *Cytisus laborinum* L. (golden rain acacia). It has been used as an aid to smoking cessation in former socialist economies for over 40 years, although West *et al.*[17] report that it has been withdrawn from many of these countries following their entry into the European Union. It is manufactured by the Bulgarian pharmaceutical company Sopharma. Varenicline is a synthetic product developed by Pfizer, with a similar structure to cytisine. Like cytisine, varenicline is a partial agonist of nicotinic acetylcholine receptors, with high affinity for $\alpha 4\beta 2$ receptors, and is licensed for use as an aid to smoking cessation in the USA, Canada and across Europe including the UK. Although both varenicline and cytisine are used as aids to smoking cessation, Etter *et al.*[18] reported a dearth of scientific evidence on the properties of cytisine and its safety and efficacy profile. They provide an overview of the in vitro and in vivo profiles of both drugs. Cytisine is considerably less expensive than varenicline and, although costs vary between countries (Poland US$12 for a course, Russian Federation US$6 for a course), the cost of a course of cytisine is generally about 10–20% that of varenicline.[17] The standard dosage for varenicline according to the *British National Formulary* (BNF) is for adults over 18 years, the treatment to start with is usually 1–2 weeks before the target stop date (up to a maximum of 5 weeks before the target stop date). Initially, the dosage is 500 μg q.d. [quaque die (every day)] for 3 days, the dosage is increased to

500 μg b.i.d. [bis in die (twice a day)] for 4 days, followed by 1 mg b.i.d. for 11 weeks (the dose is reduced to 500 μg b.i.d. if it is not tolerated) and a 12-week course can be repeated in abstinent individuals to reduce the risk of relapse.[19] Although cytisine is not licensed for use in the UK or the USA, the usual starting dose is 1.5 mg six times daily.[20]

Measurement of abstinence

Clinical trials of interventions for smoking cessation may use a range of outcome measurements to evaluate abstinence. The Russell Standard[21] is a set of criteria widely used to define smoking abstinence. These guidelines were developed in response to results from smoking cessation trial data historically being reported in a number of different ways. The Russell Standard outlines criteria important to the measurement and reporting of outcome data in such trials. A full description of these criteria are found in West *et al.*[21] Regarding the measurement of abstinence, the criteria recommend a duration of 6 months or 12 months, either from a designated quit date or allowing for a predefined grace period. Shorter periods of abstinence are reported to be insufficient in their ability to accurately predict long-term cessation. Regarding the definition of abstinence, historically a number of methods of measuring abstinence have been used. These include continuous abstinence, defined as abstinence between quit day and follow-up; prolonged abstinence, defined as sustained abstinence after an initial grace period, or to a period of sustained abstinence between two follow-ups; point prevalence abstinence, defined as the prevalence of abstinence during a time window immediately preceding follow-up and repeated point prevalence abstinence, defined as point prevalence abstinence measured at two or more follow-ups between which smoking is allowed.[22] Abstinence is often biochemically verified by measurement of carbon monoxide (CO). However, CO is eliminated from the body in around 24 hours;[15] therefore, abstinence cannot be verified for longer periods than this. The Russell Standard recommends that abstinence should be defined as 'a self-report of smoking not more than five cigarettes from the start of the abstinence period, supported by a negative biochemical test at the final follow-up'.[21]

Current service provision

Stop smoking clinics in the UK typically include the option to attend specialist one-to-one sessions with a trained stop smoking advisor, group sessions or drop-in sessions.[23] Clinics generally involve some form of assessment of current smoking behaviour and willingness to quit, including CO monitoring, prescription of some form of pharmacotherapy if desired (NRT, bupropion hydrochloride or varenicline) and behavioural support focused on managing withdrawal symptoms and preventing relapse (including preparing to quit, setting a quit date and making plans for situations where the client may be tempted to smoke).[24]

Success rates for the NHS smoking cessation treatments

Eight hundred thousand smokers each year attempt cessation through the NHS stop smoking services.[25] In any given quit attempt 0.5% of smokers attempt cessation using varenicline with specialist individual behavioural support through NHS stop smoking clinics, 0.2% use varenicline with specialist group behavioural support, 0.1% use varenicline with specialist drop-in behavioural support and 2.8% obtain a prescription for varenicline in NHS settings (e.g. primary care, hospital).[23] The estimated 52-week continuous abstinence rates for NHS specialist individual behavioural support clinics are 15% when combined with NRT monotherapy, 20% with NRT combination therapy, 17% with bupropion hydrochloride and 24% with varenicline. The estimated 52-week continuous abstinence rates for NHS specialist group behavioural support clinics are 20% when combined with NRT monotherapy, 26% with NRT combination therapy, 23% with hydrochloride and 31% with varenicline. The estimated 52-week continuous abstinence rates for NHS specialist drop-in behavioural support clinics are 11% when combined with NRT monotherapy, 15% with NRT combination therapy, 13% with bupropion hydrochloride and 19% with varenicline. The estimated 52-week continuous abstinence rates for brief interventions in NHS settings (e.g. primary care, hospital) are 7% for NRT monotherapy, 10% for NRT combination therapy, 8% for bupropion hydrochloride and 12% for varenicline.[23]

A recent Cochrane review of nicotinic receptor partial agonists as aids to smoking cessation showed a modest efficacy for cytisine over placebo in helping people to stop smoking, although the study reports low absolute quit rates for these trials.[15] The authors report a twofold increase in quit rates for varenicline over placebo. These analyses, comparing each drug with placebo, found no difference in their efficacy. The authors highlight that trials have now been conducted in real-world settings, for example in smokers with underlying diseases or medical conditions who might under ordinary circumstances be excluded from clinical trials, and report that the findings remain stable in these populations. A recent review of the efficacy and safety of cytisine found it to be an effective treatment for smoking cessation.[26] The review highlights the low cost of cytisine and suggests that licensing of this drug may therefore be warranted because of its potential public health benefit. No head-to-head trials between varenicline and cytisine were identified in either review and, to date, no indirect comparisons of the two drugs have been conducted in the absence of such trials.

Safety profile of varenicline

Concerns have been raised regarding the safety profile of varenicline. The US Food and Drug Administration (FDA) has issued a series of warnings, resulting from post-marketing reports of increased risk of suicidal behaviour or depression, serious adverse cardiac events and gastrointestinal complaints including a recently added warning highlighting a small increased risk of certain cardiovascular events in smokers with pre-existing cardiac conditions. A meta-analysis of adverse gastrointestinal events by Leung *et al.*[27] showed an increased risk after treatment with varenicline. In a review of 10 trials, Tonstad *et al.*[28] found no evidence of a link between varenicline and serious neuropsychiatric events. Reviews by Singh *et al.*[29] and Prochaska[30] report conflicting findings, with Singh *et al.* showing an increased risk of serious cardiovascular events after treatment with varenicline and Prochaska finding no evidence of a link. Cahill *et al.*[15] found a lack of trial evidence indicating serious adverse events for varenicline. However, the studies do not rule out the possibility of a link, in light of the FDA warnings. Data extracted from randomised control trials (RCTs) may not provide a comprehensive account of all possible adverse events – participants may be excluded for having a history of a number of relevant medical conditions, for example depression or cardiovascular disease. In addition, the follow-up time period of trials may not be long enough to sufficiently capture all relevant adverse events.

This assessment aimed to review the efficacy of varenicline and cytisine as an aid to smoking cessation by updating the Cahill *et al.*[15] review and to conduct indirect comparisons where appropriate. A mathematical model compared the cost-effectiveness of cytisine with varenicline in the context of NHS stopping smoking services. Recommendations regarding the need for a head-to-head trial were made.

Chapter 2 Definition of the decision problem

This assessment addresses the question: what is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? Specifically, the assessment will (i) review evidence on the clinical effectiveness and safety of cytisine in smoking cessation compared with varenicline; (ii) develop an economic model to estimate the cost-effectiveness of cytisine in the context of NHS smoking cessation services and (iii) provide recommendations based on the value of information analyses whether or not a head-to-head trial of cytisine and varenicline would represent an effective use of resources.

Decision problem

Population: adult smokers.

Intervention and relevant comparators: cytisine, a nicotinic receptor partial agonist, used as an aid in the treatment of smoking cessation, and varenicline, in any formulation. In the likely absence of data from head-to-head studies of cytisine with varenicline, any comparators (e.g. placebo, NRT, bupropion) were considered that would allow an indirect comparison or network meta-analysis.

Outcomes: the primary outcome was smoking cessation, as defined by the study's strictest reported definition of abstinence, at a minimum of 6 months' follow-up, i.e. continuous abstinence rate (CAR) data were used in preference to point prevalence abstinence (PPA) data where both were reported.[22] Secondary outcomes were adverse events. The four most frequently reported adverse events, as reported in the Cahill[15] review, were analysed and these were nausea, headache, insomnia and abnormal dreams. Serious adverse events (SAEs) were also analysed.

Overall aims and objectives of assessment

The overall aims and objectives of this assessment were to:

1. Update the Cahill *et al.*[15] search to identify additional clinical effectiveness and safety data for cytisine compared with varenicline in helping people to stop smoking.
2. In the absence of head-to-head trials, conduct indirect treatment comparisons for efficacy and adverse events for cytisine compared with varenicline.
3. Model the cost-effectiveness of cytisine and varenicline within the context of NHS smoking cessation services.
4. Make recommendations for commissioning a full head-to-head trial of varenicline compared with cytisine.

Chapter 3 Assessment of clinical effectiveness

Methods for reviewing clinical effectiveness

Identification of studies

A good-quality recent Cochrane review evaluating the clinical effectiveness and safety profile of both cytisine and varenicline was identified.[15] This Cochrane review will be referred to subsequently as Cahill *et al.*[15] The current review aimed to use the data from Cahill *et al.*[15] to inform clinical effectiveness and cost-effectiveness analyses. An update of this search was conducted, which aimed to identify any recent studies evaluating the clinical effectiveness of varenicline or cytisine. The aim of the current review was to compare the clinical effectiveness and cost-effectiveness of varenicline and cytisine, but in the likely absence of head-to-head trials between cytisine and varenicline, any comparators were considered that would enable an indirect comparison, for example placebo, NRT and bupropion.

The search was conducted in January 2013 and the search strategy from Cahill *et al.*[15] was rerun for trials and systematic reviews in the period December 2011 to January 2013. Although dianicline was included in the Cahill *et al.*[15] searches, development of the drug has been discontinued and, therefore, will not be included in the comparisons for this report. This term was therefore excluded from the search. Additionally, a search was run for the terms Champix or Chantix (brand names for varenicline) with no date restrictions, in order to identify earlier trials using brand rather than generic names, as these terms were not included in Cahill *et al.*[15]

The search was also rerun with a cost-effectiveness filter with no date restriction for cost-effectiveness literature. The purpose of the cost-effectiveness search was to obtain data to inform the model and no systematic review of this literature was conducted. Cost-effectiveness methods and analyses are reported in *Chapter 4*.

Searches were conducted by an information specialist (AC). Examples of each of the search strategies in MEDLINE are provided in *Appendix 1*.

The following electronic databases were searched for published and unpublished research evidence, from December 2011 to January 2013 for the efficacy searches and from database inception for the cost-effectiveness searches:

- MEDLINE (Ovid) 1950–
- EMBASE (Ovid) 1980–
- Cumulative Index to Nursing and Allied Health Literature (CINAHL; EBSCO*host*) 1982–
- The Cochrane Library including the Cochrane Systematic Reviews Database, Cochrane Controlled Trials Register, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database and NHS Economic Evaluation Database (NHS EED) 1991–
- Biological Abstracts (via Web of Science) 1969–
- Science Citation Index (via Web of Science) 1900–
- Social Science Citation Index (via Web of Science) 1956–
- EconLit 1961–
- Conference Proceedings Citation Index–Science (CPCI–S) (via Web of Science) 1990–
- UK Clinical Trials Research Network (UKCRN) and the National Research Register archive (NRR)
- Current Controlled Trials 1898–
- ClinicalTrials.gov 1998–.

All citations were imported into Reference Manager (Thomson ResearchSoft, San Francisco, CA, USA) software and duplicates deleted.

Inclusion and exclusion criteria

- Study design: RCTs.
- Intervention or comparators: cytisine, in any formulation; varenicline, in any formulation. In the likely absence of data from head-to-head studies of cytisine compared with varenicline, any other comparators (e.g. placebo, NRT, bupropion) were considered that would allow an indirect comparison.
- Population: smokers.
- The primary outcome was abstinence at a minimum 6 months' follow-up.

Based on the above inclusion/exclusion criteria, study selection was conducted by two reviewers (JL and EEH). In the first instance titles and abstracts were examined for inclusion. Both reviewers independently screened all retrieved citations. Discrepancies between reviewers were discussed and any remaining disagreement resulted in retrieval of the full paper for further consideration. The full manuscripts of citations judged to be potentially relevant were retrieved and further assessed for inclusion. Any remaining discrepancies between reviewers at full-paper stage were discussed and, if no agreement could be reached, were resolved by referring to the review's clinical experts. A table of studies excluded at full-paper stage with reasons for exclusion is presented in *Appendix 3*.

Data extraction

Data were extracted without blinding to either authors or journal. Data from studies included in the Cahill review[15] were extracted directly from the review by one reviewer (JL or EEH). Data from studies included following the updated search were extracted by one reviewer (JL) and checked by a second (EEH). Any data for doses not reported in Cahill *et al.*[15] were extracted directly from the original papers. Efficacy data for newly included studies were calculated using the same method reported in Cahill *et al.*[15] – based on the numbers of people randomised to an intervention and excluding any deaths or untraceable moves in accordance with the Russell Standard.[31] Drop-outs or those patients lost to follow-up are treated as continuing smokers. It is beyond the scope of this short report to conduct a systematic review of adverse events for varenicline and cytisine, taking into account long-term observational studies. Therefore, this assessment will adopt the same approach to adverse events as the Cahill *et al.*[15] review, extracting this information from RCTs retrieved through an update of their efficacy search. Adverse events data were extracted on the basis of number of participants who had taken at least one dose of treatment. Data from the strictest reported measurement of smoking cessation were extracted for use in the analyses, i.e. 7-day PPA or CAR. Where studies reported both CAR and 7-day PPA, CAR data were extracted in preference to 7-day PPA[22] and only data from studies measuring CAR were used in the network meta-analysis for efficacy. Data from both types of studies were used for adverse events analyses. Efficacy data from studies that reported only PPA were extracted with the purpose of conducting a sensitivity analysis for significant differences in results by method of outcome measurement. Adverse events data were extracted for the four most common adverse events, as identified in the Cahill review, and these were abnormal dreams, nausea, headache and insomnia. Data for SAEs were also extracted.

Critical appraisal strategy

Critical appraisals of the quality of studies, retrieved by the updated search, followed the same format as reported by Cahill,[15] using the Cochrane risk of bias tool (Higgins *et al*).[32] Studies were critically appraised by JL or EEH and checked by the second reviewer. Discrepancies were resolved by discussion between reviewers. Quality assessments aimed to evaluate the risk of bias in the current evidence base for the clinical effectiveness of both varenicline and cytisine.

Methods of data synthesis

The continuous abstinence data and adverse events data including abnormal dreams, headache, insomnia, nausea and SAEs were synthesised using a network meta-analysis. The analysis combines evidence across studies in which there is at least one treatment in a study that is common to at least one other study.

A random (treatment) effects model was used to allow for heterogeneity in treatment effects between studies. The model assumed a fixed (i.e. unconstrained) baseline effect in each study so that treatment effects were estimated within study and combined across studies. All analyses were implemented in WinBUGS (MRC Biostatistics Unit, Cambridge, UK).[33]

The continuous abstinence, abnormal dreams, headache, insomnia, nausea and SAEs data were modelled using a complementary log-log link function to allow for variation in duration of follow-up between studies (see *Appendix 4*). This assumes that the times to event follow an exponential distribution and, hence, that the treatment effect is constant over time. Although these are strong assumptions, they are expected to be better than assuming there is no effect of duration of follow-up.

Results of the network meta-analyses are reported in terms of the hazard ratios (HRs) and 95% credible intervals (CrIs) relative to the baseline intervention (i.e. placebo). The posterior medians of the between-study standard deviations (SDs) together with their 95% CrIs are also presented.

Convergence of the models to their posterior distributions was assessed using the Gelman–Rubin convergence statistic.[34] Convergence occurred after 50,000 iterations for all outcome measures except for SAEs, which converged after 60,000 iterations. There was some suggestion of moderate autocorrelation between successive iterations of the Markov chains; to compensate for this the Markov chains were thinned every five iterations for continuous abstinence, nausea and SAEs, and every 10 iterations for abnormal dreams, headache and insomnia. Parameter estimates were based on 10,000 iterations of the Markov chains for continuous abstinence and nausea; 5000 iterations of the Markov chains for abnormal dreams, headache and insomnia and 8000 iterations of the Markov chains for SAEs to ensure that the Monte Carlo error was < 5% of the posterior SD. Although fewer samples would have been sufficient for estimating parameters for continuous abstinence, 10,000 samples were taken for the purpose of the expected value of sample information (EVSI).

The total residual deviance was used to assess formally whether or not the statistical model provided a reasonable representation of the sample data. The total residual deviance is the mean of the deviance under the current model minus the deviance for the saturated model, so that each data point should contribute about one to the deviance.[35]

To enable the estimation of intervention-specific CARs, as required for the economic model, a separate random-effects meta-analysis was conducted on the placebo intervention arms. Absolute estimates of CARs were generated for each intervention by projecting the estimates of treatment effect (i.e. the log-hazard ratio) from the network meta-analysis onto the baseline CAR.

Results

Updated search

The updated bibliographic search for clinical effectiveness retrieved 476 papers. *Figure 1* shows the results of this search. For the clinical effectiveness search, 32 full papers were retrieved after screening of titles and abstracts. After the reading of these full papers, a further 29 papers were excluded (reasons given in *Appendix 3*). Three papers were included from the updated search.[37–39] All three papers measured smoking cessation rates by PPA. The study reported in Cahill *et al.*[15] as Pfizer 2011[40] was identified in the updated search as now being a published paper.[41] There were no differences in reported data in the published paper. Data for efficacy and adverse events were extracted from all newly included studies.

Studies reported in the Cahill review

Cahill *et al.*[15] report 24 trials meeting their inclusion criteria. Their inclusion criteria considered any selective nicotinic receptor partial agonists, e.g. cytisine, varenicline, dianicline, or any other class of drug as they reach Phase III trial stage. Any comparators were considered, which included placebo, NRT, counselling and bupropion. RCTs of adult smokers were included. For outcomes, studies had to report a minimum of

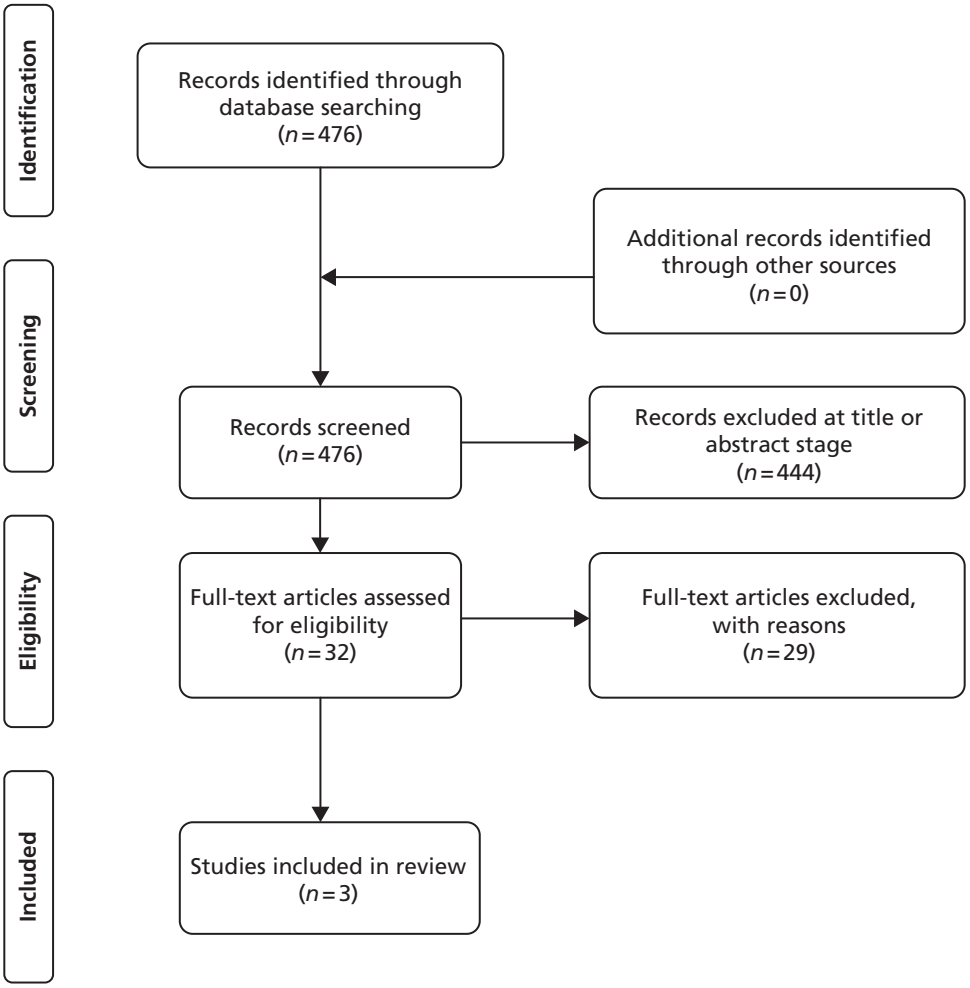

FIGURE 1 Study flow chart [adapted from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009;**6**:e1000097[36]].

6 months' abstinence. Three of the reported trials evaluated cytisine, one trial evaluated dianicline and 20 trials evaluated varenicline. Four studies included in Cahill were not included in the current review for reasons outlined below.

Studies from Cahill not included in the current review

As the current review did not seek to evaluate dianicline as a result of its discontinuation, the trial evaluating dianicline reported in Cahill *et al.*[15] is not included here. Three studies of cytisine or varenicline that were included in the Cahill review (but not in their analyses) are not reported in the current review. Scharfenberg *et al.*[42] studied the efficacy of cytisine against placebo. In their review, Cahill *et al.*[15] reported the design and conduct of this early trial to be of indeterminate quality, using self-reported PPA and without biochemical verification. They therefore did not combine the results of this study with the two more recent cytisine studies.[17,43] Their sensitivity analysis combining these three trials indicated substantial heterogeneity between this older study and the newer ones. Therefore, this study has not been included in the current report. Two further studies from the Cahill review were not included in the current review.[44,45] Swan *et al.*[44] compared different counselling methods alongside varenicline treatment, with all groups receiving varenicline, and no non-treatment control groups. Tonstad[45] studied varenicline as maintenance therapy, with both arms completing an initial course of varenicline before the comparison of varenicline and placebo for maintenance of the quit.

A summary of characteristics of all included studies is presented in *Tables 1* and *2*. A more detailed account of studies from the Cahill review is not provided in this update, but these characteristics are fully reported in Cahill *et al.*[15]

TABLE 1 Summary characteristics for cytisine studies

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Vinnikov 2008[43]	Kyrgyzstan	197	Cytisine mean age 38.3 years, placebo 39.4 years; cytisine percentage male 99%, placebo 95%; cytisine mean years smoking 19.8 years, placebo 21.9 years	Aged > 20 years, smoked ≥ 15 cigarettes per day during the year prior to inclusion into the trial, had claimed high motivation to quit smoking and readiness to do so immediately and had no previous experience of cytisine use	Cytisine (1.5-mg tablets): six times daily (one every 2 hours) on days 1–3; five times per day on days 4–12; four times per day on days 13–16; three tablets per day on days 17–20; two tablets per day on days 21–22; one tablet per day on days 23–25	Placebo: tablets same regimen	CO-validated CAR. Day 5, week 8. Day 5, week 26
West 2011[17]	Poland	740	Cytisine mean age: 49.5 years, placebo 43.5 years; cytisine percentage male 49.5%, placebo 43.5%; cytisine mean years smoking 28.1 years, placebo 28.6 years	Adults who smoked ≥ 10 cigarettes per day, willing to attempt to stop smoking permanently	Cytisine (1.5-mg tablets): six times daily (one every 2 hours) on days 1–3; five times per day on days 4–12; four times per day on days 13–16; three tablets per day on days 17–20; two tablets per day on days 21–25	Placebo: tablets same regimen	CO-validated abstinence (fewer than five cigarettes during preceding 6 months) 12 months after end of treatment

TABLE 2 Study characteristics for varenicline trials

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Aubin 2008[46]	Multinational (Belgium, France, the Netherlands, UK and the USA)	757 (randomised), 746 (treated)	Varenicline: mean age 42.9 years, percentage male 48.4%, mean years smoking 25.9 years NRT: mean age 42.9 years, percentage male 50%, mean years smoking 25.2 years	Smokers aged 18–75 years, smoking at least 15 cigarettes per day with no period of abstinence > 3 months in the previous year	Varenicline: 1 mg b.i.d. for 12 weeks, titrated during week 1	Nicotine transdermal patch (21 mg weeks 2–6, 14 mg weeks 7–9, 7 mg weeks 10–11)	CO-confirmed CAR Varenicline: 9–12 weeks, 9–24 weeks, 9–52 weeks NRT: 8–11 weeks, 8–24 weeks, 8–52 weeks
Bolliger 2011[47]	Multinational (11 countries in Latin America, the Middle East and Africa)	593	Varenicline: mean age 43.1 years, percentage male 57.7%, mean years smoking 25.0 years Placebo: mean age 43.9 years, percentage male 65.7%, mean years smoking 26.8 years	Smokers aged 18–75 years; motivated to stop smoking and had smoked a mean ≥ 10 cigarettes per day during the past 12 months; no cumulative period of abstinence > 3 months in the previous 12 months	Varenicline: 1 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: tablets same regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks
de Dios 2012[38]	USA	32	Varenicline: mean age 45.7 years, percentage male 40% NRT: mean age 39.1 years, percentage male 54.5% Placebo: mean age 44.2 years, percentage male 45.5%	Adult Latino light smokers ≤ 10 cigarettes per day for the past 3 months	Varenicline 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Nicotine patch for 12 weeks: 14 mg for 4 weeks, tapering to 7 mg for 8 weeks Placebo: matched to varenicline regimen	CO-validated 7-day PPA: 2 weeks, 1 month, 2 months, 3 months, 4 months, 6 months

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Gonzales 2006[48]	USA (multicentre)	1025	Varenicline: mean age 42.5 years, percentage male 50%, mean years smoked 24.3 years Bupropion: mean age 42.0 years, percentage male 58.4%, mean years smoked 24.1 years Placebo: mean age 42.6 years, percentage male 54.1%, mean years smoked 24.7 years	Smokers aged 18–75 years, smoking 10 or more cigarettes per day, had < 3 months of smoking abstinence in the past year, motivated to stop smoking	Varenicline: 1 mg b.i.d. for 12 weeks, titrated week 1	Bupropion: SR for 12 weeks, 150 mg b.i.d. through week 12, titrated days 1–3 Placebo: tablets same regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks, 9–52 weeks
Heydari 2012[39]	Iran	272	Mean age: counselling, 42.2 years, varenicline 43.5 years, NRT 41.8 years. Percentages for individual group sex unclear. Mean years smoked not reported. NB study includes smokers of < 10 cigarettes per day	Smokers who attended the clinic for help in quitting	Varenicline: 1.0 mg b.i.d. for 8 weeks, titrated during week 1, plus counselling	NRT: 15 mg daily nicotine patches for 8 weeks, plus counselling Counselling only	CO-verified 'smoke-free': 1 month, 6 months, 12 months
Jorenby 2006[16]	USA (multicentre)	1027	Varenicline: mean age 44.6 years, percentage male 55.2%, mean years smoked 27.1 years Bupropion: mean age 42.9 years, percentage male 60.2%, mean years smoked 25.4 years Placebo: mean age 42.3 years, percentage male 58.1%, mean years smoked 24.4 years	Smokers aged 18–75 years, smoking 10 or more cigarettes per day, had < 3 months of smoking abstinence in the past year	Varenicline: 1 mg b.i.d. for 12 weeks, titrated during week 1	Bupropion: sustained release 150 mg b.i.d. through week 12, titrated to full strength during week 1 Placebo: tablets matching regimen	CO-validated CAR: 9–12: weeks, 9–24 weeks, 9–52 weeks

continued

TABLE 2 Study characteristics for varenicline trials (*continued*)

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Nakamura 2007[49]	Japan	619	Varenicline 0.25 mg (*n* = 128): mean age 40.2 years, percentage male 72.7%, mean years smoked 11.5 years Varenicline 0.5 mg (*n* = 128): mean age 39 years, percentage male 71.1%, mean years smoked 20.1 years Varenicline 1 mg (*n* = 130): mean age 40.1 years, percentage male 79.2%, mean years smoked 21.5 years Placebo (*n* = 129): mean age 39.9 years, percentage male 76%, mean years smoked 20.9 years	Smokers aged between 20–75 years. Motivated to stop smoking, smoking more than 10 cigarettes per day for previous year without a period of abstinence > 90 days	Varenicline at 3 doses: 0.25 mg b.i.d., 0.5 mg b.i.d., 1 mg b.i.d. 12 weeks of treatment, titrated during week 1	Placebo: tablets matching regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks, 9–52 weeks
Niaura 2008[50]	USA	320	Varenicline (*n* = 157): mean age 41.5 years, percentage male 50.3%, mean years smoked 24.9 years Placebo (*n* = 155): mean age 42.1 years, percentage male 53.5%, mean years smoked 25.7 years	Healthy adult cigarette smokers, motivated to quit, aged 18–65 years, smoked at least 10 cigarettes per day with no period of abstinence > 3 months in the past year	Varenicline: 1 week dose titration up to 0.5 mg b.i.d. Participants then chose dosing schedule, at least one 0.5-mg tablet daily, no more than two 0.5-mg tablets b.i.d.	Placebo: same regimen	CO-validated CAR: 4–7 weeks, 9–12 weeks, 9–52 weeks

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Nides 2006[51]	USA	638	Varenicline 0.3 mg (*n* = 126): mean age 41.9 years, percentage male 50%, years smoked 24.6 years Varenicline 1.0 mg once per day (*n* = 126): mean age 42.9 years, percentage male 43.7%, mean years smoked 25.4 years Varenicline 1.0 mg b.i.d. (*n* = 125): mean age 41.9 years, percentage male 50.4%, mean years smoked 23.4 years Bupropion hydrochloride (*n* = 126): mean age 40.5 years, percentage male 45.2%, mean years smoked 23.4 years Placebo (*n* = 123): mean age 41.6 years, percentage male 52.0%, mean years smoked 23.9 years	Male and female smokers aged 18–65 years who were in good general health, required to have smoked an average 10 cigarettes per day during the previous year without a period of abstinence > 3 months	Varenicline at one of three dose regimens: 0.3 mg q.d., 1.0 mg q.d., or 1.0 mg b.i.d. Subjects dosed for 6 weeks, then received blinded placebo for week 7	Bupropion hydrochloride: dosed for 7 weeks, titrated days 1–3 to 150 mg b.i.d. through week 7 Placebo: at matching regimen	CO-validated 4-week abstinence for any part of treatment Continuous quit rate: 4–7 weeks, 2–12 weeks, 4–24 weeks, 4–52 weeks

continued

TABLE 2 Study characteristics for varenicline trials (*continued*)

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Oncken 2006[52]	USA	647	Varenicline 0.5 mg b.i.d. non-titrated: mean age 42.9 years, percentage male 45%, mean years smoked 26.0 years Varenicline 0.5 mg b.i.d. titrated: mean age 43.5 years, percentage male 53.1%, mean years smoked 25 years Varenicline 1.0 mg b.i.d. non-titrated: mean age 43.7 years, percentage male 48.8%, mean years smoked 25.7 years Varenicline 1.0 mg b.i.d. titrated: mean age 42.2 years, percentage male 48.5%, mean years smoked 24.0 years Placebo: mean age 43.0 years, percentage male 51.9%, mean years smoked 25.3 years	Healthy cigarette smokers aged 18–65 years, who smoked at least 10 cigarettes per day	Varenicline: 0.5 mg b.i.d. non-titrated (12 weeks); 0.5 mg b.i.d. titrated (0.5 mg q.d. for 1 week, then b.i.d. through 12 weeks); 1.0 mg b.i.d. non-titrated (12 weeks); 1.0 mg b.i.d. titrated (0.5 mg once a day for 3 days, 0.5 mg b.i.d. for 4 days, then 1.0 mg b.i.d. through 12 weeks)	Placebo: tablets b.i.d. for 12 weeks	CO-validated continuous 4-week abstinence: 4–7 weeks, 9–12 weeks Continuous-verified abstinence: 2–12 weeks, 9–52 weeks

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Pfizer 2011 [40]/ Williams 2012[41]	USA and Canada	128	Varenicline: male 65/85; age 18–34 years, *n* = 33; age 35–44 years, *n* = 10; age 45–64 years, *n* = 42 Placebo: male 33/43; age 18–34 years, *n* = 11; age 35–44 years, *n* = 9; age 45–64 years, *n* = 23	Aged 18–75 years, male and female, have a diagnosis of schizophrenia or schizoaffective disorder and judged to be stable on psychiatric treatment. Current smokers, at least 15 cigarettes per day during the past year with no period of abstinence > 3 months in the past year. Motivated to stop smoking	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	CO-validated PPA: 12 weeks, 24 weeks
Rennard 2012[53]	Multinational (14 countries)	659	Varenicline (*n* = 493): mean age 43.9 years, percentage male 60%, mean years smoked 26 years Placebo (*n* = 166): mean age 43.2 years, percentage male 59.6%, mean years smoked 24.6	Male and female smokers aged 18–75 years, who had smoked ≥ 10 cigarettes per day during the past year, with no period of abstinence > 3 months in the past year and who were motivated to stop smoking	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks

continued

TABLE 2 Study characteristics for varenicline trials (*continued*)

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Rigotti 2010[54]	Multinational (15 countries)	714	Varenicline: mean age 57 years, percentage male 75.2%, mean years smoked 40 years Placebo: mean age 55.9 years, percentage male 82.2%, mean years smoked 39 years	Adults aged 35–75 years who had smoked > 10 cigarettes per day in the year prior to enrolment, wanted to stop smoking but had not tried to quit in the past 3 months. Had stable, documented CVD that had been diagnosed > 2 months. Eligible CVD diagnosis included history of myocardial infarction, coronary revascularisation, angina pectoris, peripheral arterial vascular disease, cerebrovascular disease	Varenicline 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks, 9–52 weeks
Smith 2013[55]	Australia	392	Aged 20–75 years with smoking-related illnesses	Aged between 20–75 years recruited from hospital wards with smoking-related illnesses	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1, plus Quit South Australia counselling	Quit South Australia counselling alone	CAR < 5 cigarettes total: 2 weeks–12 months CO validation only in subset of participants

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Steinberg 2011[56]	USA	79	Mean age overall: 51 years. Mean years smoking not reported Varenicline: age distribution ≤ 40 years, 12%; 41–50 years, 22%; 51–59 years, 35%; ≥ 60 years, 30%. Percentage male 60% Placebo: age distribution ≤ 40 years, 15%; 41–50 years, 33%; 51–59 years, 36%; ≥ 60 years, 15%. Percentage male 59%	Patients admitted to the hospital who smoked ≥ 10 cigarettes per day within the past month, were not being discharged into a setting of forced abstinence (e.g. institutionalised)	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	7-day PPA: 4 weeks, 26 weeks, 12 weeks
Tashkin 2011[57]	Multinational (four countries)	504	Varenicline: mean age 57.2 years, percentage male 62.5%, mean years smoking 40.4 years Placebo: mean age 57.1 years, percentage male 62.2%, mean years smoking 40.6 years	Adults aged ≥ 35 years with a clinical diagnosis of mild to moderate COPD, motivated to stop smoking, smoking an average of ≥ 10 cigarettes per day over the past year with no period of abstinence > 3 months over that time	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks, 9–52 weeks

continued

TABLE 2 Study characteristics for varenicline trials (*continued*)

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Tsai 2007[58]	Republic of Korea and Taiwan, province of China	250	Varenicline: mean age 39.7 years, percentage male 84.9%, mean years smoking 20.2 years Placebo: mean age 40.9 years, percentage male 92.7%, mean years smoking 22.1 years	Male and female smokers aged 18–75 years, who had smoked ≥ 10 cigarettes per day during the past year, with no period of abstinence > 3 months in the past year, and who were motivated to stop smoking	Varenicline 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: (no details reported)	CO-validated CAR: 9–12 weeks, 9–24 weeks
Tsukahara 2010[59]	Japan	32	Varenicline: mean age 45.4 years, percentage male 85.7%. mean years smoking 25.4 years Nicotine patch: mean age 46.8 years, percentage male 78.6%, mean years smoking 27.1 years	Adult smokers who all wished to stop smoking immediately	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Transdermal nicotine patch for 8 weeks, 52.5 mg for 4 weeks; 35 mg for 2 weeks; 17.5 mg for 2 weeks	CO-validated CAR: 9–12 weeks Self-reported CAR: 9–24 weeks
Wang 2009[60]	China, Singapore and Thailand	333	Varenicline: mean age 39.0 years, percentage male 96.4%, mean years smoking 20.5 years Placebo: mean age 38.5 years, percentage male 97.0%, mean years smoking 19.6 years	Adults aged 18–75 years, smoked on average ≥ 10 cigarettes per day during the year prior to the screening visit with no period of abstinence > 3 months, motivated to stop smoking	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	CO-validated CAR: 9–12 weeks, 9–24 weeks

Study name	Country	*n*	Participants	Inclusion criteria	Intervention	Comparator	Smoking cessation (strictest definition)
Williams 2007[61]	USA and Australia	377	Varenicline: mean age 48.2 years, percentage male 50.6%, mean years smoking 30.7 years Placebo: mean age 46.6 years, percentage male 48.4%, mean years 29.9 years	Adult smokers, aged 18–75 years, who had smoked an average of ≥ 10 cigarettes per day during the past year, with no period of abstinence > 3 months	Varenicline: 1.0 mg b.i.d. for 52 weeks, titrated during week 1	Placebo: matching regimen	CO-validated 7-day PPA
Wong 2012[37]	Canada	286	Varenicline: mean age 51.9 years, percentage male 55% Placebo: mean age 53.3 years, percentage male 50.4%	Adult patients 18 years or older who attended the preoperative clinic for surgery within 8–10 days, smoked a minimum of 10 cigarettes per day, with no period of abstinence > 3 months in the past year	Varenicline: 1.0 mg b.i.d. for 12 weeks, titrated during week 1	Placebo: matching regimen	7-day PPA CO-validated for some participants, but mailed in urinary cotinine validation for all: 3 months, 6 months, 12 months

COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease.

Description of studies from updated search

We found three additional studies that met our inclusion criteria, covering 590 participants.[37–39] All three studies were single-country studies, carried out in Canada, the USA, and Iran respectively. Wong *et al.*[37] conducted the study at two sites – both pre-operative clinics in hospitals in Canada. The Heydari *et al.*[39] study was set in tobacco cessation clinics in Iran and de Dios *et al.*[38] focused on Latino smokers in the USA. All studies evaluated varenicline 1.0 mg b.i.d. The duration of varenicline treatment for Wong *et al.*[37] and de Dios *et al.*[38] was 12 weeks, whereas for Heydari *et al.*[39] treatment duration was 8 weeks. Wong *et al.*[37] compared varenicline with placebo, while the remaining two studies had three arms: Heydari *et al.*[39] compared varenicline with nicotine patch or counselling and de Dios *et al.*[38] compared varenicline with nicotine patch or placebo. Wong *et al.*[37] only included adults who smoked more than 10 cigarettes per day, Heydari *et al.*[39] included smokers of both more or fewer than 10 cigarettes per day, and de Dios *et al.*[38] focused only on 'light smokers', i.e. those who smoked fewer than 10 cigarettes per day. Wong *et al.*[37] evaluated smoking cessation in a sample of patients who were due to undergo surgery.

Wong *et al.*[37] and de Dios *et al.*[38] measured smoking cessation using 7-day PPA. Heydari *et al.*[39] report their outcome measurement as being smoke free. An attempt to contact the authors to establish whether this was 7-day PPA or CAR failed and, therefore, we have made the conservative assumption that PPA was used. CO validation of smoking cessation outcomes was recorded in all three studies. Wong *et al.*[37] and Heydari *et al.*[39] followed up their participants for 12 months, while the longest follow-up for de Dios *et al.*[38] was 6 months. The target quit date for Heydari *et al.*[39] was day 14 of treatment, for Wong *et al.*[37] was 1 week after treatment began and in de Dios *et al.*[38] was not reported.

Risk of bias in included studies

A summary of the risk of bias judgements for all included studies is presented in *Table 3*. Support for judgements for quality assessments from Cahill *et al.*[15] is fully described in their review. Support for judgements of risk of bias for newly included studies is presented in *Appendix 2*. Both cytisine trials were judged to be of good quality. For varenicline trials, most studies were judged to be low risk for most of the risk of bias categories, although several studies were judged to have an unclear risk in one or more categories. For the newly included studies, Wong *et al.*[37] was assessed as low risk in all recorded categories of the Cochrane risk of bias tool.[32] De Dios *et al.*[38] was assessed as being unclear risk for both random sequence generation and allocation concealment as a result of unclear reporting, but was assessed as low risk for incomplete outcome data and selective reporting. Methods of randomisation, allocation concealment or blinding were not described in Heydari *et al.*,[39] and the study was therefore assessed as unclear risk for these categories. An assessment of low risk was given for incomplete outcome data as the authors report no dropouts from the study. Data on efficacy, the stated primary outcome, were reported and, therefore, the study was also assessed as low risk for this category.

TABLE 3 Risk of bias summary using the Cochrane risk of bias tool for all included studies

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
[a]Vinnikov 2008[43]	Low risk	Low risk	Low risk	Unclear risk	Low risk
[a]West 2011[17]	Low risk	Low risk	Low risk	Low risk	Low risk
[b]Bolliger 2011[47]	Low risk	Low risk	Low risk	Low risk	Low risk
[b]Gonzales 2006[48]	Low risk	Low risk	Low risk	Low risk	Low risk
[b]Jorenby 2006[16]	Low risk	Low risk	Unclear risk	Low risk	Low risk
[b]Nakamura 2007[49]	Low risk	Low risk	Low risk	Unclear risk	High risk
[b]Niaura 2008[50]	Low risk	Low risk	Unclear risk	Low risk	Low risk
[b]Nides 2006[51]	Low risk	Low risk	Unclear risk	Unclear risk	Low risk
[b]Oncken 2006[52]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
[b]Pfizer 2011[40]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	NR
[b]Rennard 2012[53]	Low risk	Low risk	Low risk	Low risk	Low risk
[b]Rigotti 2010[54]	Low risk	Low risk	Low risk	Low risk	Low risk
[b]Steinberg 2011[56]	Low risk	Low risk	Low risk	Unclear risk	Low risk
[b]Tashkin 2011[57]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
[b]Tsai 2007[58]	Low risk	Low risk	Low risk	Unclear risk	Unclear risk
[b]Wang 2009[60]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
[b]Williams 2007[61]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
[b]Smith 2013[55]	Low risk	Low risk	Unclear risk	Unclear risk	NR
[b]Aubin 2008[46]	Low risk	Low risk	High risk	Low risk	Low risk
[b]Tsukahara 2010[59]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk
[c]Heydari 2012[39]	Unclear risk	Unclear risk	Low risk	Low risk	Low risk
[c]Wong 2012[37]	Low risk	Low risk	Low risk	Low risk	Low risk
[c]de Dios 2012[38]	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk

NR, not reported.
a Cytisine studies, quality assessment from Cahill *et al.*[15]
b Varenicline studies, quality assessment from Cahill *et al.*[15]
c Varenicline studies from updated search, quality assessment for current review.

Summary of data used in the network meta-analyses (cytisine and varenicline compared with placebo)

A full description of the data used for each meta-analysis for all interventions and comparators can be found in *Appendix 5*. *Tables 4* and *5* present a summary of the CAR and adverse events data used in the analyses of cytisine and varenicline compared with placebo.

TABLE 4 Cytisine (1.5 mg) compared with placebo (number of events/number of patients) for CAR and adverse events

	CAR		Abnormal dreams		Headache		Insomnia		Nausea		SAEs	
Study	Cytisine	Placebo	Cytisine	Placebo	Cytisine	Placebo	Cytisine	Placebo	Cytisine	Placebo	Cytisine	Placebo
Vinnikov 2008[43]	9/100	1/97	–	–	1/86	1/85	–	–	2/85	1/86	–	–
West 2011[17]	31/370	9/370	–	–	7/370	8/370	–	–	10/370	14/370	4/370	3/370

TABLE 5 Varenicline (1.0 mg b.i.d.) compared with placebo (number of events/number of patients) for CAR and adverse events

	CAR		Abnormal dreams		Headache		Insomnia		Nausea		SAEs	
Study	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo	Varenicline	Placebo
Bolliger 2011[47]	157/394	26/199	–	–	64/390	24/198	50/390	13/198	103/390	16/198	11/394	2/199
Niaura 2008[50]	35/160	12/160	–	–	25/157	20/155	34/157	17/155	21/157	8/155	3/160	0/160
Pfizer 2011[40]/ Williams 2012[41]	–	–	6/84	43/4	9/84	8/43	8/84	2/43	20/84	6/43	5/85	4/43
Rennard 2012[53]	171/493	21/166	61/486	5/165	55/486	20/165	43/486	6/165	142/486	15/165	6/493	1/166
Rigotti 2010[54]	68/355	26/359	28/353	6/350	45/353	39/350	42/353	23/350	104/353	30/350	23/353	21/354
Steinberg 2011[56]	–	–	–	–	–	–	–	–	10/38	2/37	6/40	5/39
Tashkin 2011[57]	47/250	14/254	27/248	7/251	20/248	20/251	24/248	15/251	67/248	20/251	12/248	15/253
Tsai 2007[58]	59/126	27/124	7/126	1/124	–	–	19/126	17/124	55/126	14/124	3/126	3/124
Smith 2013[55]	61/196	42/196	12/196	2/196	12/196	3/196	10/196	4/196	32/196	3/196	6/119	3/117
Aubin 2008[46]	98/378	75/379	44/376	31/370	72/376	36/376	80/376	71/370	140/376	36/370	2/376	8/370
Wang 2009[60]	63/165	42/168	–	–	9/165	7/168	10/165	5/168	48/165	20/168	0/165	2/168
Tsukahara 2010[59]	–	–	–	–	–	–	6/14	2/14	4/14	0/14	–	–
Wong 2012[37]	–	–	3/151	0/135	5/151	0/135	–	–	20/151	5/135	–	–
Heydari 2012[39]	–	–	3/89	0/91	–	–	–	–	8/89	0/91	–	–
Gonzales 2006[48]	77/352	29/344	36/349	19/344	54/349	42/344	49/349	44/344	98/349	29/344	4/349	9/344
Jorenby 2006[16]	79/344	35/341	45/343	12/340	44/343	43/340	49/343	42/340	101/343	33/340	8/344	6/341
Oncken 2006[52]	58/259	5/129	46/253	6/121	59/253	21/121	75/253	14/121	97/253	18/121	–	–
Nakamura 2007[49]	56/156	35/154	–	–	16/156	4/154	–	–	38/156	12/154	3/156	3/154
Nides 2006[51]	18/127	6/127	19/125	10/123	30/125	33/123	44/125	27/123	65/125	23/123	1/125	0/127

Assessment of clinical effectiveness

Results

Continuous abstinence

A network meta-analysis was used to compare the hazard of having continuous abstinence when treating with nicotine patch, cytisine 1.5 mg six times daily, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d. and bupropion hydrochloride 150 mg b.i.d. compared with placebo. A total of 16 studies comparing pairs, triplets or quintuplets of interventions provided information at various study durations.[16,17,43,46–55,57,58,60]

Figure 2 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for continuous abstinence is provided (see *Appendix 5, Table 38*).

The network meta-analysis model fitted the data well, with a total residual deviance close to the total number of data points included in the analysis. The total residual deviance was 40.99, which compared favourably with the 39 data points being analysed.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.20, 95% CrI 0.02 to 0.45). All interventions apart from varenicline 0.3 mg q.d. and varenicline 1.0 mg q.d. were associated with a statistically significant effect on having continuous abstinence at a conventional 5% significance level relative to placebo. Cytisine 1.5 mg produced the greatest effect (HR 4.27, 95% CrI 2.05 to 10.05) relative to placebo (*Table 6*; see also *Appendix 5, Figure 13*). Cytisine 1.5 mg was the intervention with the highest probability of being the most effective intervention ($p = 0.87$) (*Table 7*).

Since repeated 7-day PPA may be used as a proxy for continuous abstinence,[22] a sensitivity analysis was conducted including studies used measurement such as continuous abstinence or repeated 7-day PPA. Both the estimates and 95% CrIs of all treatment effects were similar to the results from the analysis including only studies that used continuous abstinence (see *Appendix 5*). However, the goodness of the model fit suggested that some studies, in particular those by Steinberg *et al.*,[56] Oncken *et al.*,[52] Heydari *et al.*[39] and de Dios *et al.*,[38] may come from a different model. The measurement used by Steinberg *et al.*,[56] Heydari *et al.*[39] and de Dios *et al.*[38] was the repeated 7-day PPA. Hence, the treatment

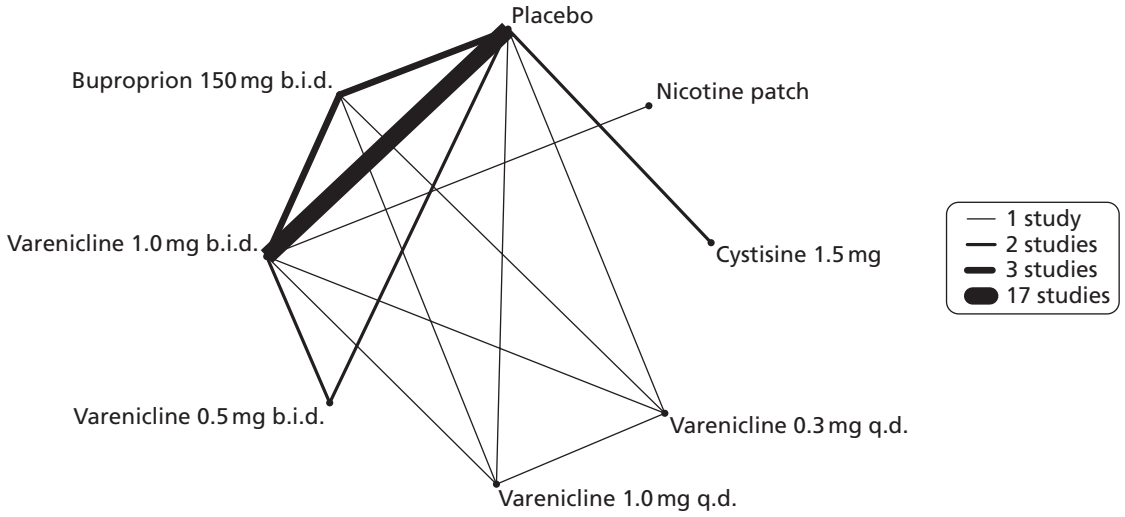

FIGURE 2 Network diagram of different interventions for continuous abstinence. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

TABLE 6 Continuous abstinence: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	1.89 (1.06 to 3.49)
Cytisine 1.5 mg[a]	4.27 (2.05 to 10.05)
Varenicline 0.3 mg q.d.	1.58 (0.65 to 3.53)
Varenicline 1.0 mg q.d.	1.08 (0.40 to 2.63)
Varenicline 0.5 mg b.i.d.	2.16 (1.54 to 3.38)
Varenicline 1.0 mg b.i.d.	2.58 (2.16 to 3.15)
Bupropion hydrochloride 150 mg b.i.d.	1.59 (1.10 to 2.32)
Between-study SD	0.20 (0.02 to 0.45)

a See *Table 1* for regime details.

TABLE 7 Probability of treatment rankings [$p(j = b)$]

	Treatment (j)							
Rank (b)	Placebo	Nicotine patch	Cytisine 1.5 mg[a]	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.
1	0.00	0.02	0.87	0.02	0.00	0.03	0.06	0.00
2	0.00	0.09	0.07	0.08	0.02	0.14	0.61	0.00
3	0.00	0.17	0.04	0.09	0.03	0.37	0.27	0.03
4	0.00	0.30	0.02	0.14	0.05	0.28	0.05	0.16
5	0.00	0.22	0.01	0.18	0.08	0.12	0.01	0.38
6	0.09	0.14	0.00	0.24	0.15	0.05	0.00	0.33
7	0.42	0.06	0.00	0.15	0.26	0.01	0.00	0.10
8	0.48	0.01	0.00	0.09	0.41	0.00	0.00	0.00

a See *Table 1* for regime details.

effects were estimated using studies having continuous abstinence as the measurement and these were used in the economic model.

Abnormal dreams

A network meta-analysis was used to compare the hazard of having abnormal dreams when treating with nicotine patch, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks or placebo. A total of 14 studies comparing pairs or triplets of interventions provided information at various study durations.[16,37,39,41,46,48,51–55,57,58,61] No data were available for cytisine for abnormal dreams.

Figure 3 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for abnormal dreams is provided (see *Appendix 5, Table 39*).

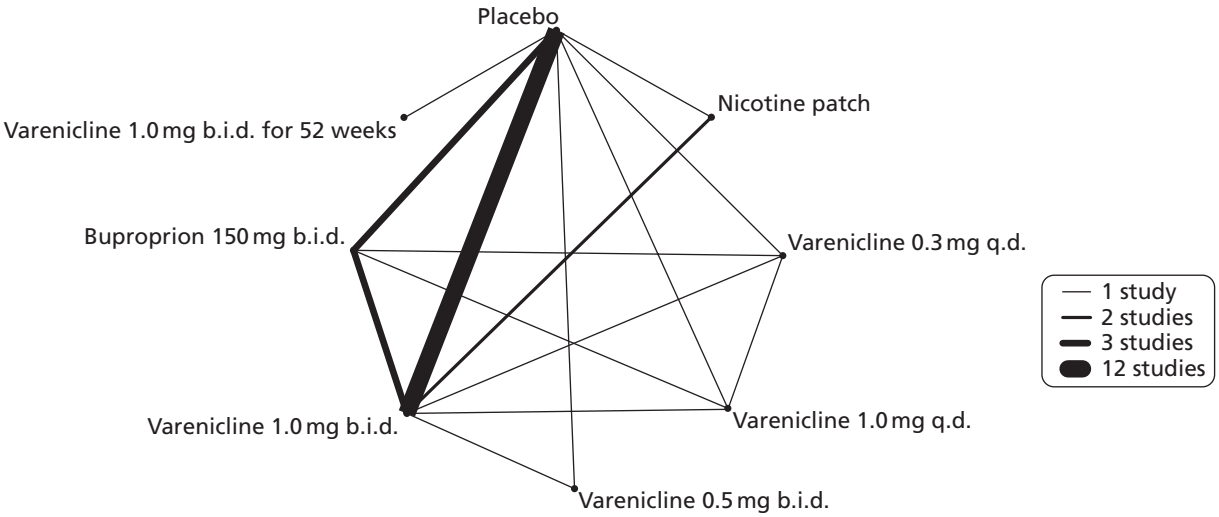

FIGURE 3 Network diagram of different interventions for abnormal dreams. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

The network meta-analysis model fitted the data reasonably well, with a total residual deviance close to the total number of data points included in the analysis. The total residual deviance was 37.98, which was slightly less than the 39 data points being analysed.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.24, 95% CrI 0.02 to 0.74). Varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks were associated with statistically significant effects of having abnormal dreams at a conventional 5% level relative to placebo. Varenicline 1.0 mg b.i.d. for 52 weeks produced the greatest effect (HR 3.64, 95% CrI 1.44 to 10.01) relative to placebo (*Table 8*; see also *Appendix 5, Figure 14*). Varenicline 1.0 mg b.i.d. for 52 weeks was the intervention with the highest probability of being the most likely intervention to be associated with abnormal dreams ($p = 0.54$) (*Table 9*).

TABLE 8 Abnormal dreams: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	2.01 (0.82 to 4.43)
Varenicline 0.3 mg q.d.	1.21 (0.46 to 2.99)
Varenicline 1.0 mg q.d.	1.75 (0.71 to 4.10)
Varenicline 0.5 mg b.i.d.	2.56 (1.23 to 5.91)
Varenicline 1.0 mg b.i.d.	3.29 (2.40 to 4.77)
Bupropion hydrochloride 150 mg b.i.d.	1.58 (0.96 to 2.70)
Varenicline 1.0 mg b.i.d. for 52 weeks	3.64 (1.44 to 10.01)
Between-study SD	0.24 (0.02 to 0.74)

TABLE 9 Abnormal dreams: probability of treatment rankings [$p(j = b)$]

	Treatment (j)							
Rank (b)	Placebo	Nicotine patch	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.	Varenicline 1.0 mg b.i.d. for 52 weeks
1	0.00	0.03	0.00	0.03	0.12	0.28	0.00	0.54
2	0.00	0.08	0.01	0.05	0.19	0.51	0.01	0.16
3	0.00	0.18	0.03	0.11	0.32	0.18	0.04	0.13
4	0.00	0.28	0.06	0.19	0.22	0.03	0.13	0.08
5	0.01	0.20	0.11	0.23	0.09	0.00	0.31	0.05
6	0.08	0.12	0.18	0.20	0.04	0.00	0.35	0.02
7	0.32	0.08	0.29	0.13	0.02	0.00	0.15	0.01
8	0.58	0.03	0.31	0.06	0.00	0.00	0.01	0.00

Headache

A network meta-analysis was used to compare the hazard of experiencing headaches when treating with nicotine patch, cytisine 1.5 mg, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.25 mg b.i.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d. and bupropion hydrochloride 150 mg b.i.d. compared with placebo. A total of 17 studies comparing pairs, triplets, quadruplets or quintuplets of interventions provided information at various study durations.[16,17,37,41,43,46–55,58,61]

Figure 4 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for headache is presented in *Appendix 5, Table 40*.

The network meta-analysis model did not fit the data very well. The total residual deviance was 49.95, which was higher than would be expected given the 42 data points being analysed. In particular, the model did not fit the Smith *et al.*[55] and Nakamura *et al.*[49] studies particularly well. For Smith *et al.*[55] the model predicted six events in the placebo arm, which is twice as much as the number of events reported. For Nakamura *et al.*,[49] the model predicted nine events in the placebo arm, which is more than double the number of events reported in the study, which was only four. There was no obvious explanation in terms

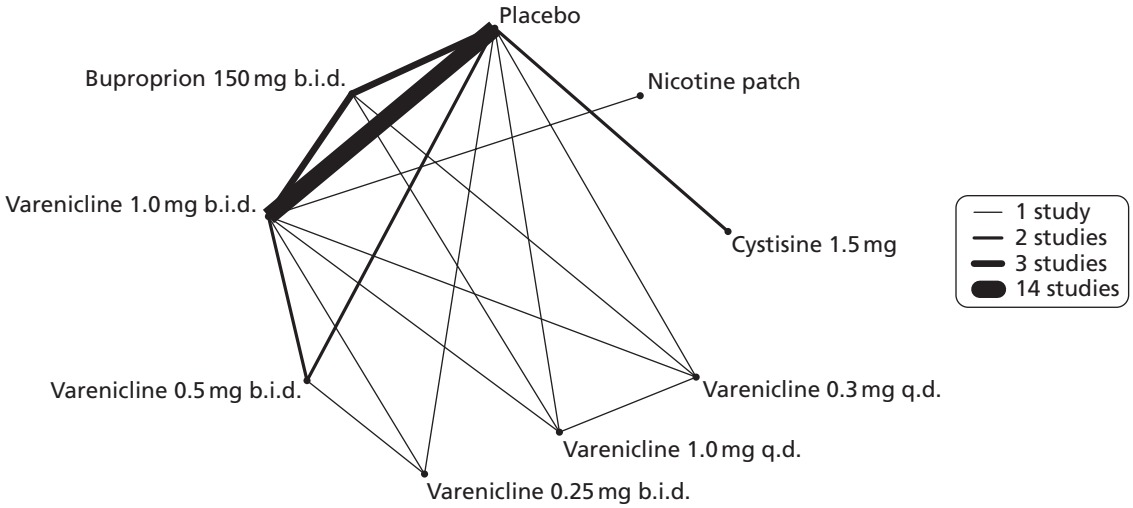

FIGURE 4 Network diagram of different interventions for hazard of experiencing headaches. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

of the characteristics of the two studies, although we did not attempt a meta-regression because of limited available data.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.19, 95% CrI 0.01 to 0.50). Varenicline 1.0 mg b.i.d. was the only intervention associated with a statistically significant increase in the hazard of experiencing headaches at a conventional 5% significance level relative to placebo (HR 1.23, 95% CrI 1.01 to 1.55). Varenicline 0.25 mg b.i.d. produced the greatest effect (HR 1.58, 95% CrI 0.78 to 3.47) relative to placebo (*Table 10*; see also *Appendix 5*, *Figure 15*), although the treatment effect was not statistically significant at a conventional 5% significance level. Varenicline 0.25 mg b.i.d. was the intervention with the highest probability of being associated with headaches ($p = 0.46$) (*Table 11*).

TABLE 10 Headache: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	0.59 (0.30 to 1.16)
Cytisine 1.5 mg[a]	0.85 (0.31 to 2.54)
Varenicline 0.3 mg q.d.	1.06 (0.61 to 1.92)
Varenicline 1.0 mg q.d.	1.08 (0.61 to 1.90)
Varenicline 0.25 mg b.i.d.	1.58 (0.78 to 3.47)
Varenicline 0.5 mg b.i.d.	1.48 (0.97 to 2.50)
Varenicline 1.0 mg b.i.d.	1.23 (1.01 to 1.55)
Bupropion hydrochloride 150 mg b.i.d.	1.03 (0.76 to 1.48)
Between-study SD	0.19 (0.01 to 0.50)

a See *Table 1* for regime details.

TABLE 11 Headache: probability of treatment rankings [$p(j = b)$]

	Treatment (j)								
Rank (b)	Placebo	Nicotine patch	Cytisine 1.5 mg	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.25 mg b.i.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.
1	0.00	0.00	0.10	0.06	0.05	0.46	0.30	0.02	0.01
2	0.00	0.00	0.06	0.09	0.10	0.21	0.37	0.12	0.03
3	0.01	0.00	0.06	0.11	0.12	0.10	0.16	0.36	0.07
4	0.09	0.01	0.06	0.14	0.14	0.06	0.08	0.29	0.14
5	0.21	0.02	0.06	0.13	0.14	0.05	0.04	0.14	0.21
6	0.30	0.02	0.06	0.14	0.13	0.04	0.02	0.05	0.23
7	0.27	0.05	0.08	0.16	0.17	0.04	0.01	0.01	0.20
8	0.10	0.24	0.26	0.14	0.12	0.03	0.01	0.00	0.10
9	0.01	0.66	0.25	0.03	0.03	0.01	0.00	0.00	0.01

Nicotine patch and cytisine 1.5 mg were less likely than placebo to be associated with headache, although the effects were not statistically significant at a conventional 5% significance level. The HR for nicotine patch compared with placebo was 0.59 (95% CrI 0.30 to 1.16) and for cytisine 1.5 mg compared with placebo was 0.85 (95% CrI 0.31 to 2.54).

Insomnia

A network meta-analysis was used to compare the hazard of experiencing insomnia when treating with nicotine patch, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks. A total of 16 studies comparing pairs, triplets or quintuplets of interventions provided information at various study durations.[16,41,46–48,50–55,57–61]

Figure 5 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for insomnia is presented in *Appendix 5, Table 41*.

The network meta-analysis model fitted the data reasonably well, with a total residual deviance close to the total number of data points included in the analysis. The total residual deviance was 36.91, which was slightly less than the 38 data points being analysed.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.15, 95% CrI 0.00 to 0.40). Varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks were associated with a statistically significant increase in the hazard of experiencing insomnia at a conventional 5% significance level relative to placebo. Bupropion hydrochloride 150 mg b.i.d. produced the greatest effect (HR 2.27 95% CrI 1.70 to 3.05) relative to placebo (*Table 12*; see also *Appendix 5*, *Figure 16*). Bupropion hydrochloride 150 mg b.i.d. was the intervention with the highest probability of being associated with insomnia ($p = 0.45$) (*Table 13*).

Varenicline 0.3 mg q.d. was less likely than placebo to be associated with insomnia, although the effect was not statistically significant at a conventional 5% significance level (HR 0.84, 95% CrI 0.48 to 1.47).

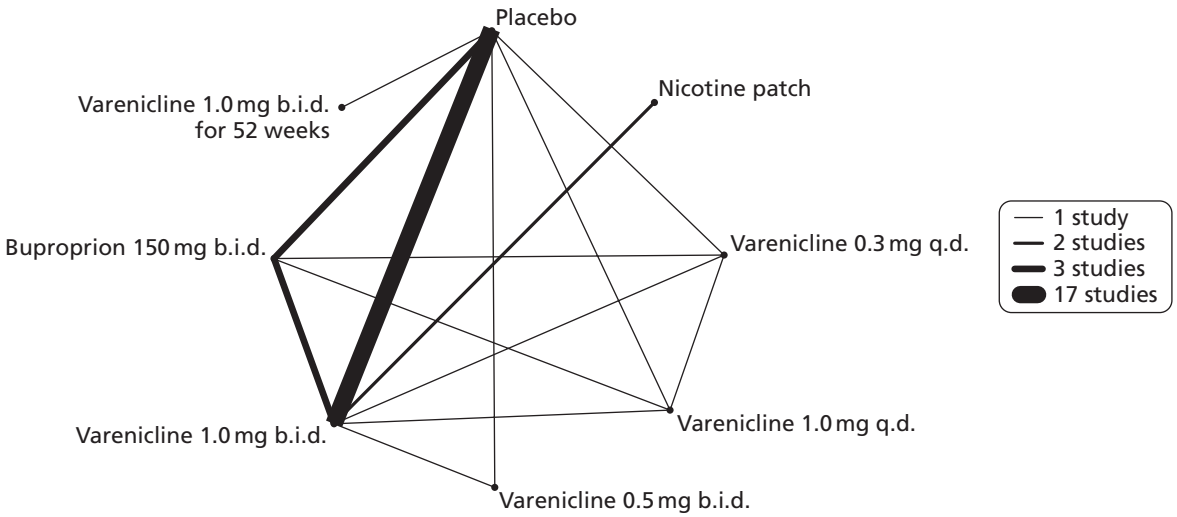

FIGURE 5 Network diagram of different interventions for insomnia. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

TABLE 12 Insomnia: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	1.36 (0.79 to 2.20)
Varenicline 0.3 mg q.d.	0.84 (0.48 to 1.47)
Varenicline 1.0 mg q.d.	1.22 (0.72 to 2.02)
Varenicline 0.5 mg b.i.d.	1.76 (1.09 to 3.03)
Varenicline 1.0 mg b.i.d.	1.68 (1.40 to 2.07)
Bupropion hydrochloride 150 mg b.i.d.	2.27 (1.70 to 3.05)
Varenicline 1.0 mg b.i.d. for 52 weeks	2.16 (1.03 to 4.79)
Between-study SD	0.15 (0.00 to 0.40)

TABLE 13 Insomnia: probability of treatment rankings [$p(j = b)$]

	Treatment (j)							
Rank (b)	Placebo	Nicotine patch	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.	Varenicline 1.0 mg b.i.d. for 52 weeks
1	0.00	0.01	0.00	0.00	0.10	0.00	0.45	0.43
2	0.00	0.04	0.00	0.02	0.20	0.09	0.44	0.21
3	0.00	0.08	0.00	0.04	0.29	0.37	0.08	0.12
4	0.00	0.14	0.01	0.09	0.21	0.43	0.02	0.10
5	0.03	0.37	0.04	0.24	0.14	0.10	0.00	0.08
6	0.24	0.21	0.09	0.36	0.05	0.01	0.00	0.03
7	0.53	0.09	0.17	0.18	0.01	0.00	0.00	0.01
8	0.19	0.05	0.68	0.07	0.00	0.00	0.00	0.01

Nausea

A network meta-analysis was used to compare the hazard of experiencing nausea when treating with nicotine patch, cytisine 1.5 mg, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.25 mg b.i.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks. A total of 22 studies comparing pairs, triplets, quadruplets or quintuplets of interventions provided information at various study durations.[16,17,37,39,41,43,46–61]

Figure 6 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for nausea is presented in *Appendix 5, Table 42.*

The network meta-analysis model fitted the data reasonably well, with a total residual deviance close to the total number of data points included in the analysis. The total residual deviance was 55.20, which compared favourably with the 53 non-zero data points being analysed.

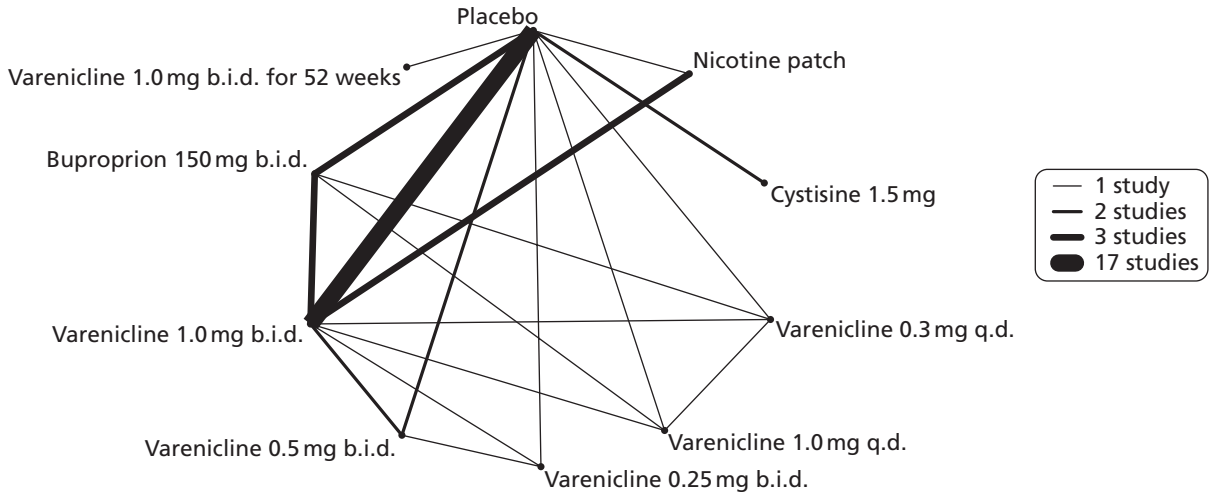

FIGURE 6 Network diagram of different interventions for hazard of experiencing nausea. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.08, 95% CrI 0.00 to 0.29). Varenicline 1.0 mg q.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks were more likely than placebo to be associated with nausea. Varenicline 1.0 mg q.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks were associated with a statistically significant increase in the hazard of experiencing nausea at a conventional 5% significance level relative to placebo. Varenicline 1.0 mg b.i.d. for 52 weeks produced the greatest effect (HR 6.20, 95% CrI 3.30 to 13.61) relative to placebo (*Table 14*; see also *Appendix 5*, *Figure 17*). Varenicline 1.0 mg b.i.d. for 52 weeks was the intervention with the highest probability of being associated with nausea ($p = 0.95$) (*Table 15*).

Nicotine patch, cytisine 1.5 mg, varenicline 0.3 mg q.d. and varenicline 0.25 mg b.i.d. were less likely than placebo to be associated with nausea, although the effects were not statistically significant at a conventional 5% significance level.

TABLE 14 Nausea: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	0.73 (0.44 to 1.10)
Cytisine 1.5 mg[a]	0.78 (0.36 to 1.74)
Varenicline 0.3 mg q.d.	0.92 (0.55 to 1.52)
Varenicline 1.0 mg q.d.	2.26 (1.50 to 3.44)
Varenicline 0.25 mg b.i.d.	0.98 (0.48 to 1.82)
Varenicline 0.5 mg b.i.d.	1.48 (1.03 to 2.10)
Varenicline 1.0 mg b.i.d.	3.63 (3.10 to 4.27)
Bupropion hydrochloride 150 mg b.i.d.	1.12 (0.83 to 1.48)
Varenicline 1.0 mg b.i.d. for 52 weeks	6.20 (3.30 to 13.61)
Between-study SD	0.08 (0.00 to 0.29)

a See *Table 1* for regime details.

TABLE 15 Nausea: probability of treatment rankings [$p(j = b)$]

	Treatment (j)									
Rank (b)	Placebo	Nicotine patch	Cytisine 1.5 mg	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.25 mg b.i.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.	Varenicline 1.0 mg b.i.d. for 52 weeks
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.00	0.95
2	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.94	0.00	0.05
3	0.00	0.00	0.01	0.00	0.92	0.01	0.04	0.01	0.00	0.00
4	0.00	0.00	0.05	0.04	0.06	0.09	0.70	0.00	0.06	0.00
5	0.08	0.01	0.07	0.11	0.01	0.20	0.18	0.00	0.34	0.00
6	0.25	0.02	0.07	0.15	0.00	0.12	0.05	0.00	0.32	0.00
7	0.38	0.06	0.08	0.16	0.00	0.13	0.02	0.00	0.17	0.00
8	0.22	0.16	0.15	0.21	0.00	0.16	0.01	0.00	0.08	0.00
9	0.06	0.34	0.22	0.20	0.00	0.16	0.00	0.00	0.03	0.00
10	0.00	0.40	0.35	0.12	0.00	0.12	0.00	0.00	0.01	0.00

Serious adverse events

A network meta-analysis was used to compare the hazard of experiencing SAEs when treating with nicotine patch, cytisine 1.5 mg, varenicline 0.3 mg q.d., varenicline 1.0 mg q.d., varenicline 0.25 mg b.i.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks or placebo. A total of 18 studies comparing pairs, triplets, quadruplets or quintuplets of interventions provided information at various study durations.[16,17,41,46–58,60,61]

Figure 7 presents the network of evidence. A summary of all the trials (data) included in the network meta-analysis for SAEs is presented in *Appendix 5, Table 43*.

The network meta-analysis model fitted the data reasonably well, with a total residual deviance close to the total number of data points included in the analysis. The total residual deviance was 46.67, which compared favourably with the 43 data points being analysed.

There was evidence of mild heterogeneity in treatment effects between studies (between-study heterogeneity SD 0.25, 95% CrI 0.01 to 0.86). Nicotine patch, cytisine 1.5 mg, varenicline 0.25 mg b.i.d., varenicline 0.5 mg b.i.d., varenicline 1.0 mg b.i.d., bupropion hydrochloride 150 mg b.i.d. and varenicline 1.0 mg b.i.d. for 52 weeks were associated with a higher risk of experiencing SAEs relative to placebo.

Varenicline 0.3 mg q.d. and varenicline 1.0 mg q.d. weeks were associated with a lower risk of experiencing SAEs relative to placebo, although none of the treatment effects was statistically significant at a conventional 5% significance level.

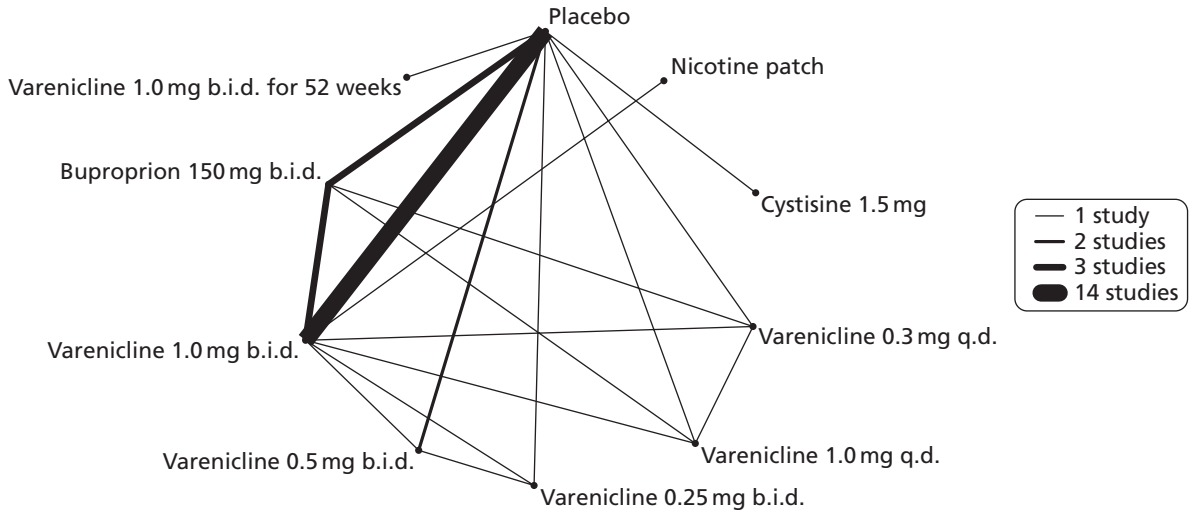

FIGURE 7 Network diagram of different interventions for risk of experiencing SAEs. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

Nicotine patch produced the greatest effect (HR 5.33, 95% CrI 0.98 to 45.21) relative to placebo (*Table 16*; see also *Appendix 5*, *Figure 18*). Nicotine patch was the intervention with the highest probability of being associated with SAEs ($p = 0.62$) (*Table 17*).

Strengths and limitations

A strength of the network meta-analysis is that it enabled a comprehensive comparison of all interventions of interest taking into account all available information. Parameters were estimated using a Bayesian framework which allowed for uncertainty in the estimate of the between-study SD and the ability to make probabilistic statements about the rankings of the interventions.

The continuous abstinence and adverse events data were modelled using a complementary log-log link function to allow for variation in the duration of follow-up between studies. This model assumes that the times to event follow an exponential distribution and, hence, that the treatment effect is constant over time. While these are strong assumptions, they are expected to be better than assuming there is no effect of duration of follow-up on the observed event rates.

In practice, the exponential models fitted the data for each outcome measure reasonably well except for the headache data. There was no obvious reason for this in terms of study characteristics, although there were insufficient data to perform a meta-regression.

A sensitivity analysis of the continuous abstinence data, assuming that the repeated 7-day PPA measurement is equivalent to the continuous abstinence measurement, made negligible difference to the results and inferences. The results based on the analysis of the continuous abstinence data only were incorporated into the economic model because the goodness-of-fit of the model suggested that data from some of the studies using repeated 7-day PPA measurement may not belong to the same model.

The estimation of intervention-specific continuous abstinence rates as required for the economic model was calculated by projecting the estimates of treatment effect (i.e. the log-hazard ratio) from the network meta-analysis onto the absolute risk of continuous abstinence for the placebo group. The absolute risk of continuous abstinence for the placebo group was estimated from a separate random-effects meta-analysis of studies in which the control arm was the placebo intervention. The predictive distribution of the absolute risk in a new study was used to represent uncertainty to reflect heterogeneity between studies.

TABLE 16 SAEs: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	5.3 (0.98 to 45.21)
Cytisine 1.5 mg[a]	1.27 (0.24 to 8.58)
Varenicline 0.3 mg q.d.	0.049 (0.00 to 1.34)
Varenicline 1.0 mg q.d.	0.078 (0.00 to 1.32)
Varenicline 0.25 mg b.i.d.	2.06 (0.46 to 7.83)
Varenicline 0.5 mg b.i.d.	1.02 (0.31 to 3.46)
Varenicline 1.0 mg b.i.d.	1.10 (0.74 to 1.65)
Bupropion hydrochloride 150 mg b.i.d.	1.29 (0.61 to 2.78)
Varenicline 1.0 mg b.i.d. for 52 weeks	2.61 (0.69 to 15.16)
Between-study SD	0.25 (0.01 to 0.86)

a See *Table 1* for regime details.

TABLE 17 SAEs: probability of treatment rankings [$p(j = b)$]

	Treatment (j)									
Rank (b)	Placebo	Nicotine patch	Cytisine 1.5 mg[a]	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.25 mg b.i.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.	Varenicline 1.0 mg b.i.d. for 52 weeks
1	0.00	0.62	0.06	0.00	0.00	0.10	0.01	0.00	0.01	0.20
2	0.00	0.19	0.14	0.00	0.00	0.23	0.04	0.00	0.05	0.33
3	0.01	0.10	0.14	0.01	0.01	0.26	0.08	0.04	0.14	0.20
4	0.05	0.04	0.12	0.01	0.01	0.15	0.14	0.14	0.22	0.11
5	0.15	0.02	0.09	0.01	0.01	0.07	0.13	0.25	0.22	0.06
6	0.29	0.01	0.06	0.01	0.01	0.06	0.11	0.28	0.13	0.03
7	0.33	0.01	0.09	0.01	0.01	0.06	0.16	0.19	0.11	0.03
8	0.15	0.01	0.23	0.04	0.03	0.06	0.26	0.09	0.10	0.03
9	0.01	0.00	0.05	0.36	0.48	0.01	0.06	0.01	0.01	0.00
10	0.00	0.00	0.01	0.55	0.44	0.00	0.01	0.00	0.00	0.00

a See *Table 1* for regime details.

Chapter 4 Assessment of cost-effectiveness

Systematic review of existing cost-effectiveness evidence

The search strategy reported in *Chapter 3, Methods for reviewing clinical effectiveness*, did not identify any recent relevant economic evaluations that were not known to the authors at the time of the submission of the protocol. As such, as detailed in the protocol, the model structure was based on an existing and widely used model, the Benefits of Smoking Cessation on Outcomes (BENESCO) model.[62–72]

Independent economic assessment

The economic analysis was focused on a population of smokers in England and Wales aged 18 years or over who are motivated to quit smoking, and explicitly evaluated the cost-effectiveness of a standard 25-day course of cytisine [six 1.5-mg tablets per day for 3 days (days 1–3), five tablets per day for 9 days (days 4–12), four tablets per day for 4 days (days 13–16), three tablets per day for 4 days (days 17–20), and two tablets per day for the final 5 days (days 21–25)][23] with a standard 12-week course of varenicline [500 μg q.d. for 3 days, increased to 500 μg b.i.d. for 4 days, then 1 mg b.i.d. for 11 weeks).[19,73]

Methods

The conceptual model

The BENESCO model is a state transition model designed to capture important long-term outcomes of smoking cessation treatments. The BENESCO model has been used in numerous previous evaluations.[63–73]

The model uses an annual cycle length and assumes that all smokers die at age 100 years, if death has not been simulated at an earlier age. A hypothetical cohort of 10,000 smokers enters the model, with each smoker assumed to make a single quit attempt, assisted by either varenicline or cytisine. The distribution of the cohort in terms of sex, age (three age categories are used – 18–34 years, 35–64 years and 65–100 years) and chronic smoking-related diseases [lung cancer, chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD) and stroke] is assumed to be representative of smokers in England and Wales.

At the start of the model, every cohort member begins in the smoker state. At the end of the first year, a proportion of smokers successfully cease smoking and become quitters; this proportion is determined by the efficacy of the cessation aid treatment received. The model assumes that no further attempts to quit are made and that those who fail to quit remain smokers until death. However, there is a possibility that quitters may relapse and start smoking again in future years. Potential to relapse to smoking is incorporated into the model as a decreasing function of time since cessation and is independent of cessation treatment (varenicline or cytisine). For the four model cycles following cessation, cohort members are assigned recent quitter status and risk of relapse is highest. After four cycles without relapse, recent quitters attain long-run quitter status. The annual relapse rate is lower for long-run quitters than for recent quitters in the next five cycles and lower still in subsequent cycles, with this underlying relapse rate continuing for the duration of the model.

At the end of each year, the cohort is distributed into different smoking states (smoker, quitter, relapsed smoker) according to their current smoking state and relapse rates. *Figure 8* details the possible transitions between smoking states.

Within these broad smoking states, cohort members are distributed between the following disease states: no current morbidity, lung cancer, COPD, CHD, stroke and asthma exacerbation. These health states were

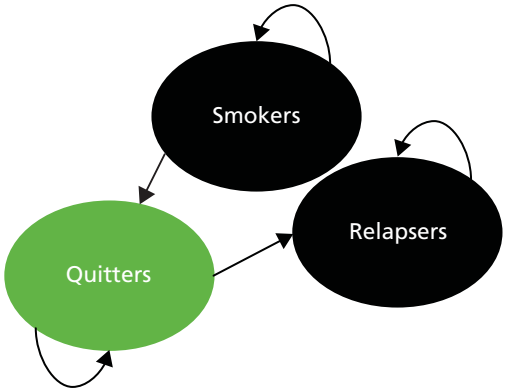

FIGURE 8 Transitions between smoking states.

selected by the authors of the BENESCO model to correspond to the diseases accounting for the greatest morbidity, mortality and cost attributable to smoking.[65] The health states are mutually exclusive and death is an absorbing state. The probability of transition between disease states at the end of each cycle is dependent on current disease state, smoking status, age and sex, as these factors have been shown to be independent determinants of risk.

The model has categorised four of the health states as either acute (CHD and stroke) or chronic (COPD and lung cancer) conditions. Transitions within acute and chronic conditions are not allowed and, therefore, it is not possible for a cohort member to experience a CHD event following a stroke. Transitions from acute disease states to chronic disease states are possible, but not from chronic conditions to acute conditions. Asthma exacerbations were transient in nature and assumed to resolve within 1 year, and could only occur from the no current morbidity health state. *Figure 9* illustrates possible transitions between health states in the model.

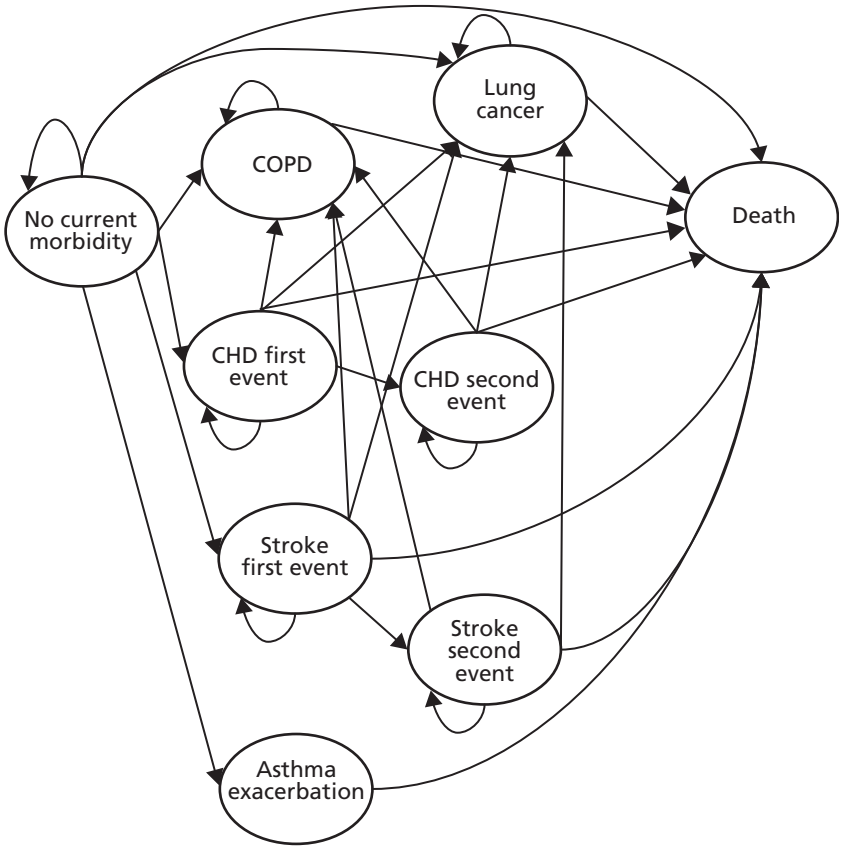

FIGURE 9 Transitions between health states.

Each health state is associated with utility and cost values as detailed later. Therefore, cohort members accumulate costs and health outcomes each cycle until death. Adverse events are not considered within the BENESCO model framework.

Future costs and benefits were discounted at a rate of 3.5% per annum, and the perspective is that of the UK NHS for costs and health effects on the individual for outcomes, in line with National Institute for Health and Care Excellence (NICE) guidance.[74] Attention now turns to parameter values and distributions used in the probabilistic sensitivity analysis (PSA). As detailed in the protocol, many model inputs are derived from a previous manufacturer's single technology appraisal (STA) report.[65] As this is a slight limitation, it is unlikely to affect the key conclusions from this report regarding the relative cost-effectiveness of varenicline and cytisine.

The assumed characteristics of the initial cohort

The distribution of the cohort across sex and age categories at the start of the model was designed to reflect the distribution of smokers in the UK. Data on the demographics of the cohort and prevalence and incidence of diseases among smokers and non-smokers are assumed to be equal to those reported by Pfizer.[65] For convenience, these are reproduced in this report together with all-cause mortality risk along with the original source (*Table 18*). The proportion of male and female adults in each of the three age categories was determined from general population data.[75] Smoking prevalence data[76] were applied to these data to calculate the distribution across age and sex groups for a representative sample of 10,000 UK smokers. Pfizer[65] used interim life tables calculated by the UK Government Actuary's Department for 2002–4, weighted by population size and averaged to fit the age categories in the model.

The prevalence of smoking-related diseases in the cohort was estimated by Pfizer[65] from data on the prevalence of each disease in the general UK population. Relative risks for the incidence of each disease in the model for smokers were taken from the literature and used to calculate the expected number of cases in the cohort of smokers.[78,79] These data are reproduced in *Table 19*.

TABLE 18 Data informing demographic distribution of cohort

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
General population (*n*)	Office for National Statistics 2006[75] – population trends	6,727,400	11,843,600	4,040,000	6,660,700	12,140,100	5,189,300
Smoking prevalence (% of population)	Office for National Statistics 2004[76]	36.20%	27.70%	12.70%	28.00%	28.50%	26.70%
Risk of all-cause mortality (annual probability of all-cause mortality)	Government Actuary's Department 2006[77]	0.09%	0.47%	4.88%	0.04%	0.30%	3.87%

TABLE 19 Prevalence of disease in simulated cohort of UK smokers. Pfizer[65] was not consistent in reporting to a set number of decimal places or significant figures. In this report, for consistency, prevalence, incidence and mortality data, though taken from the manufacturer's submission, are reported to at least two decimal places

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Soriano 2000[80]	0.00%	1.00%	3.00%	0.00%	1.00%	2.00%
Lung cancer	Forman 2003[81]	0.00%	0.10%	0.70%	0.00%	0.06%	0.24%
History of CHD	Office for National Statistics 2005[82] (GHS)	0.00%	1.60%	8.00%	0.00%	1.00%	5.90%
History of stroke	Office for National Statistics 2005[82]	0.00%	0.50%	3.00%	0.00%	0.30%	2.00%
Asthma	Asthma UK 2004[83]; Hoskins 2000[84]	6.00%	5.00%	6.50%	6.40%	5.30%	5.30%

GHS, General Household Survey.

Transition probabilities

Annual incidence of disease was estimated by Pfizer,[65] divided by age and sex categories, for smokers, recent quitters and long-run quitters. These values relied on estimates from the literature in the majority of cases,[82,83,85–87] but for COPD there was a lack of available data and incidence was based on mortality data.[65] Office for National Statistics data were used to estimate stroke incidence and these data provided a split between first event and all events.[82] *Tables 20–22* show estimates for smokers, recent and long-run quitters, respectively, along with original data sources. Relative risks for smokers, short-run and recent quitters were generated from the literature[78,79] and used to generate absolute probabilities of incidence. As can be seen, the incidence of smoking-related diseases is at least as high in smokers compared with recent quitters and in recent quitters compared with long-run quitters.

TABLE 20 Incidence of diseases in smokers by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Pfizer 2007[65]	0.00%	0.02%	0.55%	0.00%	0.02%	0.44%
Lung cancer	Office for National Statistics 2005[82]	0.00%	0.10%	1.00%	0.00%	0.08%	0.5%
CHD (first non-fatal)	British Heart Foundation 2006[85]	0.00%	0.10%	1.00%	0.00%	0.05%	0.86%
CHD (subsequent non-fatal)	Volmink 1998[86]	0.00%	0.19%	1.74%	0.00%	0.05%	1.18%
Stroke (first non-fatal)	Office for National Statistics 2001[87]	0.00%	0.26%	0.92%	0.00%	0.20%	0.74%
Stroke (subsequent non-fatal)	Office for National Statistics 2001[87]	0.00%	0.35%	1.55%	0.00%	0.28%	1.33%
Asthma exacerbation	Asthma UK 2004[83]	0.08%	0.05%	0.07%	0.08%	0.05%	0.06%

TABLE 21 Incidence of diseases in recent quitters by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Pfizer 2007[65]	0.00%	0.02%	0.40%	0.00%	0.01%	0.43%
Lung cancer	Office for National Statistics 2005[82]	0.00%	0.04%	0.43%	0.00%	0.03%	0.20%
CHD (first non-fatal)	British Heart Foundation 2006[85]	0.00%	0.08%	0.81%	0.00%	0.02%	0.71%
CHD (subsequent non-fatal)	Volmink 1998[86]	0.00%	0.12%	1.39%	0.00%	0.02%	0.97%
Stroke (first non-fatal)	Office for National Statistics 2001[87]	0.00%	0.11%	0.61%	0.00%	0.08%	0.55%
Stroke (subsequent non-fatal)	Office for National Statistics 2001[87]	0.00%	0.14%	1.03%	0.00%	0.11%	1.00%
Asthma exacerbation	Asthma UK 2004[83]	0.05%	0.05%	0.06%	0.06%	0.05%	0.06%

TABLE 22 Incidence of diseases in long-run quitters, by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Pfizer 2007[65]	0.00%	0.02%	0.05%	0.00%	0.00%	0.04%
Lung cancer	Office for National Statistics 2005[82]	0.00%	0.04%	0.43%	0.00%	0.03%	0.20%
CHD (first non-fatal)	British Heart Foundation 2006[85]	0.00%	0.05%	0.68%	0.00%	0.01%	0.50%
CHD (subsequent non-fatal)	Volmink 1998[86]	0.00%	0.07%	1.16%	0.00%	0.02%	0.69%
Stroke (first non-fatal)	Office for National Statistics 2001[87]	0.00%	0.11%	0.61%	0.00%	0.05%	0.46%
Stroke (subsequent non-fatal)	Office for National Statistics 2001[87]	0.00%	0.0014%	0.010%	0.00%	0.0007%	0.0083%
Asthma exacerbation	Asthma UK 2004[83]	0.05%	0.05%	0.06%	0.06%	0.05%	0.05%

Annual mortality probability by condition was estimated by Pfizer[65] for smokers, recent quitters and long-run quitters, by age- and sex-specific category. Mortality associated with asthma exacerbation was assumed to equal all-cause mortality (see *Table 18*). Mortality for chronic diseases, COPD and lung cancer is the probability of death from these diseases given the disease state is present. Mortality from acute events, CHD and stroke is the probability of a fatal event that differs by smoking status, age and sex. *Tables 23–25* show disease-specific mortality estimates for smokers, recent quitters and long-run quitters, respectively, as reported by the manufacturer's submission for the NICE varenicline STA,[65] along with the original data sources. Relative risks of mortality for smokers, recent quitters and long-run quitters were generated from the literature.[78,79] The probability of smoking-related mortality is equivalent or lower for recent quitters compared with smokers, and for long-run quitters relative to recent quitters.

TABLE 23 Mortality for smokers, by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Office for National Statistics 2006[75]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung cancer	Office for National Statistics 2006[75]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation 2006[85]	0.00%	0.10%	0.81%	0.00%	0.04%	0.69%
CHD (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.15%	1.39%	0.00%	0.04%	0.94%
Stroke (first event fatal)	Office for National Statistics 2006[75]	0.00%	0.02%	0.30%	0.00%	0.02%	0.38%
Stroke (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.03%	0.50%	0.00%	0.03%	0.56%

TABLE 24 Mortality for recent quitters, by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Office for National Statistics 2006[75]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung cancer	Office for National Statistics 2006[75]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation 2006[85]	0.00%	0.06%	0.65%	0.00%	0.02%	0.56%
CHD (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.09%	1.12%	0.00%	0.02%	0.78%
Stroke (first event fatal)	Office for National Statistics 2006[75]	0.00%	0.01%	0.20%	0.00%	0.01%	0.28%
Stroke (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.01%	0.33%	0.00%	0.01%	0.42%

TABLE 25 Mortality for long-run quitters, by age and sex category

Data	Original source	Males, 18–34 years	Males, 35–64 years	Males, 65 + years	Females, 18–34 years	Females, 35–64 years	Females, 65 + years
COPD	Office for National Statistics 2006[75]	0.00%	0.98%	10.12%	0.00%	0.70%	9.16%
Lung cancer	Office for National Statistics 2006[75]	0.00%	26.89%	47.69%	0.00%	40.48%	75.35%
CHD (first event fatal)	British Heart Foundation 2006[85]	0.00%	0.04%	0.54%	0.00%	0.01%	0.40%
CHD (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.06%	0.93%	0.00%	0.01%	0.55%
Stroke (first event fatal)	Office for National Statistics 2006[75]	0.00%	0.01%	0.20%	0.00%	0.01%	0.24%
Stroke (subsequent event fatal)	Office for National Statistics 2006[75]	0.00%	0.01%	0.33%	0.00%	0.01%	0.35%

Relapse rates

In the previous manufacturer's submission for the NICE varenicline STA,[65] the annual probability of relapse to smoking for the first 5 years following cessation was calculated from a longitudinal US 4-year follow-up study of a health improvement initiative in the workplace ($n = 1143$).[88] The probability used was criticised by the evidence review group, as it was incorrectly derived from baseline length of abstinence data.[89] Although it was possible to estimate annual probability of relapse from this study, using follow-up data for the subsample of participants who had been abstinent for 1–2 years at baseline, this subsample comprises only 79 participants.

A more recent study has used British Household Panel Survey data to analyse relapse to smoking ($n = 1578$).[90] The article shows numbers of previous smokers relapsing who reported cessation for a minimum of 1 year up to 10 years. These data were used to calculate the annual relapse probability for short-run quitters (< 5 years since quit) and a proportion of long-run quitters (> 5 years but < 10 years post-quit). Data on annual relapse probability 10 or more years post cessation are scarce and, in the absence of more robust data, the same data (as used by Pfizer[65]) were employed here.[91]

Table 26 shows the probabilities of relapse that were used in the model. The probability of relapse in the first 10 years post 1 year of cessation is higher than estimates used in some previous models,[62,63,65,66,69] but is in line with other research which suggests that around half of those abstinent at 1 year will relapse to smoking in the next 7 years.[92,93] The annual probability of relapse after 10 years of abstinence was assumed to be 1% in the STA submission and several other applications of the BENESCO model,[62,66,69] all of which based their estimate on a longitudinal study.[91] The authors of this longitudinal study report that 'the (annual) rate of smoking relapse . . . fell to less than 1% after 10 years of abstinence'. Using the data reported by Krall *et al.*,[91] the annual probability of relapse is much lower than 1%. Uncertainty around relapse rates is modelled in this current report as a beta distribution, using event data from the original studies.[90,91]

Costs

Costs included in the model were costs relevant to disease states and intervention costs. The mean costs for COPD, CHD and asthma are those reported in Hind *et al.*[89] The source for COPD cost is the average direct cost of treatment, weighted by severity, taken from a study estimating burden of disease in the UK.[94] The annual cost of lung cancer was taken from a NICE rapid review,[95] sourced from a UK epidemiology study.[96] The annual patient cost for CHD is an estimate of the aggregate cost of CHD to the

TABLE 26 Relapse probabilities by duration of abstinence

Data	Original source	Mean probability (3 SF)	95% CI (3 SF)	Distribution over relapse category time period[a]
Annual relapse probability, > 1 and < 5 years post cessation (time period 4 years)	Hawkins 2010[90]	0.129	0.117 to 0.141	β(395–535)
Annual relapse probability, ≥ 5 and < 10 years post cessation (time period 5 years)	Hawkins 2010[90]	0.0331	0.0230 to 0.0452	β(33–180)
Annual relapse probability, > 10 years post cessation (time period 26 years)	Krall 2002[91]	0.00112	0.000402 to 0.00153	β(9–390)

CI, confidence interval; SF, significant figures.
a Parameter values correspond to total time period in 'Data' column: 4 years for relapse 1–5 years post cessation, 5 years for relapse 6–10 years post cessation and 26 years for relapse over 10 years post cessation (reflecting the follow-up period of Krall *et al.*[91]). Instantaneous relapse rates were first calculated from the data, and then converted to 1-year probabilities.

NHS,[97] divided by estimated prevalence. The cost of asthma exacerbations represented a mixture of the estimated cost of an accident and emergency (A&E) attendance and NHS reference cost of inpatient attendance, with the ratio of A&E to inpatient admissions estimate taken from Hoskins *et al.*[84] Costs for stroke were taken from a recent National Institute for Health Research (NIHR) commissioned technology assessment report,[98] and incorporates the one-off and ongoing costs of stroke in addition to the reported difference in costs and prevalence of dependent and independent patient states following a stroke incident.[99] All costs have been adjusted for inflation to 2010/11 prices.[100]

Uncertainty around cost estimates were incorporated into the probabilistic analysis. In the absence of data, the standard errors for COPD, lung cancer, CHD and asthma exacerbation were assumed to be 10% of the mean estimate. These data were assumed to follow a gamma distribution, as is common practice for cost data.[101] Confidence intervals around costs following stroke events were reported in Simpson *et al.*[98] and informed the uncertainty around mean costs for stroke, which was assumed to fit a normal distribution. *Table 27* reports the source, summary estimates and distributions used for the disease state costs employed in the model.

TABLE 27 Disease state costs

Data	Original source	Mean cost (£)	95% CrI	Distribution[a]
COPD	Britton 2003[94]	971.31	780.93 to 1161.69	Gamma (100, 9.71)
Lung cancer	Sanderson 2004[96]	6524.02	5245.31 to 7802.72	Gamma (100, 65.24)
CHD (non-fatal event)	McMurray 1993[97]	1162.50	934.45 to 1390.05	Gamma (100, 11.62)
Stroke (non- fatal event)	Simpson 2011[98]	5484.31	4996.99 to 5970.85	0.741 × [normal(576.51,15.74) + normal(3398.40,175.83)] + 0.259 × [normal(3010.17,66.21) + normal(6792.55,345.70)]
Asthma exacerbation	Hoskins 2000[84]	1162.25	846.73 to 1259.56	Gamma (100, 10.53)

a Numbers in brackets refer to scale and shape for gamma distributions, and mean and standard deviation for normal distributions.

Intervention costs comprised the cost of the drug regimen. Costs of brief counselling and support of a health professional are also likely to occur but were not likely to differ between drug treatments, thus not impacting relative cost–utility, and were not included in the economic analysis. For the comparator intervention, standard treatment with varenicline, BNF data on dosage and pricing are used.[19] The cost of treatment is the cost of a starter pack covering the first 2 weeks of tapered treatment (£27.30) plus the cost of 10 weeks at full dose (5 × £27.30), £163.80 in total. The cost of cytisine treatment within a UK setting is not determined. The manufacturers of cytisine were contacted by the research team, but no reply was received. In the absence of firm evidence, it is strongly suspected that a course of cytisine will be significantly cheaper than a standard course of varenicline.[23,102] A previous model of the costs and effects of cytisine for smoking cessation assumed treatment costs to be US$10 per smoker.[102] It is possible to buy Tabex (active ingredient cytisine) online in the UK for £16.79 for 100 1.5-mg tablets,[103] which represents approximately a standard course, and this cost is used in the model. *Table 28* shows the treatment costs used in the model.

Utilities associated with health states

Baseline utility for smokers with no current comorbidity was taken from the general population utility profile estimated by Ara and Brazier using Health Survey for England (HSE) data.[104] These data are a function of age and sex. Disease-specific utility values for smoking-related diseases are the same as reported by the manufacturer submission team.[65] For lung cancer utility,[105] asthma exacerbation utility[106] and a second non-fatal stroke event utility,[107] a utility multiplier associated with the disease was estimated by comparing the reported utility value with the expected value for a person of the same age within the general population, assuming that age-specific values from the UK were applicable for all populations. The average ages of the samples from which utility values were drawn were 62 years, 49 years and 65 years for lung cancer, asthma exacerbations and a second non-fatal stroke respectively. The mean ages of the population for which the utilities were provided for a first non-fatal stroke event,[108] COPD[109] and following any CHD event[110] were not reported. For these disease states, an average age of 60 years is assumed with the sensitivity of the results to this assumption is explored by altering baseline utility estimates for these diseases to correspond to ages 50 and 70 years respectively.

Disease state utility was determined using a multiplicative approach, i.e. baseline utility is multiplied by an estimate of the impact of the disease. Thus, a male aged 40 years with lung cancer would have an estimated utility of 0.44 (0.88 × 0.50). *Table 29* displays the mean utility values for health states in the model.

Uncertainty around utility estimates is explored in the probabilistic analysis. Normally distributed error terms from ordinary least squares regressions used to predict baseline utility by Ara and Brazier[104] represent uncertainty around utility inputs and are used to explore uncertainty in model outputs as part of the PSA. Uncertainty in the values reported for each health state was not considered and, therefore, the true uncertainty will be underestimated.

TABLE 28 Treatment costs

Data	Original source	Total cost (£)
Cytisine treatment cost	Assumption	16.79
Varenicline treatment cost	BNF 2012[19]	163.80

TABLE 29 Health state mean utility values

Health state	Utility source	Mean age (years)	Mean utility
NCM, males, 18–34 years	Ara 2010[104]	26.5	0.94
NCM, males, 35–64 years	Ara 2010[104]	49	0.88
NCM, males, 65–100 years	Ara 2010[104]	82.5	0.72
NCM, females, 18–34 years	Ara 2010[104]	26.5	0.92
NCM, females, 35–64 years	Ara 2010[104]	49	0.86
NCM, females, 65–100 years	Ara 2010[104]	82.5	0.70
Lung cancer	Trippoli 2001[105]	62	0.50
COPD	Spencer 2005[109]	60	0.63
CHD	Hay 2005[110]	60	0.63
Stroke (first event)	Tengs 2003[108]	60	0.62
Stroke (second event)	Gage 1998[107]	65	0.12
Asthma exacerbation	Szende 2004[106]	49	0.45

NCM, no current morbidity.

Intervention effectiveness

The absolute probabilities of cessation at 1 year for interventions were generated by combining the results of the network meta-analysis with an estimate of the placebo response, as described in *Chapter 3*. The median and mean probability of 1-year continuous abstinence for cytisine and varenicline and 95% CrIs are shown in *Table 30*. The absolute quit rates for cytisine appear low (see *Table 4*). However, when the rates of abstinence shown in *Table 5* are analysed, a quit rate of 33% for varenicline is reasonable.
The greater relative effectiveness for cytisine against placebo compared with varenicline against placebo results in the 45% quit rate. The wide CrIs are reflective of uncertainty around the baseline (placebo) effect. There is much less uncertainty about the treatment effects and the order of the clinical effectiveness of the two treatment comparators. The probability that cytisine 1.5 mg was the most effective treatment of the eight compared in the meta-analysis was 0.86, as shown in *Table 3* (see *Chapter 3*). When only cytisine 1.5 mg and varenicline 1 mg b.i.d. are compared, the probability that cytisine is the most clinically effective treatment is estimated to be 0.90. The 95% CrI around the difference between clinical effectiveness of the interventions (probability of quit with cytisine minus probability of quit with varenicline) includes zero (95% CrI –0.048 to 0.389).

Discussion of key assumptions

The modelling approach involves several assumptions, as noted throughout *Chapter 4*, *Independent economic assessment*. A key assumption implicit in the model is that cohort members can only quit after treatment for smoking cessation, within the first model cycle, and at no other point until death. In reality, smokers who are willing to quit but fail during one attempt will have a probability of successfully quitting at a later stage in their lives. This assumption is likely to favour interventions with greater efficacy. If the 1-year probability of cessation is significantly higher for one treatment than another, that treatment will have greater health outcomes across the cohort over the lifetime horizon. This assumption is a feature of all previous applications of the BENESCO model.[62–72]

TABLE 30 Absolute probability of 1-year continuous cessation

1-year continuous abstinence probability	Median	Mean	95% CrI
Cytisine	0.394	0.449	0.040 to 0.998
Varenicline	0.257	0.330	0.026 to 0.958

The economic model has relied, in part, on input data from a previous manufacturer's submission for the NICE varenicline STA,[65] as set out in the protocol. It is not known if these inputs are the best available as (i) at least 5 years have elapsed since these data were identified and (ii) identification of input studies was not always clearly reported. The majority of cost, utility and relapse data were from the UK, but a proportion of these data were from non-UK studies.[78,79,91] The model assumes transferability of these data to a UK NHS setting. Additionally, the model assumes treatments are not associated with adverse events. This assumption is justified on the basis of the finding of no significant difference in SAEs between the two treatments (see *Chapter 3*), but may favour the varenicline treatment strategy.

Analysis of uncertainty

The uncertainty around key parameter estimates was modelled by the use of probability distributions which allowed PSA to be undertaken. Ten thousand draws from distributions of treatment effectiveness, health state utility, disease costs and relapse probabilities were used as model inputs. Furthermore, univariate sensitivity analysis was performed to ascertain the key drivers of model outputs.

Value of information analyses was undertaken to establish whether or not a direct head-to-head trial of cytisine compared with varenicline might represent a cost-effective use of resources. The methodological plan was to undertake the analysis in three stages. The first stage involved the calculation of the expected value of perfect information (EVPI).[111] If the value produced appeared to be greater than the cost for which a RCT comparing the efficacies of the two interventions could be undertaken, then the second stage would be performed.

The second stage would estimate the expected value of partial perfect information (EVPPI)[112] jointly on the efficacies of varenicline and cytisine. If the value produced appeared to be above the cost for which a RCT comparing the efficacies of the two interventions could be undertaken, then the third stage would be performed.

The third stage involves the calculation of the EVSI.[113] This value explicitly evaluates the potential inaccuracy associated with trials of smaller sizes, contrasting with EVPPI, which assumes that the information is perfect and, thus, in essence, is derived from a trial of infinite size.

Results

Mean costs and mean treatment effects associated with each treatment

The results of the PSA are presented as the primary results of interest, as, unlike deterministic estimates, they take into account the distributions of input parameters and interaction between parameters and, therefore, are the more accurate estimates. *Table 31* shows the primary results of the PSA analysis: per smoker total discounted costs, life-years (LYs) and quality-adjusted life-years (QALYs) for the two treatments. Cytisine is expected to be less costly and more effective than varenicline and, so, can be said to dominate varenicline based on the expected values.

Figure 10 presents the cost-effectiveness acceptability curve[114] for the two treatments. At any threshold of willingness to pay, up to £100,000 per QALY gained, cytisine was the optimal intervention in over 90% of the simulations within the PSA. This reflects the higher costs associated with varenicline treatment. As the willingness to pay increases, the probability that cytisine is preferable falls and the likelihood that varenicline is optimal rises. Given that cytisine was estimated to be the more effective treatment in 90% of simulations, the value for cytisine on the cost-effectiveness acceptability curve will asymptote at 90%.

TABLE 31 Mean per smoker discounted total and incremental costs, LYs and QALYs from the economic analysis

	Costs		LYs		QALYs	
Treatment	Total	Incremental	Total	Incremental	Total	Incremental
Cytisine	£4973	–£251	17.53	0.03	14.38	0.03
Varenicline	£5225	–	17.50	–	14.35	–

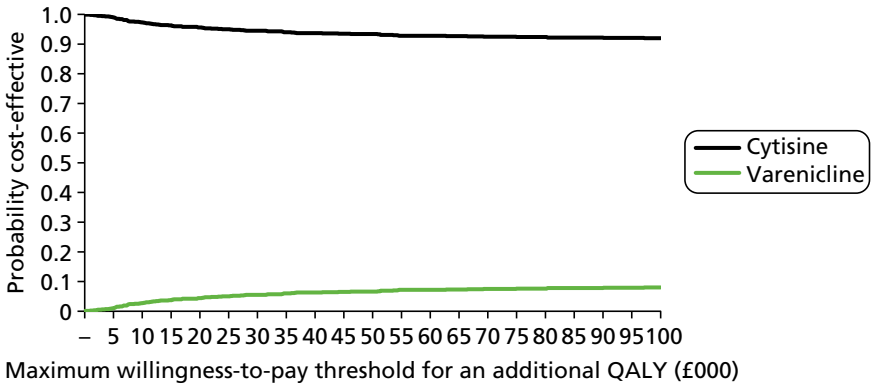

FIGURE 10 Cost-effectiveness acceptability curves for cytisine and varenicline.

Univariate sensitivity analyses

Table 32 details the results from the univariate sensitivity analyses. In all the analyses, bar one, the conclusion that cytisine dominates varenicline is upheld. The exception was in altering the relative efficacies of varenicline and cytisine. This analysis was operationalised by ranking the output from the network meta-analysis based on the value in the differences of the absolute quit rates between cytisine and varenicline and using the 2.5th and 97.5th percentile. When using the value most favourable to varenicline, an additional 0.01 QALYs at an additional cost of £87, resulting in a cost per QALY gained of just under £6700, would be typically seen as cost-effective under typical NICE thresholds.[74]

The assumed treatment cost for cytisine is lower than that for varenicline, but the cytisine cost estimate if adopted for use within the NHS is uncertain. In a threshold analysis it was estimated that the price of the cytisine regimen would have to rise to over £250 (from an estimate of £16.79, a greater than 14-fold rise) for the total expected lifetime cost with cytisine treatment to equal the total expected lifetime cost with varenicline treatment.

Calculation of the expected value of perfect information

Expected value of perfect information is defined as the value of eliminating all uncertainty around the adoption decision. The value is determined by both (i) the probability that a wrong adoption decision will be made and (ii) the costs of forgoing the optimal treatment strategy.

In order to calculate the EVPI, an estimate of the number of people affected using more accurate information was required. A recent Office for National Statistics report estimated that 21% of the UK adult population smoke, around 10 million people, and the same report found that 63% of smokers want to quit smoking.[115] If even half of those with a desire to quit attempt assisted cessation, while the choice between cytisine and varenicline is relevant, the adoption decision will affect more than 3 million UK smokers. Elsewhere, it has been estimated that 800,000 smokers currently access stop smoking services in England each year,[116] supporting the notion that 3 million smokers could be affected in England and Wales.

Analysis of US data from the 2003 Tobacco Use Cessation Supplement to the Current Population Survey found that, of those attempting to quit (43.5% of all smokers), one-third (32.2%) used medication.[117] This figure was lower in the UK at the turn of the century, but increasing as NRT and bupropion hydrochloride became available on prescription.[118] However, a study into the reasons smokers shy away from medications suggests that perceived clinical effectiveness has lessened use of smoking cessation drugs in the past.[119] The high efficacy of the dopamine inhibitors cytisine and varenicline, in comparison with NRT, will probably attenuate this effect. Ease of access has also been cited as a factor.[119] This all suggests that with a focus on implementation in UK stop smoking services, to overcome these barriers, the proportion of quit attempts assisted by medication could rise significantly in the next 10 years. The figure of 3 million

TABLE 32 Univariate sensitivity analysis result, per smoker model outcomes

			Costs		LYs		QALYs	
Variable	Sensitivity analysis	Treatment	Total	Incremental	Total	Incremental	Total	Incremental
Baseline	–	Cytisine	£4972	–£256	17.53	0.04	14.38	0.03
		Varenicline	£5228	–	17.49	–	14.35	–
COPD utility	Assumed age of study sample 50 years	Cytisine	£4972	–£256	17.53	0.04	14.39	0.03
		Varenicline	£5224	–	17.49	–	14.36	–
	Assumed age of study sample 70 years	Cytisine	£4972	–£256	17.53	0.04	14.37	0.03
		Varenicline	£5228	–	17.49	–	14.33	–
CHD utility	Assumed age of study sample 50 years	Cytisine	£4972	–£256	17.53	0.04	14.40	0.03
		Varenicline	£5228	–	17.49	–	14.37	–
	Assumed age of study sample 70 years	Cytisine	£4972	–£256	17.53	0.04	14.36	0.03
		Varenicline	£5228	–	17.49	–	14.32	–
Stroke first event utility	Assumed age of study sample 50 years	Cytisine	£4972	–£256	17.53	0.04	14.40	0.03
		Varenicline	£5228	–	17.49	–	14.36	–
	Assumed age of study sample 70 years	Cytisine	£4972	–£256	17.53	0.04	14.36	0.03
		Varenicline	£5228	–	17.49	–	14.30	–
Cytisine cost	Double	Cytisine	£4989	–£239	17.53	0.04	14.38	0.03
		Varenicline	£5228	–	17.49	–	14.35	–
COPD cost	Upper 95% CI value	Cytisine	£5053	–£240	17.53	0.04	14.38	0.03
		Varenicline	£5293	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4925	–£238	17.53	0.04	14.38	0.03
		Varenicline	£5163	–	17.49	–	14.35	–

continued

TABLE 32 Univariate sensitivity analysis result, per smoker model outcomes (*continued*)

			Costs		LYs		QALYs	
Variable	Sensitivity analysis	Treatment	Total	Incremental	Total	Incremental	Total	Incremental
Lung cancer cost	Upper 95% CI value	Cytisine	£5078	–£242	17.53	0.04	14.38	0.03
		Varenicline	£5321	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4899	–£236	17.53	0.04	14.38	0.03
		Varenicline	£5135	–	17.49	–	14.35	–
CHD event cost	Upper 95% CI value	Cytisine	£5142	–£240	17.53	0.04	14.38	0.03
		Varenicline	£5382	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4836	–£238	17.53	0.04	14.38	0.03
		Varenicline	£5074	–	17.49	–	14.35	–
Stroke event cost	Upper 95% CI value	Cytisine	£5289	–£246	17.53	0.04	14.38	0.03
		Varenicline	£5535	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4688	–£231	17.53	0.04	14.38	0.03
		Varenicline	£4920	–	17.49	–	14.35	–
Asthma event cost	Upper 95% CI value	Cytisine	£4991	–£239	17.53	0.04	14.38	0.03
		Varenicline	£5230	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4987	–£239	17.53	0.04	14.38	0.03
		Varenicline	£5226	–	17.49	–	14.35	–
Relapse probability 1–4 years	Upper 95% CI value	Cytisine	£5008	–£234	17.52	0.03	14.37	0.03
		Varenicline	£5242	–	17.49	–	14.34	–
	Lower 95% CI value	Cytisine	£4970	–£244	17.54	0.04	14.38	0.03
		Varenicline	£5214	–	17.50	–	14.35	–

Variable	Sensitivity analysis	Treatment	Costs		LYs		QALYs	
			Total	Incremental	Total	Incremental	Total	Incremental
Relapse probability 5–9 years	Upper 95% CI value	Cytisine	£5005	–£234	17.52	0.03	14.37	0.03
		Varenicline	£5240	–	17.49	–	14.34	–
	Lower 95% CI value	Cytisine	£4975	–£243	17.53	0.04	14.38	0.03
		Varenicline	£5218	–	17.50	–	14.35	–
Relapse probability 10 + years	Upper 95% CI value	Cytisine	£4991	–£239	17.53	0.03	14.38	0.03
		Varenicline	£5229	–	17.49	–	14.35	–
	Lower 95% CI value	Cytisine	£4988	–£240	17.53	0.04	14.38	0.03
		Varenicline	£5227	–	17.49	–	14.35	–
Difference between treatment effectiveness (cytisine minus varenicline)	Upper 95% CrI value	Cytisine	£4760	–£487	17.60	0.12	14.45	0.11
		Varenicline	£5246	–	17.49	–	14.34	–
	Lower 95% CrI value	Cytisine	£5223	–£87	17.45	–0.01	14.31	–0.01
		Varenicline	£5309	–	17.47	–	14.32	–

CI, confidence interval.

affected smokers is considered reasonable, but the EVPI was also calculated with the assumption of 1 million smokers affected.

The incremental net benefit (INB) of cytisine compared with varenicline was calculated per smoker for each of the PSA runs for willingness-to-pay thresholds for an additional QALY of £20,000 and £30,000. In over 90% of PSA runs the INB was positive, indicating that varenicline was not cost-effective. However, in the remainder of the PSA runs the value was negative, indicating that varenicline was cost-effective. The maximum INB was calculated as the sum of all positive INB, divided by the number of PSA runs (10,000). The expected INB was calculated as the sum of all INB, divided by the number of PSA runs. The EVPI was calculated as the difference between maximum INB and expected INB. This value was £12 per smoker assuming a willingness to pay of £20,000 per QALY gained and £21 per smoker assuming a willingness to pay of £30,000 per QALY.

Although these are small EVPI values per person, the value becomes much greater when multiplied by 3 million to represent the likely population affected by the decision, resulting in EVPI values of £35M and £63M at a willingness-to-pay level of £20,000 and £30,000 per QALY respectively. Even with a conservative value of only 1 million smokers affected by the decision and with willingness to pay £20,000 for an additional QALY, the EVPI was over £11M.

The EVPI is far greater than the potential cost of a head-to-head trial comparing cytisine and varenicline, and, so, according to the protocol, the second stage of the value of information analysis calculating the EVPPI was necessary.

Expected value of partial perfect information analyses

Rather than use a traditional two-loop procedure for calculating the EVPPI[112] a novel method was employed that allows the computational time to be markedly reduced. This method has been shown to replicate the EVPPI in examples where an analytical solution existed; a manuscript describing the methodology is currently under consideration for publication in the peer-reviewed journal *Medical Decision Making*.

The results of key parameters are shown in *Table 33* assuming a willingness to pay of £20,000 per QALY. The EVPPI on the HR of varenicline compared with cytisine, which would be the information garnered from the direct head-to-head trial of the two interventions, was estimated to be £33.6M. The EVPPI of conducting a trial of each intervention against placebo was additionally estimated showing that the bulk of the uncertainty existed regarding cytisine efficacy rather than varenicline efficacy (EVPPIs of £25.3M and £0.4M respectively). *Table 34* replicates this analysis assuming a threshold of £30,000 per QALY.

TABLE 33 The EVPPI assuming a willingness to pay of £20,000 per QALY

Parameter	EVPPI (£M)
HR of cytisine vs. varenicline	33.6
HR of cytisine vs. placebo	25.3
HR of varenicline vs. placebo	0.4

TABLE 34 The EVPPI assuming a willingness to pay of £30,000 per QALY

Parameter	EVPPI (£M)
HR of cytisine vs. varenicline	58.6
HR of cytisine vs. placebo	46.7
HR of varenicline vs. placebo	0.7

The EVPPI associated with the HR of cytisine and varenicline were large, in excess of £33M. This was deemed sufficient to fund a trial and, therefore, EVSI analyses were conducted.

Expected value of sample information analyses

Similarly to EVPPI, a novel method was undertaken that allowed the computational time required to be markedly reduced. Within this method the posterior expectation for the INB conditional on each new simulated trial data were approximated using approximate Bayesian computation. The method produced results comparable to those present by Ades *et al.*[113] in the pivotal methodological paper. A manuscript is current being prepared for submission to a peer-reviewed journal.

Within the EVSI calculation it was assumed that 3 million people would benefit from the increased information regarding the relative efficacies of cytisine and varenicline. The EVSI for a year-long trial that directly compares varenicline 1.0 mg b.i.d. with cytisine 1.5 mg was estimated using trial sample sizes ranging from 50 to 20,000 participants per arm, and at willingness-to-pay values of £20,000 and £30,000. The net value of the RCT was estimated assuming that to enrol a person in a RCT was £1000, as previously used by Stevenson *et al.*[120] This paper stated that 'although in reality there will be fixed costs and some form of economies of scale to be exploited, this value appears a reasonable approximation to the costs of successfully funded bids in the United Kingdom'.

A graphical depiction of the results of the EVSI analyses are shown in *Figure 11* (when a threshold of £20,000 per QALY is used) and *Figure 12* (when a value of £30,000 per QALY is used).

In both analyses, conducting a RCT of varenicline compared with cytisine with 1000 smokers per arm appeared optimal, although the results were comparable to trials of 500 or 2000 smokers per arm. Sensitivity analyses (not shown) were conducted reducing the cost per person in the RCT to £500 to acknowledge the relatively small duration of the trial. Assuming a willingness to pay of £20,000 per QALY, the conclusions did not alter; at £30,000 per QALY a trial of 2000 in each arm was estimated to be slightly preferable to 1000 in each arm, although the results were very similar for these trial sizes.

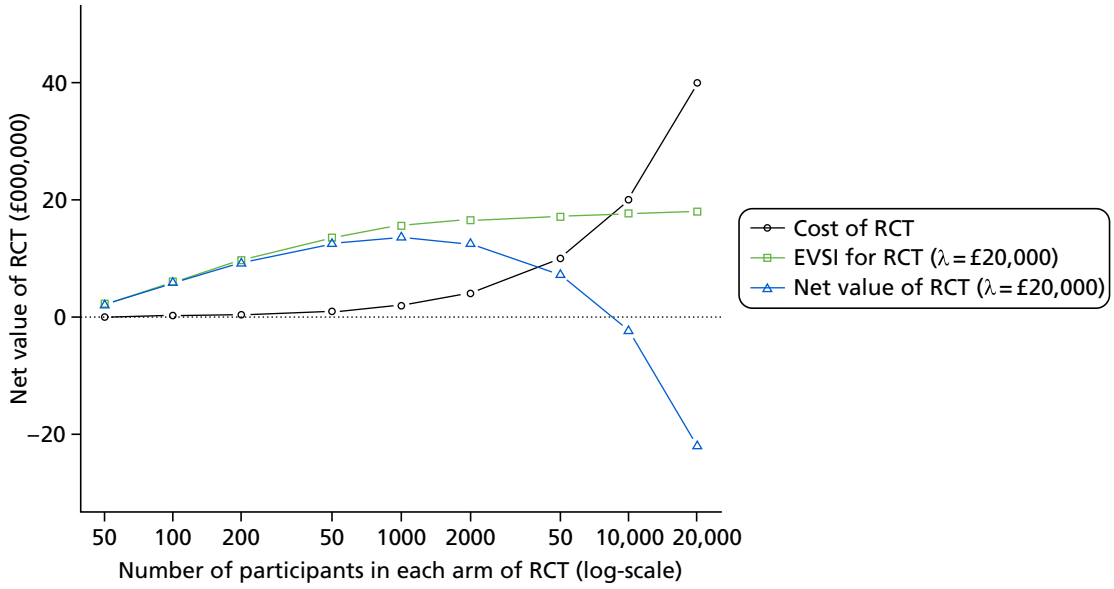

FIGURE 11 Results from the EVSI analyses assuming a willingness to pay of £20,000 per QALY.

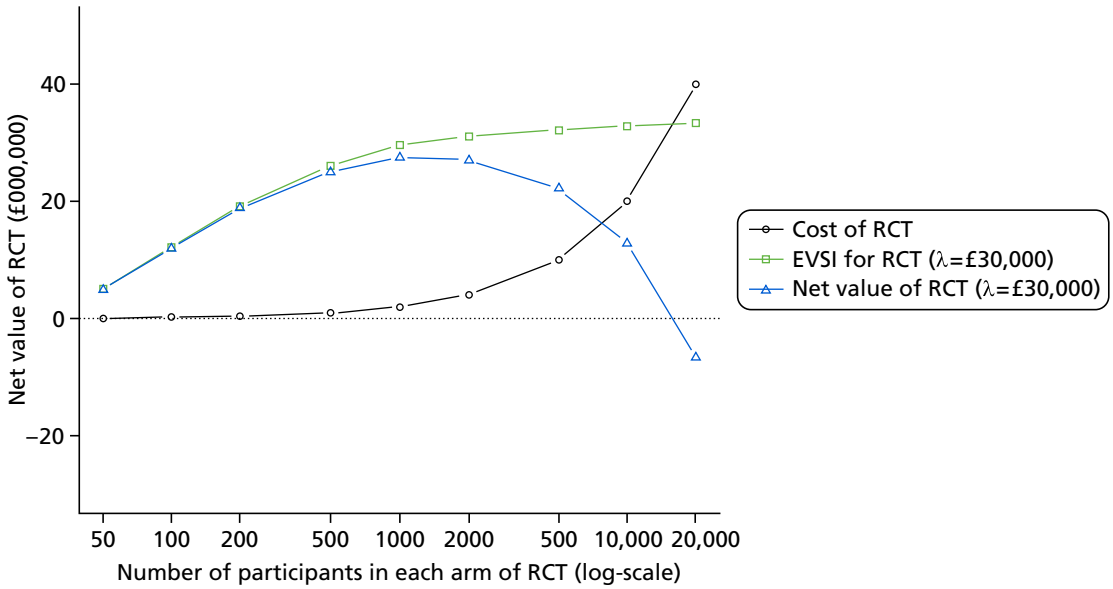

FIGURE 12 Results from the EVSI analyses assuming a willingness to pay of £30,000 per QALY.

Discussion on modelling aspects

Probabilistic sensitivity analysis outputs from the economic model suggest that cytisine for smoking cessation will produce greater mean LYs and QALYs, and lower mean lifetime costs than varenicline, which was previously considered to be the most cost-effective smoking cessation treatment strategy. At a willingness-to-pay threshold of £20,000 for an additional QALY, the probability that cytisine treatment is preferable to varenicline treatment is 0.95, and this probability does not fall below 0.9. Despite this, the value of further information on the relative effectiveness of the two strategies is high because of the very large numbers of smokers treated.

A key driver of the dominance of cytisine treatment over varenicline treatment in the economic analysis is the relative effectiveness of cytisine compared with varenicline, as shown in the univariate sensitivity analysis. In summary, the treatment which generates the greatest number of quitters will have the best long-term health outcomes as efficacious treatment also has the impact of reducing costs associated with longer-term conditions associated with smoking. If treatment costs were equal for varenicline and cytisine, the probability that cytisine is the optimal choice is 0.9 (at any willingness-to-pay value), reflecting the 0.9 probability that cytisine has the greater 1-year continuous cessation probability.

It was not possible to validate the economic model outputs against results in the STA report, as the number in the simulated cohort in the latter was not reported and, therefore, per smoker values are unknown.[89] Other previous applications of the BENESCO model have used non-UK populations and parameter inputs, making comparison of total LYs and QALYs difficult.[62–64,66–72,89] However, results across these studies and here have been similar, in that the intervention with the greatest clinical effectiveness (short-term cessation probability) has consistently had the greatest cost–utility.

The key limitation of the model structure used is the imposed assumption of no underlying quit rate, among failed quitters or relapsed smokers, which is likely to favour treatments with higher effectiveness. Other UK studies have modelled the cost–utility of competing smoking cessation strategies and incorporated an underlying quit rate.[92,95,121] In each of these studies, unlike here, the most efficacious strategy had the highest treatment cost, but like here, the strategy with greatest short-term clinical effectiveness was the optimal strategy, at a willingness-to-pay threshold of £20,000 per QALY gained. In these models the annual probabilities of relapse to smoking, smoking-related disease incidence and death have been assumed to be constant[92,95,121] compared with the decreases related to time since cessation in the present model. Assuming a sharp fall in probabilities linked to unfavourable health outcomes, rather

than a decline over time, is less realistic, but further biases results towards those with higher clinical effectiveness if the full benefits of smoking cessation are assumed instantly obtainable.

It is difficult to incorporate both an underlying quit rate and transition probabilities that vary with time since quit into a state transition model structure, without incorporating numerous tunnel states. Individual person-level models may be a better avenue for accurately quantifying the cost–utility of smoking cessation strategies in future. At least two such models have been built to date.[122,123] Given the resources provided for this project it was agreed in the protocol that construction of a more accurate model than the BENESCO model was not feasible.

The transition probabilities and some parameter inputs in the model were taken from the manufacturer's submission for the NICE varenicline STA,[65] and it is not known whether or not these data are the best currently available. From the results of the deterministic sensitivity analysis, model outputs are robust to parameter inputs other than relative effectiveness of the two treatments. Uncertainty around the probabilities of transition to disease states has not been explored, but if the relative risks of smoking-related disease incidence and mortality can be assumed to decrease after smoking cessation, cytisine for smoking cessation will represent a better use of the health-care budget than varenicline using average values given current information.

Chapter 5 Discussion

Statement of principal findings

Clinical effectiveness findings

The systematic review of clinical effectiveness included 23 studies, comprising a total of 10,610 participants.[16,17,37–39,41,46–61] The review was an update of a previous Cochrane review by Cahill *et al.*[15] and the updated search added three new trials to the previous review. All of these trials were of varenicline. No new trials of cytisine were identified, so that only two high-quality RCTs of cytisine with outcome data after a minimum follow-up of 6 months have been conducted to date.[17,43]

A network meta-analysis was used to allow a comprehensive synthesis and comparison between smoking cessation treatments including cytisine, varenicline, nicotine patch and bupropion hydrochloride. A random (treatment)-effects model was used incorporating a log-log link function to allow for variation in the duration of follow-up between studies.

Results showed that cytisine 1.5 mg produced the greatest effect on CAR relative to placebo (HR 4.21, 95% CrI 2.11 to 9.84). Cytisine 1.5 mg was the intervention with the highest probability of being the most effective intervention (probability = 0.86). As point prevalence abstinence is often used in smoking cessation trials as a proxy for continuous abstinence, a sensitivity analysis was conducted including studies using both continuous abstinence rates and 7-day point prevalence abstinence. The results of this analysis were similar to those using only CAR data. However, the goodness of fit of the model suggested that the data from some of the trials using point prevalence as an outcome measure may arise from a different model. Consequently, only treatment effects estimated from data obtained from the CAR studies were included in the economic model.

Previous recent systematic reviews have reported both cytisine and varenicline to be clinically effective aids to smoking cessation. Cahill *et al.*[15] reported both varenicline and cytisine to be clinically effective treatments for smoking cessation. Cytisine was reported to have modest clinical efficacy, although the authors noted low absolute quit rates. Cytisine has been licensed as a treatment for smoking cessation in a number of Eastern European countries for several decades. Despite this, only two trials of good quality with a minimum of 6 months' follow-up that have evaluated the clinical efficacy of cytisine compared with placebo met the inclusion criteria for both the Cahill review[15] and the current review. The Hajek review[26] of cytisine identified more trials; however, these did not fit the inclusion criteria for the Cahill review[15] or this current review. The most common reason for this was that the length of follow-up was too short. However, their analysis of including only the high-quality trials still showed cytisine to be a clinically effective smoking cessation aid. For varenicline, the Cahill review[15] reported that participants treated with the standard dose of varenicline had a twofold increased chance of quitting than placebo. The authors note that varenicline has been shown to be clinically effective in trials in real-world settings and for participants who may ordinarily be excluded from clinical trials. These participants include patients awaiting surgery, or patients hospitalised with medical or psychiatric conditions. The trials identified in the updated search support this assertion, with varenicline showing clinical efficacy for pre-operative smokers[37] and for light smokers in a Latino community setting.[38]

Adverse events findings

Data for the four most common adverse events (abnormal dreams, headache, insomnia and nausea), as identified in the Cahill review,[15] and SAEs were analysed. Standard-dose varenicline treatment was associated with significantly higher rates of headaches, insomnia and nausea than placebo; there was no significant difference in the rates of abnormal dreams. There were no significant differences in rates of headaches or nausea between cytisine and placebo; data were not identified for abnormal dreams or

insomnia. However, these results must be interpreted with caution, as they are a result of data from RCTs only. Most of the trials reported in this review applied criteria that excluded individuals with underlying medical conditions such as a history of depression or cardiovascular illness. Such individuals may be more likely to develop SAEs than those with no history of these medical conditions. In addition, the follow-up period of many trials may not be sufficiently long to capture all relevant adverse events. Etter[124] notes with caution the toxicity of the seeds of *C. laborinum*, from which cytisine is derived. The lethal dose in humans is not currently known; however, there is no current evidence to suggest that poisoning can occur from use of cytisine used for smoking cessation. A lack of systematic reviews of adverse events that include cohort studies means that, as is emphasised by Cahill *et al.*,[15] conclusions regarding the safety profile of both varenicline and cytisine are currently limited.

Nevertheless, the current review and network meta-analysis found that there were no differences in SAEs, and that differences in mild, transient adverse events were not clinically significant. Overall, the safety evidence in the current review was weak and a full safety review was not undertaken. A full safety review of cohort studies for both varenicline and cytisine is needed. For example, a large cohort study found no evidence of an increased risk of self-harm, depression and suicidal thoughts relative to NRT or bupropion hydrochloride.[125]

A number of systematic reviews and meta-analyses report on specific adverse events of varenicline. Previous reviews have reported mixed results when considering the association of varenicline with adverse events (e.g. Singh *et al.*,[29] found an increased risk of cardiovascular events, while Prochaska *et al.*[126] found no such link). Leung *et al.*[27] found an association between varenicline and an increased risk of gastrointestinal events. Tonstad *et al.*[28] found no significant association between varenicline and serious neuropsychiatric events; however, an association has been suggested for those taking varenicline who are currently experiencing depression. The FDA's recently added warning to the product label of Chantix highlighted a small increased risk of certain cardiovascular events in patients with pre-existing cardiac conditions. This warning, coupled with its existing warnings, supports Cahill *et al.*'s conclusion that a link between varenicline and certain adverse events cannot be ruled out. Concerns about the safety of varenicline have been raised, resulting in a series of warnings from the FDA. These have arisen through post-marketing reports of an increased risk of suicidal behaviour, serious cardiac events and gastrointestinal complaints. A full and detailed account of the current available evidence is presented in the review by Cahill *et al.*[15]

Previous reviews have reported slightly more frequent adverse events among those taking cytisine than those taking placebo, which include weight gain, nausea and digestive problems, tachycardia and changes in blood pressure.[124] A review by Hajek *et al.*[26] found that many of the cytisine trials provided minimal support to participants, for example the drug was distributed by post. They highlight that more intensive support during attempted smoking cessation increases quit rates, and that this may be more relevant for participants taking cytisine, as its dosing regimen is complex. As both studies of cytisine identified in this review used the same standard dosing schedule, it has not been possible to identify advantages or disadvantages of different doses, in terms of both efficacy and adherence. In the event that cytisine were to be licensed in the UK, practitioners should consider the potential risk of adverse events when making treatment decisions for individual patients.

Cost-effectiveness findings

Probabilistic sensitivity analyses showed cytisine to produce greater expected mean LYs and QALYs, and lower mean expected lifetime costs than varenicline, and is therefore expected to dominate varenicline. The economic analysis is driven by the relative clinical effectiveness of cytisine and varenicline.
The treatment that generates the greatest number of quitters will have the best long-term health outcomes, as smoking cessation produces reduced costs associated with longer-term conditions associated with smoking. Based on the currently available data there is a greater probability that cytisine is more efficacious than varenicline. However, this conclusion is uncertain, and owing to the very large numbers of

smokers treated (around 800,000 receiving NHS treatment for smoking cessation each year), the value of further information on the relative effectiveness of the two treatments is high.

The EVPI was calculated as £12 per smoker assuming a willingness to pay of £20,000 per QALY gained and £21 per smoker assuming a willingness to pay of £20,000 per QALY gained. Although these are small EVPI values per person, the number of people affected by the decision is large – with a likely population of 3 million affected. The current economic analysis suggests EVPI values of £35M and £63M at a willingness-to-pay levels per QALY of £20,000 and £30,000 respectively. With a more conservative value of 1 million smokers affected, the values are in the region of £15M. As the EVPI is greater than the potential cost of a head-to-head trial, the second stage of the value of information analysis was necessary, i.e. calculating the EVPPI. The EVPPI of the HR of smoking cessation of cytisine compared with varenicline remained high (in excess of £33M) and, therefore, formal EVSI analyses were undertaken. This indicated that a direct head-to-head trial of cytisine and varenicline, with 1000 patients in each arm appeared an appropriate use of resources.

Recommendations for future research

It is recommended that a head-to-head trial of varenicline and cytisine is undertaken, with 1000 patients in each arm being an appropriate number.

Strengths and limitations of the review

A strength of this review was the quality of the trials included. No high-risk trials were included, with most trials judged to be at low risk of bias. Strict inclusion criteria of the trials meant that many trials excluded participants who may be more at risk of adverse events, for example those with underlying medical conditions. For this reason, the adverse events analyses may not give a comprehensive picture of adverse events associated with each treatment.

Use of a network meta-analysis allowed a comprehensive comparison of all interventions of interest, including a number of different dosing schedules. Only two studies matching the inclusion criteria that evaluated cytisine were identified,[17,43] compared with 21 studies of varenicline.[16,37–39,41,46–61] The varenicline data include studies of its clinical effectiveness in a number of real-world settings, which allows their results to be generalised to wider populations. Cytisine has yet to be studied in subpopulations.

A strength of the economic modelling is that EVSI analyses were undertaken to quantify whether or not a RCT is justified and, if so, an appropriate number of smokers to recruit. The model constructed was based on the BENESCO model and the limitations of this model, primarily no underlying quit rate, are applicable here. Furthermore, the transition probabilities and some parameter inputs were taken from a manufacturer's submission to NICE[65] and it is not known whether or not these data are the best available. However, such limitations are unlikely to significantly bias the comparison of varenicline and cytisine.

It was not possible to obtain a cost for cytisine direct from the manufacturer and costs may vary between countries. The cost of cytisine may increase if the manufacturer is required to incur costs associated with fulfilling UK licensing requirements, although this does not change the fundamental conclusion that a head-to-head trial of cytisine compared with varenicline is needed.

A potential limitation is that the review and economic evaluation contained only two trials that examined cytisine. In addition, the safety evidence in the current review was weak and a full safety review was not undertaken. The dearth of robust evidence concerning cytisine further highlights the importance of a high-quality head-to-head trial.

Chapter 6 Conclusions

Clinical effectiveness

The current review evaluated two nicotinic receptor partial agonists, varenicline and cytisine, and supported previous findings that both drugs are effective for smoking cessation when compared with placebo. Cytisine was estimated to be more clinically effective than varenicline and also more cost-effective; however, it is yet to be licensed for use in the UK and its safety profile has yet to be adequately evaluated.

Cost-effectiveness

Given current evidence cytisine appears more clinically effective and cost-effective than varenicline based on expected costs and QALY values. However, there is uncertainty in this decision and formal EVSI analyses were undertaken that indicate that a RCT of varenicline compared with cytisine recruiting 1000 smokers per arm would be an efficient use of resources.

Suggested research priorities

A head-to-head trial comparing varenicline with cytisine is recommended, with 1000 smokers per arm being an appropriate number. Concerns about the potential toxicity of *C. laborinum* support the need for observational databases with a long duration follow-up so that all potential adverse events are captured.

A review of cohort studies evaluating varenicline or cytisine in the long-term is recommended in order to provide a more accurate estimate of the occurrence of adverse events for smokers taking these drugs as an aid for cessation in real-world settings.

Implications for service provision

As cytisine is currently not licensed in the UK, there are no implications at present for service provision.

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Contributions of authors

Joanna Leaviss and **Emma Everson-Hock** carried out the systematic review and quality assessment of the studies.

William Sullivan and **Matt Stevenson** constructed the mathematical model.

Shijie Ren and **John W Stevens** provided statistical support and undertook the network meta-analyses.

Mark Strong undertook the value of information analyses and **Anna Cantrell** carried out the searches.

References

1. Peto R. Smoking and death: the past 40 years and the next 40. *BMJ* 1994;**309**:937–9. http://dx.doi.org/10.1136/bmj.309.6959.937
2. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. *JAMA* 2004;**291**:1238–45. http://dx.doi.org/10.1001/jama.291.10.1238
3. Royal College of Physicians. *Nicotine Addiction in Britain: a Report of the Tobacco Advisory Group of the Royal College of Physicians*. London: Royal College of Physicians; 2000.
4. Mukherjee D, Yadav JS. Update on peripheral vascular diseases: From smoking cessation to stenting. *Cleve Clin J Med* 2001;**68**:723–33. http://dx.doi.org/10.3949/ccjm.68.8.723
5. Musk AW, de Klerk NH. History of tobacco and health. *Respirology* 2003;**8**:286–90.
6. Office for National Statistics (ONS). *General Household Survey 2004*. London: National Statistics; 2013.
7. Scarborough P, Bhatnagar P, Wickramasinghe KK, Allender S, Foster C, Rayner M. The economic burden of ill health due to diet, physical inactivity, smoking, alcohol and obesity in the UK: an update to 2006–07 NHS costs. *J Public Health* 2011;**33**:527–35.
8. Hughes J, Stead L, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2004;**4**:CD000031. http://dx.doi.org/10.1002/14651858.CD000031
9. West R. Addressing regulatory barriers to licensing nicotine products for smoking reduction. *Addiction* 2000;**95**(Suppl. 1):S29–34. http://dx.doi.org/10.1046/j.1360-0443.95.1s1.4.x
10. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. *Cochrane Database Syst Rev* 2013;**8**:CD002850. http://dx.doi.org/10.1002/14651858.CD002850
11. Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation. *Cochrane Database Syst Rev* 2005;**2**:CD001007. http://dx.doi.org/10.1002/14651858.CD001007
12. Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation. *Cochrane Database Syst Rev* 2005;**2**:CD001292. http://dx.doi.org/10.1002/14651858.CD001292
13. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2008;**1**:CD000146. http://dx.doi.org/10.1002/14651858.CD000146.pub3
14. Hughes JR, Stead, LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2007;**1**:CD000031. http://dx.doi.org/10.1002/14651858.CD000031
15. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012;**4**:CD006103. http://dx.doi.org/10.1002/14651858.CD006103.pub2
16. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, *et al.* Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;**296**:56–63. [Erratum published in *JAMA* 2006;**296**:1355]. http://dx.doi.org/10.1001/jama.296.1.56
17. West R, Zatonski W, Cedzynska M, Lewandowska D, Pazik J, Aveyard P, *et al.* Placebo-controlled trial of cytisine for smoking cessation. *N Engl J Med* 2011;**365**:1193–200. http://dx.doi.org/10.1056/NEJMoa1102035
18. Etter JF, Lukas RJ, Benowitz NL, West R, Dresler CM. Cytisine for smoking cessation: a research agenda. *Drug Alcohol Depend* 2008;**92**:3–8. http://dx.doi.org/10.1016/j.drugalcdep.2007.06.017

19. BNF. 2013. URL: www.medicinescomplete.com/mc/bnf/current/PHP3209-champix.htm#PHP3209-champix (accessed 18 April 2013).
20. Zatonski W, Cedzynska M, Tutka P, West R. An uncontrolled trial of cytisine (Tabex) for smoking cessation. *Tob Control* 2006;**15**:481–4. http://dx.doi.org/10.1136/tc.2006.016097
21. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005;**100**:299–303. http://dx.doi.org/10.1111/j.1360-0443.2004.00995.x
22. Hughes JR. Motivating and helping smokers to stop smoking. *J Gen Intern Med* 2003;**18**:1053–7. http://dx.doi.org/10.1111/j.1525-1497.2003.20640.x
23. West R, Owen L. *Estimates of 52-week Continuous Abstinence Rates Following Selected Smoking Cessation Interventions in England. Version 2*. 2012 URL: www.smokinginengland.info/reports (accessed 4 March 2014).
24. McEwen A, Hajek P, McRobbie H, West R. *Manual of Smoking Cessation*. Oxford: Blackwell Publishing; 2006.
25. West R, May S, West M, Croghan E, McEwan A. Performance of English stop smoking services in first 10 years: analysis of service monitoring data. *BMJ* 2013;**347**:f4921. http://dx.doi.org/10.1136/bmj.f4921
26. Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. *Thorax* 2013;**68**:1037–42. http://dx.doi.org/10.1136/thoraxjnl-2012-203035
27. Leung LK, Patafio FM, Rosser WW. Gastrointestinal adverse effects of varenicline at maintenance dose: a meta-analysis. *BMC Clin Pharmacol* 2011;**11**:15. http://dx.doi.org/10.1186/1472-6904-11-15
28. Tonstad S, Davie, S, Flammer M, Russ C, Hughes J. Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis. *Drug Safe* 2010;**33**:289–301. http://dx.doi.org/10.2165/11319180-000000000-00000
29. Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;**183**:1359–66. http://dx.doi.org/10.1503/cmaj.110218
30. Prochaska JJ. Review: Varenicline for tobacco cessation does not increase CV serious adverse events. *Ann Intern Med* 2012;**157**:21.
31. West CH, Weiss JM. A selective test for antidepressant treatments using rats bred for stress-induced reduction of motor activity in the swim test. *Psychopharmacology* 2005;**182**:9–23. http://dx.doi.org/10.1007/s00213-005-0048-x
32. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. http://dx.doi.org/10.1136/bmj.d5928
33. Lunn D, Thomas A, Best N, Spiegelhalter D. WinBUGS – a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;**10**:325–37.
34. Brooks S, Gelman A. Alternative methods for monitoring convergence of iterative simulations. *J Comput Graph Stat* 1998;**7**:434–45.
35. McCullagh P. *Generalized Linear Models*. London: Chapman & Hall/CRC; 1989.
36. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 2009;**6**:e1000097. http://dx.doi.org/10.1371/journal.pmed.1000097

37. Wong J, Abrishami A, Yang Y, Zaki A, Friedman Z, Selby P, *et al.* A perioperative smoking cessation intervention with varenicline: a double-blind, randomized, placebo-controlled trial. *Anesthesiology* 2012;**117**:755–64. http://dx.doi.org/10.1097/ALN.0b013e3182698b42

38. de Dios MA, Anderson BJ, Stanton C, Audet DA, Stein M. Project Impact: A pharmacotherapy pilot trial investigating the abstinence and treatment adherence of Latino light smokers. *J Subst Abuse Treat* 2012;**43**:322–30. http://dx.doi.org/10.1016/j.jsat.2012.01.004

39. Heydari G, Talischi F, Tafti SF, Masjedi MR. Quitting smoking with varenicline: parallel, randomised efficacy trial in Iran. *Int J Tuberc Lung Dis* 2012;**16**:268–72. http://dx.doi.org/10.5588/ijtld.11.0183

40. Pfizer Inc. *Smoking Cessation Study for Patients with Schizophrenia or Schizoaffective Disorder.* 2011. URL: http://clinicaltrials.gov/ct2/show/NCT00644969?term=NCT00644969&rank=1

41. Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, *et al.* A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2012;**73**:654–60. http://dx.doi.org/10.4088/JCP.11m07522

42. Scharfenberg G, Benndorf S, Kempe G. Cytisine (Tabex) as a pharmaceutical aid in stopping smoking. *Dtsch Gesundheitsw* 1971;**26**:463–5.

43. Vinnikov D, Brimkulov N, Burjubaeva A. A double-blind, randomised, placebo-controlled trial of cytisine for smoking cessation in medium-dependent workers. *J Smok Cessat* 2008;**3**:57–62. http://dx.doi.org/10.1375/jsc.3.1.57

44. Swan G, McClure JB, Jack LM, Zbikowski SM, Javitz HS, Catz SL, *et al.* Behavioural Counselling and varenicline tretament for smoking cessation. *Am J Prev Med* 2010;**38**:482–90.

45. Tonstad S. Smoking cessation efficacy and safety of varenicline, an alpha4beta2 nicotinic receptor partial agonist. *J Cardiovasc Nurs* 2006;**21**:433–6. http://dx.doi.org/10.1097/00005082-200611000-00004

46. Aubin H-J, Bobak A, Britton JR, Oncken C, Billing CB, Gong J, *et al.* Varenicline compared with transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax* 2008;**63**:717–24.

47. Bolliger CT, Issa JS, Posadas VR, Safwat T, Abreu P, Correia EA, *et al.* Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clin Ther* 2011;**33**:465–77. http://dx.doi.org/10.1016/j.clinthera.2011.04.013

48. Gonzales D, Rennard S, Nides M, Oncken C, Azoulay S, Billing CB, *et al.* Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release buprion and placebo for smoking cessation. A randomized trial. *JAMA* 2006;**296**:47–55.

49. Nakamura M, Oshima A, Fujimoto Y, Maruyama N, Ishibashi T, Reeves K. Efficacy and tolerability of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, in a 12-week, randomized, placebo-controlled, dose-response study with 40 week follow-up for smoking cessation in Japanese smokers. *Clin Ther* 2007;**29**:1040–56.

50. Niaura R, Taylor Hays J, Jorenby DE, Leone FT, Pappas JE, Reeves KR, *et al.* The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomised controlled trial. *Curr Med Res Opin* 2008; **24**:1931–41.

51. Nides M, Oncken C, Gonzales D, Rennard S, Watsky EJ, Anziano R. Smoking cessation with varenicline, a selective α4β2 nicotinic receptor partial agonist. *Arch Intern Med* 2006;**166**:1561–77. http://dx.doi.org/10.1001/archinte.166.15.1561

52. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, *et al.* Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006;**166**:1571–7. http://dx.doi.org/10.1001/archinte.166.15.1571

53. Rennard S, Hughes J, Cinciripini PM, Kralikova E, Raupach T, Arteaga C, *et al.* A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res* 2012;**14**:343–50. http://dx.doi.org/10.1093/ntr/ntr220

54. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: A randomized trial. *Circulation* 2010;**121**:221–9. http://dx.doi.org/10.1161/CIRCULATIONAHA.109.869008

55. Smith B, Carson K, Brinn M, Labiszewski N, Peters M, Fitridge R, *et al.* Smoking Termination Opportunity for inPatients (STOP): superiority of a course of varenicline tartrate plus counselling over counselling alone for smoking cessation: a 12-month randomised controlled trial. *Thorax* 2013;**68**,485–6. http://dx.doi.org/10.1136/thoraxjnl-2012-202484

56. Steinberg MB, Randall J, Greenhaus S, Schmelzer AC, Richardson DL, Carson JL. Tobacco dependence treatment for hospitalized smokers: a randomized, controlled, pilot trial using varenicline. *Addict Behav* 2011;**36**:1127–32. http://dx.doi.org/10.1016/j.addbeh.2011.07.002

57. Tashkin DP, Rennard S, Hays J, Ma W, Lawrence D, Lee TC. Effects of varenicline on smoking cessation in patients with mild to moderate COPD. *Chest* 2011;**139**:591–9. http://dx.doi.org/10.1378/chest.10-0865

58. Tsai S-T, Cho H-J, Cheng H-S, Kim C-H, Hsueh, K-C, Billing CB, *et al.* A randomized, placebo-controlled trial of varenicline, a selective α4β2, nicotinic acetylcholine receptor partial agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther* 2007;**29**:1027–39. http://dx.doi.org/10.1016/j.clinthera.2007.06.011

59. Tsukahara H, Noda K, Saku K. A randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers. *Circ J* 2010;**74**:771–8. http://dx.doi.org/10.1253/circj.CJ-09-0803

60. Wang C, Xiao D, Chan KPW, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: A placebo-controlled, randomized study. *Respirology* 2009;**14**:384–92. http://dx.doi.org/10.1111/j.1440-1843.2008.01476.x

61. Williams KE, Reeves KR, Billing CB, Pennington AM, Gong J. A double-blind study evaluating the long-term safety of varenicline for smoking cessation. *Curr Med Res Opin* 2007;**23**:793–801. http://dx.doi.org/10.1185/030079907X182185

62. Annemans L, Nackaerts K, Bartsch, P, Prignot J, Marbaix S. Cost-effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation: a BENESCO Markov cost-effectiveness analysis. *Clin Drug Investig* 2009;**29**:655–65. http://dx.doi.org/10.2165/11317730-000000000-00000

63. Hoogendoorn M, Welsing P, Rutten-van Molken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. *Curr Med Res Opin* 2008;**24**:51–61. http://dx.doi.org/10.1185/030079907X242917

64. Linden K, Jormanainen V, Linna M, Sintonen H, Wilson K, Kotomaki T. Cost-effectiveness of varenicline compared with bupropion and unaided cessation for smoking cessation in a cohort of Finnish adult smokers. *Curr Med Res Opin* 2010;**26**:549–60.

65. Pfizer. *Manufacturers Submission for NICE STA of Varenicline for Smoking Cessation.* Tadworth, Surrey: Pfizer Ltd; 2007.

66. Bae JY, Kim CH, Lee EK. Evaluation of cost-utility of varenicline compared with existing smoking cessation therapies in South Korea. *Value Health* 2009;**12**(Suppl. 3):S70–3. http://dx.doi.org/10.1111/j.1524-4733.2009.00631.x

67. Bolin K, Mork AC, Wilson K. Smoking-cessation therapy using varenicline: the cost-utility of an additional 12-week course of varenicline for the maintenance of smoking abstinence. *J Eval Clin Pract* 2009;**15**:478–85. http://dx.doi.org/10.1111/j.1365-2753.2008.01045.x

68. Bolin K, Wilson K, Benhaddi H, de NE, Marbaix S, Mork AC, *et al.* Cost-effectiveness of varenicline compared with nicotine patches for smoking cessation – results from four European countries. *Eur J Public Health* 2009;**19**:650–4. http://dx.doi.org/10.1093/eurpub/ckp075

69. Bolin K, Mork AC, Willers S, Lindgren B. Varenicline as compared with bupropion in smoking-cessation therapy–cost-utility results for Sweden 2003. *Respir Med* 2008;**102**:699–710. http://dx.doi.org/10.1016/j.rmed.2007.12.018

70. Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline compared with existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. *Pharmacoeconomics* 2008;**26**:497–511.

71. Knight C, Howard P, Baker, CL, Marton JP. The cost-effectiveness of an extended course (12+12 weeks) of varenicline compared with other available smoking cessation strategies in the United States: an extension and update to the BENESCO model. *Value Health* 2010;**13**:209–14. http://dx.doi.org/10.1111/j.1524-4733.2009.00672.x

72. Vemer P, Rutten-van Molken MP. Crossing borders: factors affecting differences in cost-effectiveness of smoking cessation interventions between European countries. *Value Health* 2010;**13**:230–41. http://dx.doi.org/10.1111/j.1524-4733.2009.00612.x

73. European Medicines Agency. *EPAR Summary for the Public, Champix (Varenicline). EMA/266058/2011*. London: European Medicines Agency; 2012.

74. NICE. *Guide to the Methods of Technology Appraisal*. London: NICE; 2008.

75. Office for National Statistics (ONS). *Population Trends*. Newport: ONS; 2006.

76. Office for National Statistics (ONS). *General Household Survey, 2004 Report – Smoking and Drinking.* Newport: ONS; 2004.

77. Government Actuary's Department. *Historic Interim Life Tables; Interim Life Tables 2002-2004*. 2013. URL: www.gad.gov.uk/Demography%20Data/Life%20Tables/historic_interim_life_tables.html (accessed 1 March 2013).

78. Thun MJ, Apicella LF, Henley SJ. Smoking vs other risk factors as the cause of smoking-attributable deaths: confounding in the courtroom. *JAMA* 2000;**284**:706–12. http://dx.doi.org/10.1001/jama.284.6.706

79. Cassino C, Ito K, Bader I, Ciotoli C, Thurston G, Reibman J. Cigarette smoking and ozone-associated emergency department use for asthma by adults in New York City. *Am J Respir Crit Care Med* 1999;**159**:1773–9. http://dx.doi.org/10.1164/ajrccm.159.6.9809042

80. Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, Sykes J, *et al.* Recent trends in physician diagnosed COPD in women and men in the UK. *Thorax* 2000;**55**:789–94. http://dx.doi.org/10.1136/thorax.55.9.789

81. Forman D, Stockton D, Moller H, Quinn M, Babb P, De AR, *et al.* Cancer prevalence in the UK: results from the EUROPREVAL study. *Ann Oncol* 2003;**14**:648–54. http://dx.doi.org/10.1093/annonc/mdg169

82. Office for National Statistics (ONS). *Registrations of Cancer Diagnosed in 2003, England*. Newport: ONS; 2005. Series MB1, 34.

83. Asthma UK. *Where Do We Stand?: Asthma in the UK Today.* London: Asthma UK; 2004.

84. Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, Silverman S. Risk factors and costs associated with an asthma attack. *Thorax* 2000;**55**:19–24. http://dx.doi.org/10.1136/thorax.55.1.19

85. British Heart Foundation. *Coronary Heart Disease Statistics fact sheet*. London: British Heart Foundation; 2006.

86. Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, Neil HA. Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. *Heart* 1998;**80**:40–4.

87. Office for National Statistics. *Health Statistics Quarterly, No.12*. London: The Stationery Office; 2001.

88. Wetter DW, Cofta-Gunn L, Fouladi RT, Cinciripini PM, Sui D, Gritz ER. Late relapse/sustained abstinence among former smokers: a longitudinal study. *Prev Med* 2004;**39**:1156–63. http://dx.doi.org/10.1016/j.ypmed.2004.04.028

89. Hind D, Tappenden P, Peters J, Kenjegalieva K. Varenicline in the management of smoking cessation: a single technology appraisal. *Health Technol Assess* 2009;**13**(Suppl. 2).

90. Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the british household panel survey. *Nicotine Tob Res* 2010;**12**:1228–35. http://dx.doi.org/10.1093/ntr/ntq175

91. Krall EA, Garvey AJ, Garcia RI. Smoking relapse after 2 years of abstinence: findings from the VA Normative Aging Study. *Nicotine Tob Res* 2002;**4**:95–100. http://dx.doi.org/10.1080/14622200110098428

92. Godfrey C, Parrott S, Coleman T, Pound E. The cost-effectiveness of the English smoking treatment services: evidence from practice. *Addiction* 2005;**100**(Suppl. 2):70–83. http://dx.doi.org/10.1111/j.1360-0443.2005.01071.x

93. Yudkin P, Hey K, Roberts S, Welch S, Murphy M, Walton R. Abstinence from smoking eight years after participation in randomised controlled trial of nicotine patch. *BMJ* 2003;**327**:28–9. http://dx.doi.org/10.1136/bmj.327.7405.28

94. Britton M. The burden of COPD in the U.K.: results from the Confronting COPD survey. *Respir Med* 2003;**97**(Suppl. C):S71–9. http://dx.doi.org/10.1016/S0954-6111(03)80027-6

95. Flack S, Taylor M, Trueman P. *Cost-effectiveness of Interventions for Smoking Cessation*. York: York Health Economics Consortium, University of York; 2007.

96. Sanderson H, Spiro S. Cancer of the lung. In: Stevens A, Raftery J, Mant J, Simpson S, editors. *Health Care Needs Assessment: the Epidemiologically Based Needs Assessment Reviews*. 2nd edn. Abingdon: Radcliffe Publishing; 2004. pp. 503–48.

97. McMurray J, Hart W, Rhodes G. An evaluation of the cost of heart failure to the National Health Service in the UK. *J Med Econ* 1993;**6**:99–110.

98. Simpson EL, Stevenson MD, Scope A, Poku A, Minton J, Evans P. *Echocardiography in Newly Diagnosed Atrial Fibrillation Patients: A Systematic Review and Economic Evaluation*. Sheffield: School of Health and Related Research (ScHARR) Technology Assessment Group, The University of Sheffield; 2011.

99. Rivero-Arias O, Ouellet M, Gray A, Wolstenholme J, Rothwell PM, Luengo-Fernandez R. Mapping the modified Rankin scale (mRS) measurement into the generic EuroQol (EQ-5D) health outcome. *Med Decis Making* 2010;**30**:341–54. http://dx.doi.org/10.1177/0272989X09349961

100. Curtis L. *Unit Costs of Health and Social Care*. Canterbury: Personal Social Services Research Unit, The University of Kent; 2012.

101. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation (Handbooks for Health Economic Evaluation)*. Oxford: Oxford University Press; 2006.

102. Stapleton JA, West RA. *Direct Method and ICER Tables for the Estimation of the Cost-Effectiveness of Smoking Cessation Interventions in General Populations: Application to a New Cytisine Trial and Other Examples*. Oxford: Oxford University Press; 2012.

103. *Tabex Tablets* 2013 URL: www.tabextablets.co.uk/ (accessed 18 March 2013).

104. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health* 2010;**13**:509–18. http://dx.doi.org/10.1111/j.1524-4733.2010.00700.x

105. Trippoli S, Vaiani M, Lucioni C, Messori A. Quality of life and utility in patients with non-small cell lung cancer. Quality-of-life Study Group of the Master 2 Project in Pharmacoeconomics. *Pharmacoeconomics* 2001;**19**:855–63.

106. Szende A, Svensson K, Stahl E, Meszaros A, Berta GY. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level. *Pharmacoeconomics* 2004;**22**:537–47. http://dx.doi.org/10.2165/00019053-200422080-00005

107. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. *Stroke* 1998;**29**:1083–91. http://dx.doi.org/10.1161/01.STR.29.6.1083

108. Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics* 2003;**21**:191–200. http://dx.doi.org/10.2165/00019053-200321030-00004

109. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost-effectiveness of treatment interventions for chronic obstructive pulmonary disease. *Pharmacoeconomics* 2005;**23**:619–37. http://dx.doi.org/10.2165/00019053-200523060-00008

110. Hay JW, Sterling KL. Cost-effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. *Pharmacoeconomics* 2005;**23**:133–41. http://dx.doi.org/10.2165/00019053-200523020-00005

111. Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996;**5**:513–24. http://dx.doi.org/10.1002/(SICI)1099-1050(199611)5:6%3C513::AID-HEC237%3E3.0.CO;2-9

112. Felli JC, Hazen GB. Sensitivity analysis and the expected value of perfect information. *Med Decis Making* 1998;**18**:95–109. http://dx.doi.org/10.1177/0272989X9801800117

113. Ades AE, Lu G, Claxton K. Expected value of sample information calculations in medical decision modeling. *Med Decis Making* 2004;**24**:207–27. http://dx.doi.org/10.1177/0272989X04263162

114. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ* 2001;**10**:779–87. http://dx.doi.org/10.1002/hec.635

115. Robinson S, Harris H. *Smoking and Drinking Among Adults 2009, A Report on the 2009 General Lifestyle Survey*. Newport: Office for National Statistics; 2011.

116. Brown J, Michie S, West R. The case of Stop Smoking Services in England. *Br J Psychiatry* 2013;**202**:74–6.

117. Shiffman S, Brockwell SE, Pillitteri JL, Gitchell JG. Use of smoking-cessation treatments in the United States. *Am J Prev Med* 2008;**34**:102–11. http://dx.doi.org/10.1016/j.amepre.2007.09.033

118. West R, DiMarino ME, Gitchell J, McNeill A. Impact of UK policy initiatives on use of medicines to aid smoking cessation. *Tob Control* 2005;**14**:166–71. http://dx.doi.org/10.1136/tc.2004.008649

119. Vogt F, Hall S, Marteau TM. Understanding why smokers do not want to use nicotine dependence medications to stop smoking: qualitative and quantitative studies. *Nicotine Tob Res* 2008;**10**:1405–13. http://dx.doi.org/10.1080/14622200802239280

120. Stevenson MD, Oakley J, Lloyd Jones M, Brennan A, Compston J, McCloskey E, *et al.* The cost-effectiveness of an RCT to establish whether 5 or 10 years of bisphosphonate treatment is the better duration for women with a prior fracture. *Med Decis Making* 2009;**29**:678–89. http://dx.doi.org/10.1177/0272989X09336077

121. Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al.* The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation. *Health Technol Assess* 2002;**6**(16).

122. Heitjan DF, Asch DA, Ray R, Rukstalis M, Patterson F, Lerman C. Cost-effectiveness of pharmacogenetic testing to tailor smoking-cessation treatment. *Pharmacogenomics J* 2008;**8**:391–9. http://dx.doi.org/10.1038/sj.tpj.6500492

123. Xenakis JG, Kinter ET, Ishak KJ, Ward AJ, Marton JP, Willke RJ, *et al.* A discrete-event simulation of smoking-cessation strategies based on varenicline pivotal trial data. *Pharmacoeconomics* 2011;**29**:497–510. http://dx.doi.org/10.2165/11589230-000000000-00000

124. Etter JF. Cytisine for smoking cessation: a literature review and a meta-analysis. *Arch Intern Med* 2006;**166**:1553–9. http://dx.doi.org/10.1001/archinte.166.15.1553

125. Gunnell D, Irvine D, Wise L, Davies C, Martin RM. Varenicline and suicidal behaviour: a cohort study based on data from the General Practice Research Database. *BMJ* 2009;**339**:b3805. http://dx.doi.org/10.1136/bmj.b3805

126. Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ* 2012;**344**:e2856. http://dx.doi.org/10.1136/bmj.e2856

Appendix 1 Literature search strategies

MEDLINE search strategies

Cahill search

1. ('cytisine' or 'tabex' or 'varenicline' or 'nicotine receptor partial agonist').tw.

Champix or Chantix search

1. (Champix or Chantix).tw.

Clinical effectiveness

To find papers on the clinical effectiveness of cytisine or varenicline the above searches were combined with filters designed to retrieve RCTs and systematic reviews.

Randomised controlled trials filter

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized controlled trials/
4. random allocation/
5. double blind method/
6. single blind method/
7. clinical trial.pt.
8. exp Clinical Trial/
9. (clin$ adj25 trial$).ti,ab.
10. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
11. placebos/
12. placebos.ti,ab.
13. random.ti,ab.
14. research design/
15. or/1-14

Systematic reviews filter

1. Meta analysis/
2. Meta analys$.tw.
3. Metaanaly$.tw.
4. exp Literature review/
5. (systematic adj (review or overview)).tw.
6. or/1-5
7. Commentary.pt.
8. Letter.pt.
9. Editorial.pt.
10. Animals/
11. or/7-10
12. 6 not 11

Cost-effectiveness

The searches were also combined with an economics filter to find papers on the cost-effectiveness of cystisine and varenicline.

MEDLINE economics filter

1. Economics/
2. "costs and cost analysis"/
3. Cost allocation/
4. Cost-benefit analysis/
5. Cost control/
6. cost savings/
7. Cost of illness/
8. Cost sharing/
9. "deductibles and coinsurance"/
10. Health care costs/
11. Direct service costs/
12. Drug costs/
13. Employer health costs/
14. Hospital costs/
15. Health expenditures/
16. Capital expenditures/
17. Value of life/
18. exp economics, hospital/
19. exp economics, medical/
20. Economics, nursing/
21. Economics, pharmaceutical/
22. exp "fees and charges"/
23. exp budgets/
24. (low adj cost).mp.
25. (high adj cost).mp.
26. (health?care adj cost$).mp.
27. (fiscal or funding or financial or finance).tw.
28. (cost adj estimate$).mp.
29. (cost adj variable).mp.
30. (unit adj cost$).mp.
31. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
32. or/1-31

Appendix 2 Quality assessment

Tables 35–37 detail the quality assessment of newly included studies using the Cochrane risk of bias tool.[32]

TABLE 35 Quality assessment: Wong 2012[37]

Risk of bias	Author's judgment	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated stratified randomisation with blocks of 40 based on smokers stage of change
Allocation concealment (selection bias)	Low risk	Patient's assignments were placed in sequentially numbered, opaque sealed envelopes kept by independent researcher
Blinding (performance bias and detection bias)	Low risk	Patients, health-care personnel and research staff blinded to the randomisation throughout the study
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis conducted
Selective reporting (reporting bias)	Low risk	Primary outcomes (efficacy) reported

TABLE 36 Quality assessment: de Dios 2012[38]

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	Primary outcomes (efficacy) reported

TABLE 37 Quality assessment: Heydari 2012[39]

Risk of bias	Author's judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised trial, but method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Low risk	Study personnel and participants were blinded to treatment condition
Incomplete outcome data (attrition bias)	Low risk	Observations missing at follow-up were treated as smokers
Selective reporting (reporting bias)	Low risk	Primary outcomes (efficacy) reported

Appendix 3 Table of excluded studies with rationale

Paper	Reasons for exclusion
Brown University Varenicline effects in heavy-drinking smokers. *Brown Univ Psychopharmacol Update* 2011;**22**:4	Commentary/summary
Allan GM, Ivers N, Els C. Pharmacotherapy for smoking. *Can Fam Physician* 2011;**57**:47	Commentary/summary
Ashare RL, McKee, SA. Effects of varenicline and bupropion on cognitive processes among nicotine-deprived smokers. *Exp Clin Psychopharmacol* 2012;**20**:63–70	Not smoking cessation
Catz SL, Jack LM, McClure JB, Javitz HS, Deprey M, Zbikowski SM, *et al*. Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine Tob Res* 2011;**13**:361–8	Data are from Swan[44]
Christalla P, Dewenter M, El-Armouche A. Effectiveness and safety of varenicline for smoking cessation. *Dtsch Med Wochenschr* 2012;**137**:940–4	No data
Cui Q, Robinson L, Elston D, Smaill F, Cohen J, Quan C, *et al*. Safety and tolerability of varenicline tartrate Champix®/Chantix® for smoking cessation in HIV-infected subjects: a pilot open-label study. *AIDS Patient Care STDS* 2012;**26**:12–19	Not a RCT
Dutra SJ, Stoeckel LE, Carlini SV, Pizzagalli, DA, Evins AE. Varenicline as a smoking cessation aid in schizophrenia patients: Effects on smoking behavior and reward sensitivity. *Biol Psychiatry* 2011;**69**(Suppl. 9):280S	Not a RCT
Ferketich AK, Otterson GA, King M, Hall N, Browning KK, Wewers ME. A pilot test of a combined tobacco dependence treatment and lung cancer screening program. *Lung Cancer* 2012;**76**:211–15	No comparison of drugs
Fucito LM, Toll BA, Wu R, Romano DM, Tek E, O'Malley SS. A preliminary investigation of varenicline for heavy drinking smokers. *Psychopharmacology* 2011;**215**:655–63	< 6 months' follow–up of abstinence
Garrison GD. Varenicline for 4 weeks prior to target quit date reduces prequit date smoking and increases 12-week abstinence. *Evid Based Med* 2012;**17**	Comment/summary of Hajek
Grassi MC, Enea D, Ferketich AK, Lu B, Pasquariello S, Nencini P. Effectiveness of varenicline for smoking cessation: A 1-year follow-up study. *J Subst Abuse Treat* 2011;**41**:64–70	Not a RCT – participants chose whether or not to have varenicline
Hajek P, McRobbie HJ, Myers KE, Stapleton J, Dhanji AR. Use of varenicline for 4 weeks before quitting smoking: decrease in ad lib smoking and increase in smoking cessation rates. *Arch Intern Med* 2011;**171**:770–7	Studies different varenicline preloading. < 6 months' follow-up of abstinence
Hawk J, Ashare RL, Lohnes SF, Schlienz NJ, Rhodes JD, Tiffany ST, *et al*. The effects of extended pre-quit varenicline treatment on smoking behavior and short-term abstinence. *Clin Pharmacol Ther* 2012;**91**:172–80	< 6 months' follow-up data

Paper	Reasons for exclusion
Hays JT, Croghan IT, Baker CL, Cappelleri JC, Bushmakin, AG. Changes in health-related quality of life with smoking cessation treatment. *Eur J Public Health* 2012;**22**:224–9	Data are from Jorenby[16] and Gonzales[48]
Javitz HS, Swan GE, Lerman C. The dynamics of the urge-to-smoke following smoking cessation via pharmacotherapy. *Addiction* 2011;**106**:1835–45	Data are from Swan[44]
Jimenez Ruiz, CA Pinedo AR, Guerrero AC, Uibarri MM, Fernandez MC, Gonzalez GL. Characteristics of COPD smokers and effectiveness and safety of smoking cessation medications. *Nicotine Tob Res* 2012;**14**:1035–9	Not a RCT
King DP, Paciga S, Pickering, E, Benowitz NL, Bierut LJ, Conti DV, *et al*. Smoking cessation pharmacogenetics: analysis of varenicline and bupropion in placebo-controlled clinical trials. *Neuropsychopharmacology* 2012;**37**:641–50	Data is from Gonzales,[48] Jorenby[16] and Oncken[52]
Kotseva K, Jennings C, De Bacquer D, Hoes A, De Velasco J, Brusaferro S, *et al*. Euroaction Plus: A Randomised Controlled Trial on Preventive Cardiology Programme Plus Intensive Smoking Cessation with Varenicline for Vascular and High CVD Risk Smokers and Their Partners-Principal Results. *Heart* 2012; **98**:A80–1	Unclear whether or not the goal was smoking cessation. Varenicline was optional
Moon KT. Does adjusting varenicline dosing enhance smoking cessation rates? *Am Fam Physician* 2012;**85**	No new study/commentary
Nollen NL, Cox LS, Nazir N, Ellerbeck EF, Owen A, Pankey S, *et al*. A pilot clinical trial of varenicline for smoking cessation in black smokers. *Nicotine Tob Res* 2011;**13**:868–73	All groups varenicline plus different methods of counselling. < 6 months' follow-up of abstinence
Pachas GN, Cather C, Pratt SI, Hoeppner B, Nino J, Carlini SV, *et al*. Varenicline for smoking cessation in schizophrenia: safety and effectiveness in a 12-week open-label trial. *J Dual Diagn* 2012;**8**:117–25	Not a RCT
Selby P, Brosky G, Oh PI, Raymond V, Ranger S. How pragmatic or explanatory is the randomized, controlled trial? The application and enhancement of the PRECIS tool to the evaluation of a smoking cessation trial. *BMC Med Res Methodol* 2012;**12**:101	No quit data
Shim JC, Jung D, Oh M, Kong B, Ha T, Cho D, *et al*. Varenicline treatment for smoking cessation in people with schizophrenia: A randomized double-blind placebo-controlled trial. *Schizophr Bull* 2011;**37**:320–1	Not smoking cessation
Sofuoglu M, Duffey D, Mooney ME. Varenicline increases smoking abstinence at 6 months to a year compared with placebo or bupropion; nausea is the most commonly reported adverse effect. *Evid Based Med* 2011;**16**:113–14	Commentary agree
Solano RS, Vaquero LP, Solano Garcia-Tenorio R, Lopez RT, Jimenez Ruiz, CA, de Granda Orive JI Treatment of smoking habit in chronic obstructive pulmonary disease. *Revista De Patologia Respiratoria* 2012;**15**:123–8	Paper unavailable
Weiner E, Buchholz A, Coffay A, Liu F, McMahon RP, Buchanan RW, *et al*. Varenicline for smoking cessation in people with schizophrenia: a double blind randomized pilot study. *Schizophr Res* 2011;**129**:94–5	Letter with new data, but reported < 6 months' follow-up of abstinence

Paper	Reasons for exclusion
Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, *et al*. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2012;**73**:654–60	Pfizer study
Wilson K, Hettle R, Marbaix S, Diaz CS, Ines M, Santoni L, *et al*. An economic evaluation based on a randomized placebo-controlled trial of varenicline in smokers with cardiovascular disease: results for Belgium, Spain, Portugal, and Italy. *Eur J Prev Cardiol* 2012;**19**:1173–83	Economic model – not a RCT
Zhou W, Wei X, Ke H. Psychiatric adverse reactions in a prospective, randomized clinical trial of varenicline for smoking cessation in patients with COPD. *Respirology* 2011;**16**:11	< 6 months' follow-up

Appendix 4 Statistical methods used to analyse continuous abstinence and adverse event data

The analyses assumed that the studies are exchangeable in the sense that the investigators would be willing to assign each of the smokers in the studies to any of the interventions. A random-effects network meta-analysis was conducted with the reference treatment being defined as placebo.

The studies presented data in terms of the number of smokers who had an event (e.g. quit smoking when the outcome measure is continuous abstinence). Define r_{ik} as the number of events out of the total number of smokers in each arm for arm k of study i with study duration f_i. We assume that the data follow a binomial likelihood such that:

$$r_{ik} \sim \text{Binomial}(p_{ik}, n_{ik}), \tag{1}$$

where p_{ik} represents the probability of an event in arm k of study i after follow-up time f_i.

To account for different study durations, it was assumed that the time until an event occurs in arm k of study i, T_{ik}, is from an exponential distribution such that:

$$T_{ik} \sim \text{Exp}(\lambda_{ik}). \tag{2}$$

Therefore, the probability that there are no events by time f_i in arm k of study i (i.e. the survivor function of an exponential distribution) is:

$$S(f_i) = P(T_{ik} > f_i) = \exp(-\lambda_{ik} f_i). \tag{3}$$

Hence, for each study i, p_{ik}, the probability of an event in arm k of study i after study duration time f_i, can be written as:

$$p_{ik} = 1 - P(T_{ik} > f_i) = 1 - \exp(-\lambda_{ik} f_i), \tag{4}$$

which is time dependent. Since p_{ik} is a non-linear function of $\log(\lambda_{ik})$, the complementary log-log link function was used to model p_{ik}.

$$\begin{aligned} \theta_{ik} &= \text{cloglog}(\text{p}_{ik}) \\ &= \log(\text{fi}) + \mu_i + \delta_{i,bk} \text{I}_{\{k \neq \text{i}\}}, \end{aligned} \tag{5}$$

where $\delta_{i,bk}$ are the treatment effects of interest which are the log-hazard ratios relative to the baseline intervention in each study and μ_i are the study-specific baseline effects in a study i.

We treat μ_i as nuisance parameters with fixed (but known) study effects and given them weak prior distribution such that:

$$\mu_i \sim N(0,100). \tag{6}$$

We assume a random treatment effects model in which δ_{ik} are assumed to come from a common population distribution such that:

$$\begin{pmatrix} \delta_{i,12} \\ \vdots \\ \delta_{i,1k} \end{pmatrix} \sim MVN\left(\begin{pmatrix} d_{12} \\ \vdots \\ d_{1k} \end{pmatrix}, \begin{pmatrix} \sigma^2 & \sigma^2/2 & \dots & \sigma^2/2 \\ \vdots & \vdots & \ddots & \vdots \\ \sigma^2/2 & \sigma^2/2 & \cdots & \sigma^2 \end{pmatrix} \right). \tag{7}$$

The treatment effects $d_{12}, \ldots, d_{1k}$ were also given a weak prior distribution $N(0,100)$. The model is completed by giving the between-study standard deviation a uniform prior distribution.

$$\sigma \sim U(0,2). \tag{8}$$

In the case of SAEs, there were several trials with low or zero observed events. Posterior distributions based on a $N(0,100)$ prior distribution for population log-hazard ratios included implausible values for varenicline 0.3 mg q.d. and varenicline 1.0 mg q.d. Hence, a more informative $N(0,10)$ prior distribution was used for the log-hazard ratio for these two treatments.

Appendix 5 Data used in analyses

TABLE 38 Summary of the trials included in the base-case network meta-analysis on continuous abstinence data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = cytisine 1.5 mg, 4 = varenicline 0.3 mg q.d., 5 = varenicline 1.0 mg q.d., 6 = varenicline 0.5 mg b.i.d., 7 = varenicline 1.0 mg b.i.d., 8 = bupropion hydrochloride 150 mg b.i.d.

Author, year	Study duration (years)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Vinnikov 2008[43]	0.50	1	3	–	–	–	1	9	–	–	–	97	100	–	–	–
West 2011[17]	1.00	1	3	–	–	–	9	31	–	–	–	370	370	–	–	–
Bolliger 2011[47]	0.46	1	7	–	–	–	26	157	–	–	–	199	394	–	–	–
Niaura 2008[50]	1.00	1	7	–	–	–	12	35	–	–	–	160	160	–	–	–
Rennard 2012[53]	0.46	1	7	–	–	–	21	171	–	–	–	166	493	–	–	–
Rigotti 2010[54]	1.00	1	7	–	–	–	26	68	–	–	–	359	355	–	–	–
Tashkin 2011[57]	1.00	1	7	–	–	–	14	47	–	–	–	254	250	–	–	–
Tsai 2007[58]	0.46	1	7	–	–	–	27	59	–	–	–	124	126	–	–	–
Smith 2013[55]	1.00	1	7	–	–	–	42	61	–	–	–	196	196	–	–	–
Aubin 2008[46]	1.00	2	7	–	–	–	75	98	–	–	–	379	378	–	–	–
Wang 2009[60]	0.46	1	7	–	–	–	42	63	–	–	–	168	165	–	–	–
Gonzales 2006[48]	1.00	1	7	8	–	–	29	77	53	–	–	344	352	329	–	–
Jorenby 2006[16]	1.00	1	7	8	–	–	35	79	50	–	–	341	344	342	–	–
Oncken 2006[52]	1.00	1	6	7	–	–	5	48	58	–	–	129	259	259	–	–
Nakamura 2007[49]	1.00	1	6	7	–	–	35	51	56	–	–	154	156	156	–	–
Nides 2006[51]	1.00	1	4	5	7	8	6	10	7	18	8	127	128	128	127	128

TABLE 39 Summary of the trials included in the base-case network meta-analysis on abnormal dreams data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = varenicline 0.3 mg q.d., 4 = varenicline 1.0 mg q.d., 5 = varenicline 0.5 mg b.i.d., 6 = varenicline 1.0 mg b.i.d., 7 = bupropion hydrochloride 150 mg b.i.d., 8 = varenicline 1.0 mg b.i.d. for 52 weeks

Author, year	Study duration (weeks)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Pfizer 2011[40]/ Williams 2012[41]	24	1	6	–	–	–	4	6	–	–	–	43	84	–	–	–
Rennard 2012[53]	24	1	6	–	–	–	5	61	–	–	–	165	486	–	–	–
Rigotti 2010[54]	52	1	6	–	–	–	6	28	–	–	–	350	353	–	–	–
Tashkin 2011[57]	52	1	6	–	–	–	7	27	–	–	–	251	248	–	–	–
Tsai 2007[58]	24	1	6	–	–	–	1	7	–	–	–	124	126	–	–	–
Williams 2007[61]	52	1	8	–	–	–	9	57	–	–	–	126	251	–	–	–
Smith 2013[55]	52	1	6	–	–	–	2	12	–	–	–	196	196	–	–	–
Aubin 2008[46]	52	2	6	–	–	–	31	44	–	–	–	370	376	–	–	–
Wong 2012[37]	52	1	6	–	–	–	0	3	–	–	–	135	151	–	–	–
Heydari 2012[39]	52	1	2	6	–	–	0	0	3	–	–	91	92	89	–	–
Gonzales 2006[48]	52	1	6	7	–	–	19	36	18	–	–	344	349	329	–	–
Jorenby 2006[16]	52	1	6	7	–	–	12	45	20	–	–	340	343	340	–	–
Oncken 2006[52]	52	1	5	6	–	–	6	36	46	–	–	121	253	253	–	–
Nides 2006[51]	52	1	3	4	6	7	10	10	14	19	15	123	126	126	125	126

TABLE 40 Summary of the trials included in the base-case network meta-analysis on headache data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = cytisine 1.5 mg, 4 = varenicline 0.3 mg q.d., 5 = varenicline 1.0 mg q.d., 6 = varenicline 0.25 mg b.i.d., 7 = varenicline 0.5 mg b.i.d., 8 = varenicline 1.0 mg b.i.d., 9 = bupropion hydrochloride 150 mg b.i.d.

Author, year	Study duration (weeks)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Vinnikov 2008[43]	26	1	3	–	–	–	1	1	–	–	–	86	85	–	–	–
West 2011[17]	52	1	3	–	–	–	8	7	–	–	–	370	370	–	–	–
Bolliger 2011[47]	24	1	8	–	–	–	24	64	–	–	–	198	390	–	–	–
Niaura 2008[50]	52	1	8	–	–	–	20	25	–	–	–	155	157	–	–	–
Pfizer 2011[40]/ Williams 2012[41]	24	1	8	–	–	–	8	9	–	–	–	43	84	–	–	–
Rennard 2012[53]	24	1	8	–	–	–	20	55	–	–	–	165	486	–	–	–
Rigotti 2010[54]	52	1	8	–	–	–	39	45	–	–	–	350	353	–	–	–
Tashkin 2011[57]	52	1	8	–	–	–	20	20	–	–	–	251	248	–	–	–
Wang 2009[60]	24	1	8	–	–	–	7	9	–	–	–	168	165	–	–	–
Smith 2013[55]	52	1	8	–	–	–	3	12	–	–	–	196	196	–	–	–
Aubin 2008[46]	52	2	8	–	–	–	36	72	–	–	–	370	376	–	–	–
Wong 2012[37]	52	1	8	–	–	–	0	5	–	–	–	135	151	–	–	–
Gonzales 2006[48]	52	1	8	9	–	–	42	54	47	–	–	344	349	329	–	–
Jorenby 2006[16]	52	1	8	9	–	–	43	44	27	–	–	340	343	340	–	–
Oncken 2006[52]	52	1	7	8	–	–	21	59	59	–	–	121	253	253	–	–
Nakamura 2007[49]	52	1	6	7	8	–	4	16	18	16	–	154	153	155	156	–
Nides 2006[51]	52	1	4	5	8	9	33	34	34	30	38	123	126	126	125	126

TABLE 41 Summary of the trials included in the base-case network meta-analysis on insomnia data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = varenicline 0.3 mg q.d., 4 = varenicline 1.0 mg q.d., 5 = varenicline 0.5 mg b.i.d., 6 = varenicline 1.0 mg b.i.d., 7 = bupropion hydrochloride 150 mg b.i.d., 8 = varenicline 1.0 mg b.i.d. for 52 weeks

Author, year	Study duration (weeks)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Bolliger 2011[47]	24	1	6	–	–	–	13	50	–	–	–	198	390	–	–	–
Niaura 2008[50]	52	1	6	–	–	–	17	34	–	–	–	155	157	–	–	–
Pfizer 2011[40]/ Williams 2012[41]	24	1	6	–	–	–	2	8	–	–	–	43	84	–	–	–
Rennard 2012[53]	24	1	6	–	–	–	6	43	–	–	–	165	486	–	–	–
Rigotti 2010[54]	52	1	6	–	–	–	23	42	–	–	–	350	353	–	–	–
Tashkin 2011[57]	52	1	6	–	–	–	15	24	–	–	–	251	248	–	–	–
Tsai 2007[58]	24	1	6	–	–	–	17	19	–	–	–	124	126	–	–	–
Wang 2009[60]	24	1	6	–	–	–	5	10	–	–	–	168	165	–	–	–
Williams 2007[61]	52	1	8	–	–	–	12	48	–	–	–	126	251	–	–	–
Smith 2013[55]	52	1	6	–	–	–	4	10	–	–	–	196	196	–	–	–
Aubin 2008[46]	52	2	6	–	–	–	71	80	–	–	–	370	376	–	–	–
Tsukahara 2010[59]	24	2	6	–	–	–	2	6	–	–	–	14	14	–	–	–
Gonzales 2006[48]	52	1	6	7	–	–	44	49	72	–	–	344	349	329	–	–
Jorenby 2006[16]	52	1	6	7	–	–	42	49	72	–	–	340	343	340	–	–
Oncken 2006[52]	52	1	5	6	–	–	14	69	75	–	–	121	253	253	–	–
Nides 2006[51]	52	1	3	4	6	7	27	25	34	44	57	123	126	126	125	126

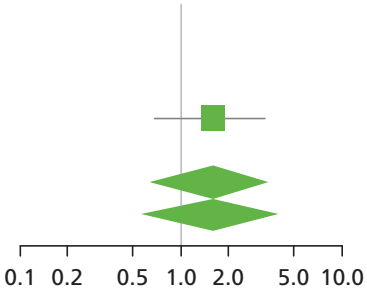
TABLE 42 Summary of the trials included in the base-case network meta-analysis on nausea data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = cytisine 1.5 mg, 4 = varenicline 0.3 mg q.d., 5 = varenicline 1.0 mg q.d., 6 = varenicline 0.25 mg b.i.d., 7 = varenicline 0.5 mg b.i.d., 8 = varenicline 1.0 mg b.i.d., 9 = bupropion hydrochloride 150 mg b.i.d., 10 = varenicline 1.0 mg b.i.d. for 52 weeks

Author, year	Study duration (weeks)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Vinnikov 2008[43]	26	1	3	–	–	–	1	2	–	–	–	86	85	–	–	–
West 2011[17]	52	1	3	–	–	–	14	10	–	–	–	370	370	–	–	–
Bolliger 2011[47]	24	1	8	–	–	–	16	103	–	–	–	198	390	–	–	–
Niaura 2008[50]	52	1	8	–	–	–	8	21	–	–	–	155	157	–	–	–
Pfizer 2011[40]/ Williams 2012[41]	24	1	8	–	–	–	6	20	–	–	–	43	84	–	–	–
Rennard 2012[53]	24	1	8	–	–	–	15	142	–	–	–	165	486	–	–	–
Rigotti 2010[54]	52	1	8	–	–	–	30	104	–	–	–	350	353	–	–	–
Steinberg 2011[56]	24	1	8	–	–	–	2	10	–	–	–	37	38	–	–	–
Tashkin 2011[57]	52	1	8	–	–	–	20	67	–	–	–	251	248	–	–	–
Tsai 2007[58]	24	1	8	–	–	–	14	55	–	–	–	124	126	–	–	–
Wang 2009[60]	24	1	8	–	–	–	20	48	–	–	–	168	165	–	–	–
Williams 2007[61]	52	1	10	–	–	–	10	101	–	–	–	126	251	–	–	–
Smith 2013[55]	52	1	8	–	–	–	3	32	–	–	–	196	196	–	–	–
Aubin 2008[46]	52	2	8	–	–	–	36	140	–	–	–	370	376	–	–	–
Tsukahara 2010[59]	24	2	8	–	–	–	0	4	–	–	–	14	14	–	–	–
Wong 2012[37]	52	1	8	–	–	–	5	20	–	–	–	135	151	–	–	–
Gonzales 2006[48]	52	1	8	9	–	–	29	98	41	–	–	344	349	329	–	–
Jorenby 2006[16]	52	1	8	9	–	–	33	101	25	–	–	340	343	340	–	–
Oncken 2006[52]	52	1	7	8	–	–	18	49	97	–	–	121	253	253	–	–
Heydari 2012[39]	52	1	8	2	–	–	0	8	0	–	–	91	89	92	–	–
Nakamura 2007[49]	52	1	6	7	8	–	12	11	15	38	–	154	153	155	156	–
Nides 2006[51]	52	1	4	5	8	9	23	22	47	65	27	123	126	126	125	126

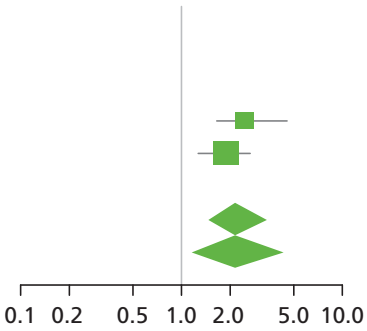
TABLE 43 Summary of the trials included in the base-case network meta-analysis on SAEs data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = cytisine 1.5 mg, 4 = varenicline 0.3 mg q.d., 5 = varenicline 1.0 mg q.d., 6 = varenicline 0.25 mg b.i.d., 7 = varenicline 0.5 mg b.i.d., 8 = varenicline 1.0 mg b.i.d., 9 = bupropion hydrochloride 150 mg b.i.d., 10 = varenicline 1.0 mg b.i.d. for 52 weeks

Author, year	Study duration (weeks)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
West 2011[17]	52	1	3	–	–	–	3	4	–	–	–	370	370	–	–	–
Bolliger 2011[47]	24	1	8	–	–	–	2	11	–	–	–	199	394	–	–	–
Niaura 2008[50]	52	1	8	–	–	–	0	3	–	–	–	160	160	–	–	–
Oncken 2006[52]	52	1	7	–	–	–	2	6	–	–	–	129	253	–	–	–
Pfizer 2011[40]/ Williams 2012[41]	24	1	8	–	–	–	4	5	–	–	–	43	85	–	–	–
Rennard 2012[53]	24	1	8	–	–	–	1	6	–	–	–	166	493	–	–	–
Rigotti 2010[54]	52	1	8	–	–	–	21	23	–	–	–	354	353	–	–	–
Steinberg 2011[56]	24	1	8	–	–	–	5	6	–	–	–	39	40	–	–	–
Tashkin 2011[57]	52	1	8	–	–	–	15	12	–	–	–	253	248	–	–	–
Tsai 2007[58]	24	1	8	–	–	–	3	3	–	–	–	124	126	–	–	–
Wang 2009[60]	24	1	8	–	–	–	2	0	–	–	–	168	165	–	–	–
Williams 2007[61]	52	1	10	–	–	–	3	15	–	–	–	126	251	–	–	–
Smith 2013[55]	52	1	8	–	–	–	3	6	–	–	–	117	119	–	–	–
Aubin 2008[46]	52	2	8	–	–	–	8	2	–	–	–	370	376	–	–	–
Gonzales 2006[48]	52	1	8	9	–	–	9	4	3	–	–	344	349	329	–	–
Jorenby 2006[16]	52	1	8	9	–	–	6	8	9	–	–	341	344	340	–	–
Nakamura 2007[49]	52	1	6	7	8	–	3	5	2	3	–	154	153	155	156	–
Nides 2006[51]	52	1	4	5	8	9	0	0	0	1	4	127	126	126	125	126

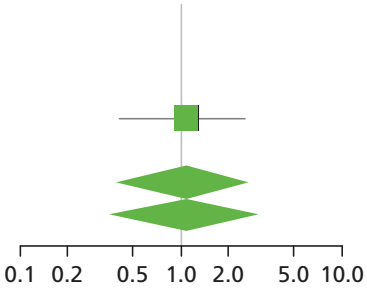
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.3 mg q.d. vs. placebo					
Nides 2006[51]	10	128	6	127	1.58 (0.69 to 3.35)
Pooled effect					**1.58 (0.65 to 3.53)**
Predictive effect					**1.58 (0.57 to 4.05)**



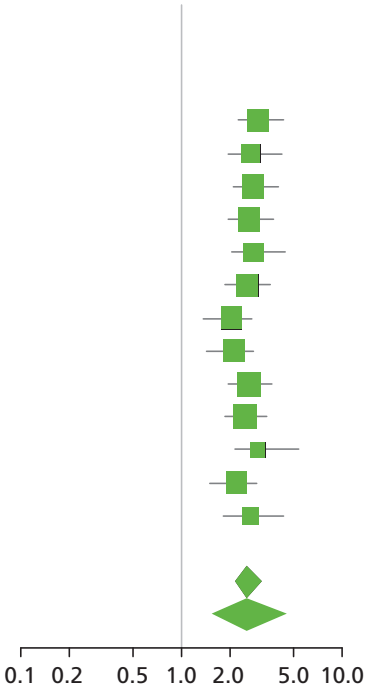
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. placebo					
Oncken 2006[52]	48	259	5	129	2.47 (1.64 to 4.51)
Nakamura 2007[49]	51	156	35	154	1.88 (1.27 to 2.67)
Pooled effect					**2.16 (1.45 to 3.38)**
Predictive effect					**2.17 (1.16 to 4.33)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg q.d. vs. placebo					
Nides 2006[51]	7	128	6	127	1.08 (0.41 to 2.53)
Pooled effect					**1.08 (0.40 to 2.63)**
Predictive effect					**1.08 (0.36 to 3.03)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. placebo					
Bolliger 2011[47]	155	394	26	199	2.96 (2.25 to 4.35)
Niaura 2008[50]	35	160	12	160	2.69 (1.93 to 4.18)
Rennard 2012[53]	171	493	21	166	2.76 (2.10 to 4.04)
Rigotti 2010[54]	68	353	26	354	2.65 (1.97 to 3.74)
Tashkin 2011[57]	46	248	14	253	2.80 (2.07 to 4.46)
Tsai 2007[58]	59	126	27	124	2.56 (1.88 to 3.60)
Smith 2013[55]	61	196	42	196	2.05 (1.37 to 2.74)
Wang 2009[60]	63	165	42	168	2.13 (1.45 to 2.82)
Gonzales 2006[48]	77	352	29	344	2.63 (1.97 to 3.65)
Jorenby 2006[16]	79	344	35	341	2.50 (1.85 to 3.38)
Oncken 2006[52]	58	259	5	129	2.99 (2.14 to 5.30)
Nakamura 2007[49]	56	155	35	154	2.21 (1.49 to 2.94)
Nides 2006[51]	18	127	6	127	2.67 (1.83 to 4.36)
Pooled effect					**2.58 (2.16 to 3.15)**
Predictive effect					**2.57 (1.53 to 4.53)**



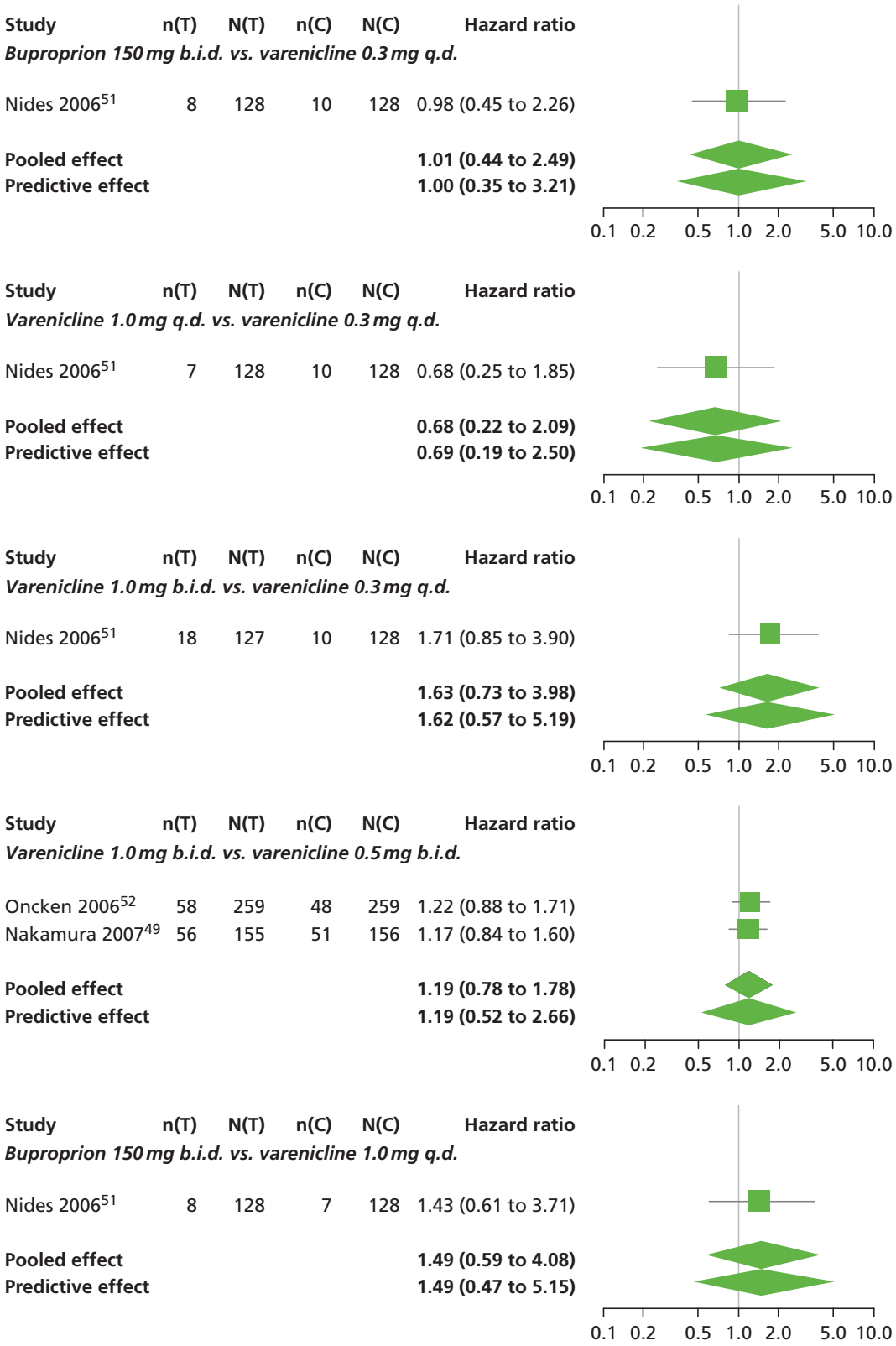
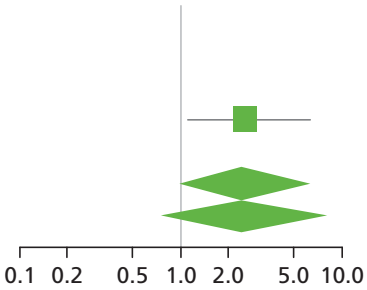
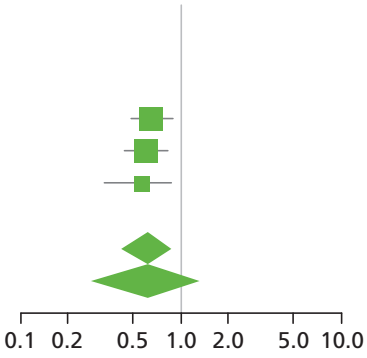


FIGURE 13 Continuous abstinence: forest plots of study-specific treatment effects and population mean treatment effects. a See *Table 1* for regime details. (*continued*)

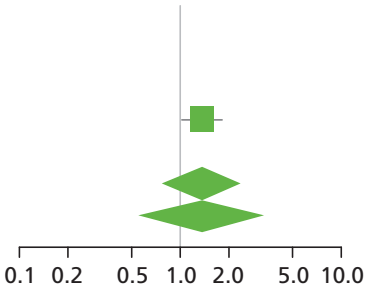
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[52]	18	127	7	128	2.52 (1.13 to 6.35)
Pooled effect					**2.40 (0.99 to 6.46)**
Predictive effect					**2.41 (0.76 to 8.17)**



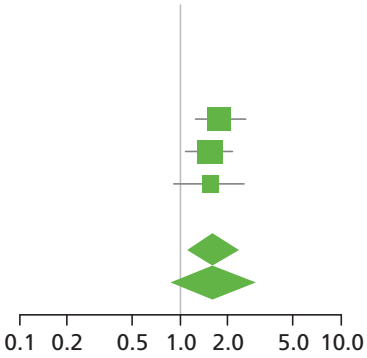
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg b.i.d.					
Gonzales 2006[48]	53	329	77	352	0.66 (0.49 to 0.90)
Jorenby 2006[16]	50	342	79	344	0.61 (0.45 to 0.83)
Nides 2006[51]	8	128	18	127	0.58 (0.34 to 0.87)
Pooled effect					**0.62 (0.43 to 0.87)**
Predictive effect					**0.62 (0.28 to 1.33)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. nicotine patch					
Aubin 2008[46]	98	378	75	379	1.36 (1.01 to 1.84)
Pooled effect					**1.36 (0.77 to 2.38)**
Predictive effect					**1.36 (0.54 to 3.34)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. placebo					
Gonzales 2006[48]	53	329	29	344	1.75 (1.25 to 2.56)
Jorenby 2006[16]	50	342	35	341	1.53 (1.08 to 2.15)
Nides 2006[51]	8	128	6	127	1.55 (0.93 to 2.52)
Pooled effect					**1.59 (1.10 to 2.32)**
Predictive effect					**1.59 (0.87 to 2.96)**



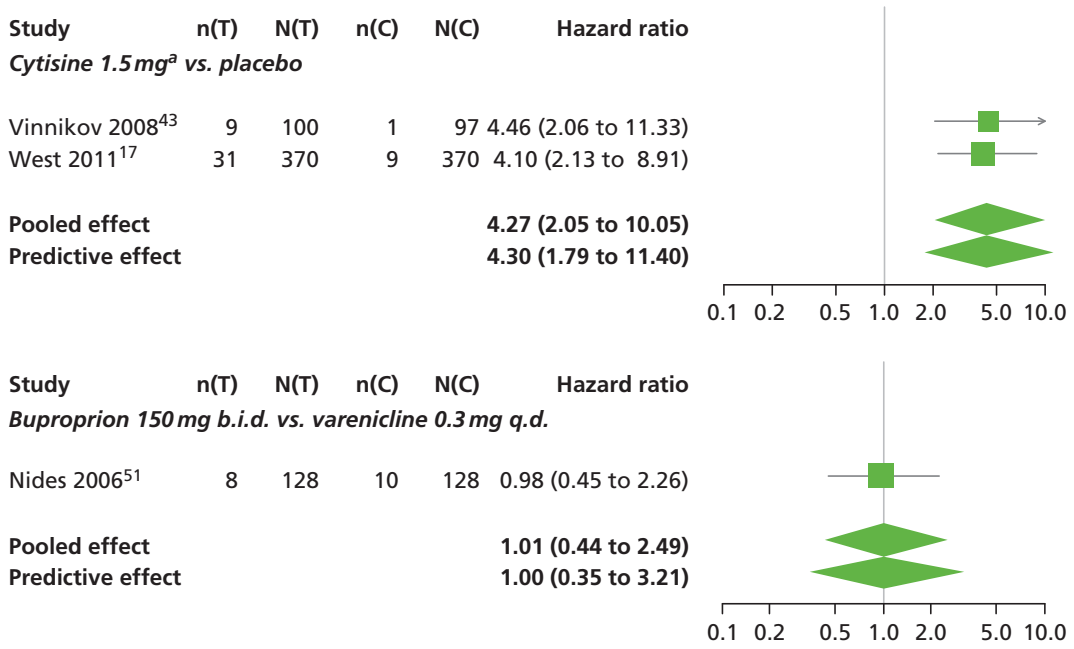
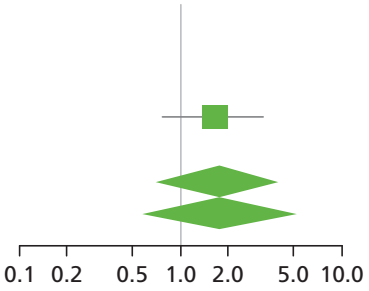


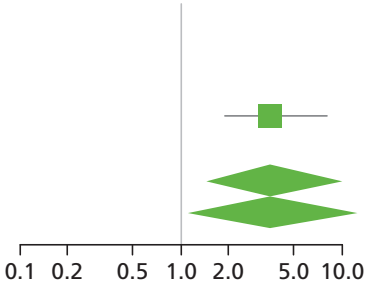
FIGURE 13 Continuous abstinence: forest plots of study-specific treatment effects and population mean treatment effects. a See *Table 1* for regime details.

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg q.d. vs. placebo					
Nides 2006[51]	14	126	10	123	1.65 (0.78 to 3.31)
Pooled effect					**1.75 (0.71 to 4.10)**
Predictive effect					**1.75 (0.58 to 5.24)**

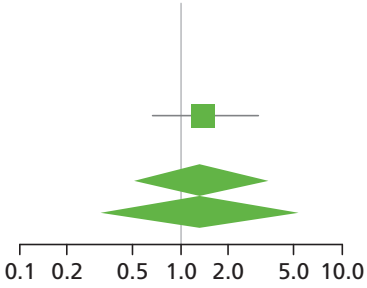


Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. placebo					
Pfizer 2011[40]/Williams 2012[41]	6	84	4	43	2.83 (1.09 to 4.58)
Rennard 2012[53]	61	486	5	165	3.45 (2.24 to 6.77)
Rigotti 2010[54]	28	353	6	350	3.54 (2.27 to 6.85)
Tashkin 2011[57]	27	248	7	251	3.42 (2.18 to 6.25)
Tsai 2007[58]	7	126	1	124	3.42 (1.97 to 8.01)
Smith 2013[55]	12	196	2	196	3.48 (2.08 to 7.94)
Wong 2012[37]	3	151	0	135	3.38 (1.85 to 8.44)
Heydari 2012[39]	3	89	0	91	3.44 (1.92 to 9.51)
Gonzales 2006[48]	36	349	19	344	2.72 (1.54 to 4.02)
Jorenby 2006[16]	45	343	12	340	3.44 (2.35 to 5.77)
Oncken 2006[52]	46	253	6	121	3.40 (2.20 to 6.21)
Nides 2006[51]	19	125	10	123	2.84 (1.49 to 4.41)
Pooled effect					**3.29 (2.40 to 4.77)**
Predictive effect					**3.24 (1.49 to 7.57)**

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. for 52 weeks vs. placebo					
Williams 2007[61]	57	251	9	126	3.62 (1.88 to 8.13)
Pooled effect					**3.64 (1.44 to 10.01)**
Predictive effect					**3.62 (1.12 to 12.66)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 0.3 mg q.d.					
Nides 2006[51]	15	126	10	126	1.37 (0.67 to 3.08)
Pooled effect					**1.31 (0.52 to 3.54)**
Predictive effect					**1.31 (0.32 to 5.37)**



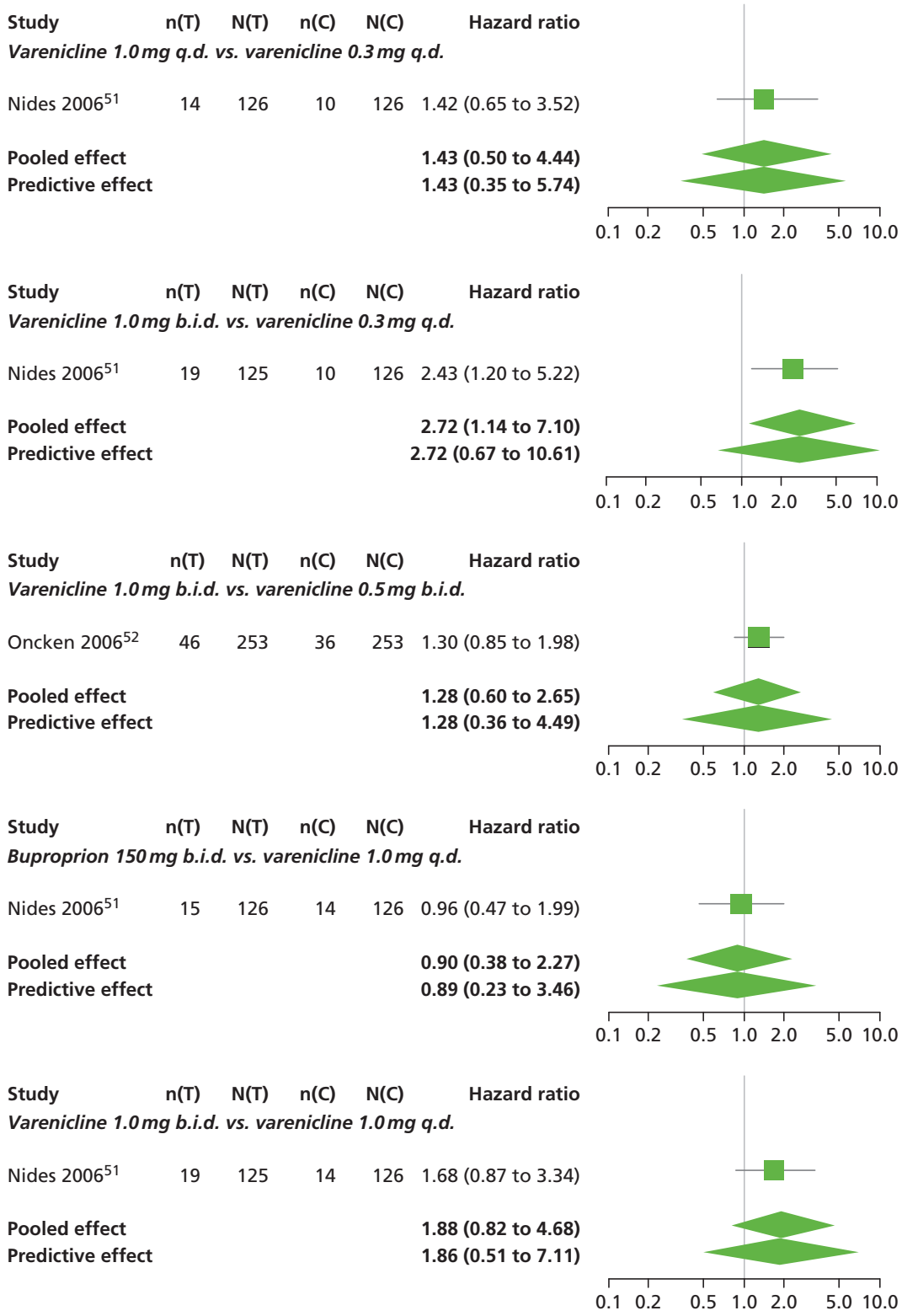
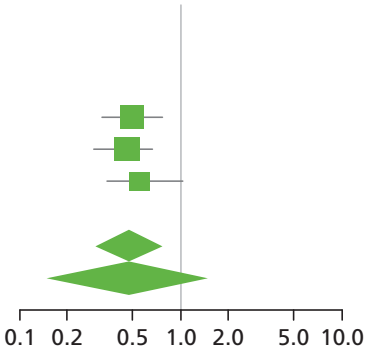
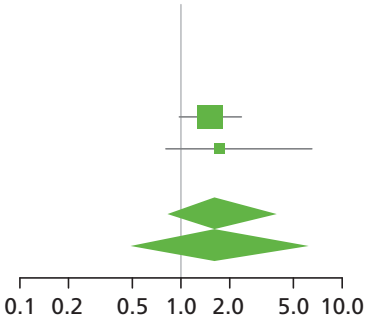


FIGURE 14 Abnormal dreams: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. (*continued*)

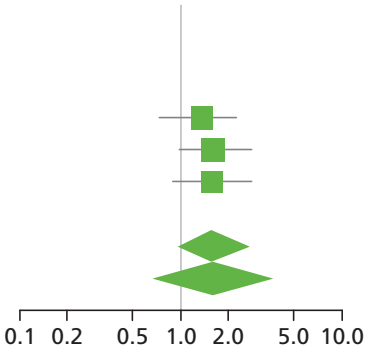
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg b.i.d.					
Gonzales 2006[48]	18	329	36	349	0.51 (0.33 to 0.78)
Jorenby 2006[16]	20	340	45	343	0.46 (0.29 to 0.68)
Nides 2006[51]	15	126	19	125	0.55 (0.35 to 1.03)
Pooled effect					**0.48 (0.30 to 0.78)**
Predictive effect					**0.49 (0.15 to 1.47)**



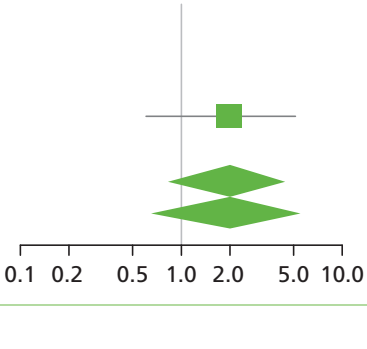
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. nicotine patch					
Aubin 2008[46]	44	376	31	370	1.51 (0.97 to 2.38)
Heydari 2012[39]	3	89	0	92	1.74 (0.81 to 6.56)
Pooled effect					**1.61 (0.82 to 3.90)**
Predictive effect					**1.60 (0.48 to 6.19)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. placebo					
Gonzales 2006[48]	18	329	19	344	1.37 (0.75 to 2.22)
Jorenby 2006[16]	20	340	12	340	1.60 (0.98 to 2.77)
Nides 2006[51]	15	126	10	123	1.58 (0.89 to 2.75)
Pooled effect					**1.58 (0.96 to 2.70)**
Predictive effect					**1.58 (0.67 to 3.80)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Nicotine patch vs. placebo					
Heydari 2012[39]	0	92	0	91	1.99 (0.61 to 5.12)
Pooled effect					**2.01 (0.82 to 4.43)**
Predictive effect					**2.02 (0.64 to 5.54)**



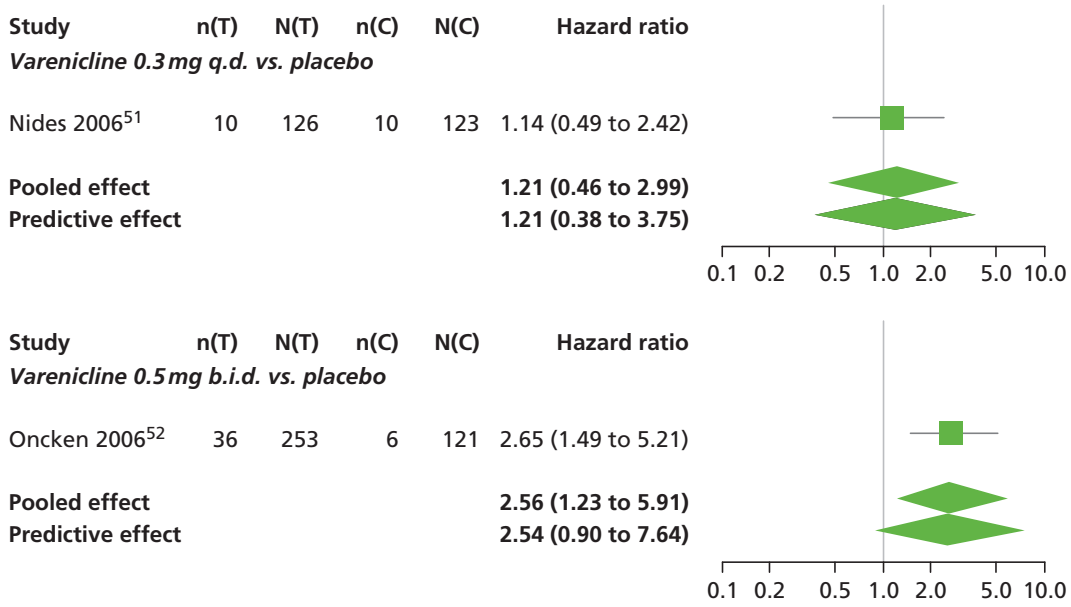
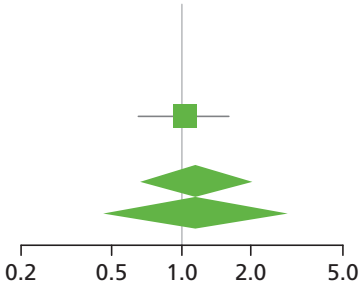
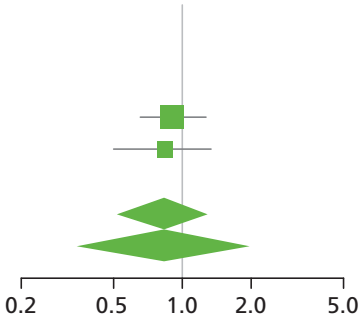


FIGURE 14 Abnormal dreams: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate.

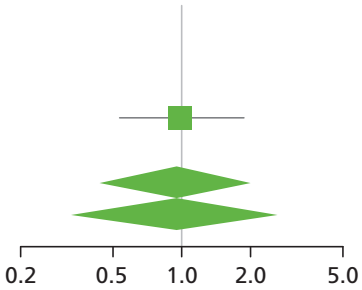
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.3 mg q.d.					
Nides 2006[51]	30	125	34	126	1.05 (0.65 to 1.62)
Pooled effect					**1.16 (0.66 to 2.04)**
Predictive effect					**1.16 (0.46 to 2.91)**



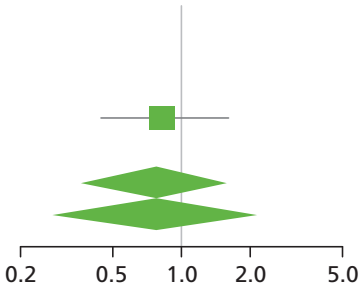
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.5 mg b.i.d.					
Oncken 2006[52]	59	253	59	253	0.90 (0.66 to 1.27)
Nakamura 2007[49]	16	156	18	155	0.84 (0.51 to 1.33)
Pooled effect					**0.83 (0.52 to 1.29)**
Predictive effect					**0.83 (0.35 to 1.97)**



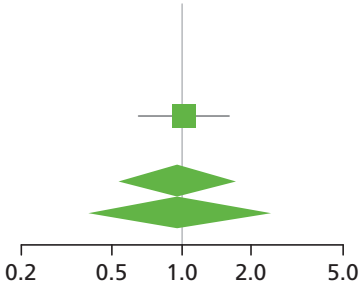
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	18	155	16	153	0.99 (0.54 to 1.86)
Pooled effect					**0.94 (0.44 to 1.98)**
Predictive effect					**0.95 (0.33 to 2.61)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	16	156	16	153	0.82 (0.45 to 1.59)
Pooled effect					**0.78 (0.36 to 1.58)**
Predictive effect					**0.78 (0.27 to 2.12)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[51]	38	126	34	126	1.03 (0.66 to 1.61)
Pooled effect					**0.95 (0.54 to 1.72)**
Predictive effect					**0.96 (0.39 to 2.47)**



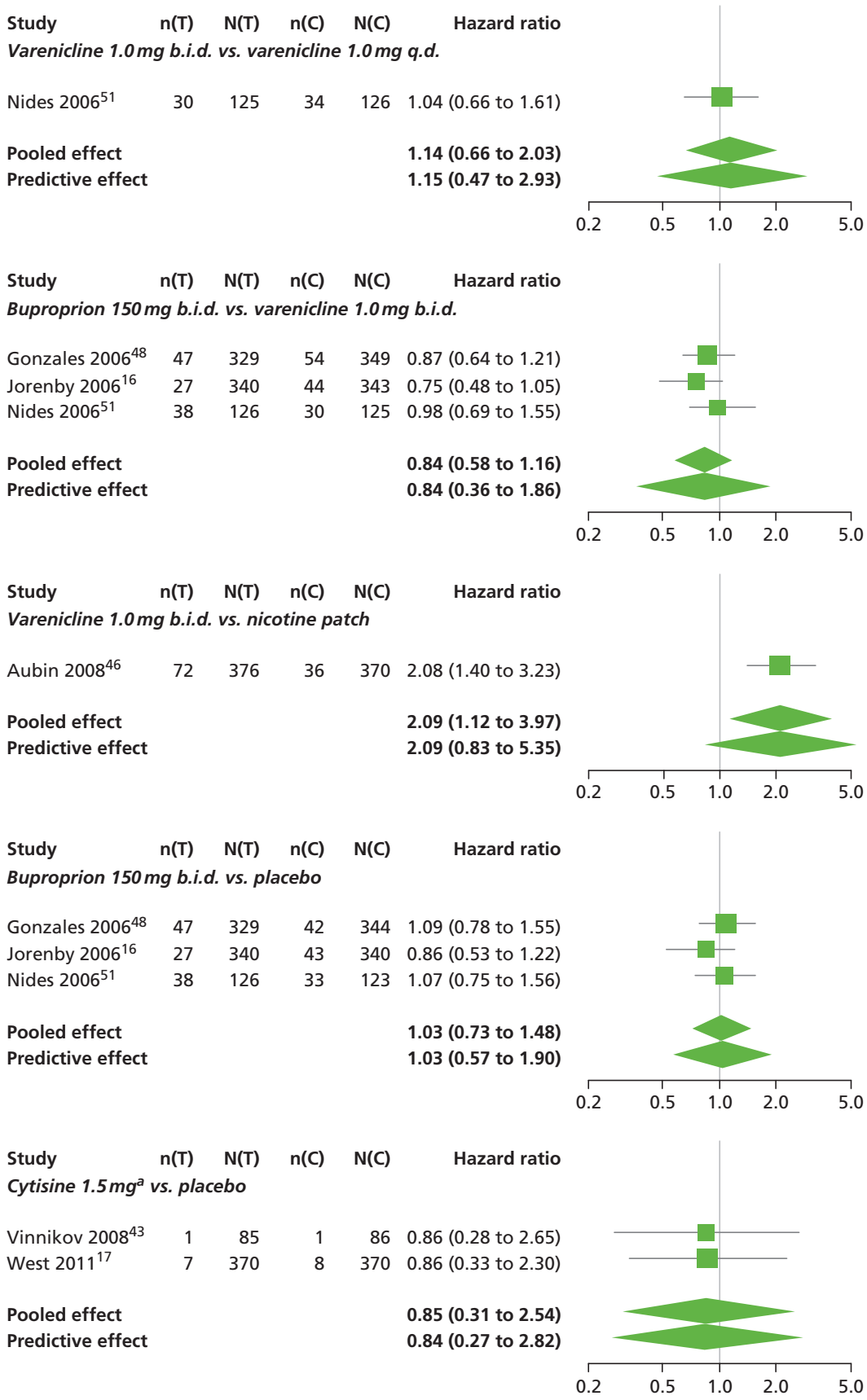
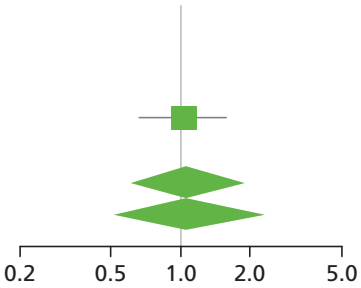
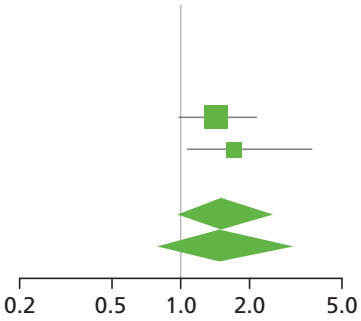


FIGURE 15 Headache: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details. (*continued*)

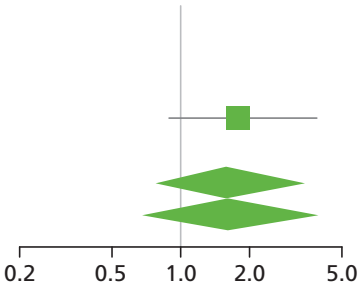
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.3 mg q.d. vs. placebo					
Nides 2006[51]	34	126	33	123	1.03 (0.66 to 1.59)
Pooled effect					**1.06 (0.61 to 1.92)**
Predictive effect					**1.06 (0.51 to 2.32)**



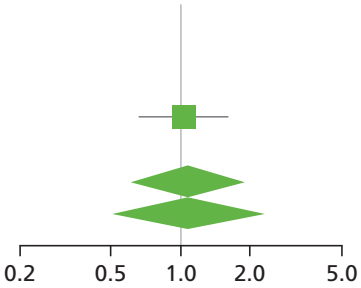
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. placebo					
Oncken 2006[52]	59	253	21	121	1.43 (0.98 to 2.13)
Nakamura 2007[49]	18	155	4	154	1.70 (1.07 to 3.71)
Pooled effect					**1.48 (0.97 to 2.50)**
Predictive effect					**1.48 (0.79 to 3.07)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.25 mg b.i.d. vs. placebo					
Nakamura 2007[49]	16	153	4	154	1.76 (0.89 to 3.92)
Pooled effect					**1.58 (0.78 to 3.47)**
Predictive effect					**1.59 (0.68 to 3.98)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. placebo					
Nides 2006[51]	34	126	33	123	1.04 (0.66 to 1.61)
Pooled effect					**1.08 (0.61 to 1.90)**
Predictive effect					**1.07 (0.51 to 2.33)**



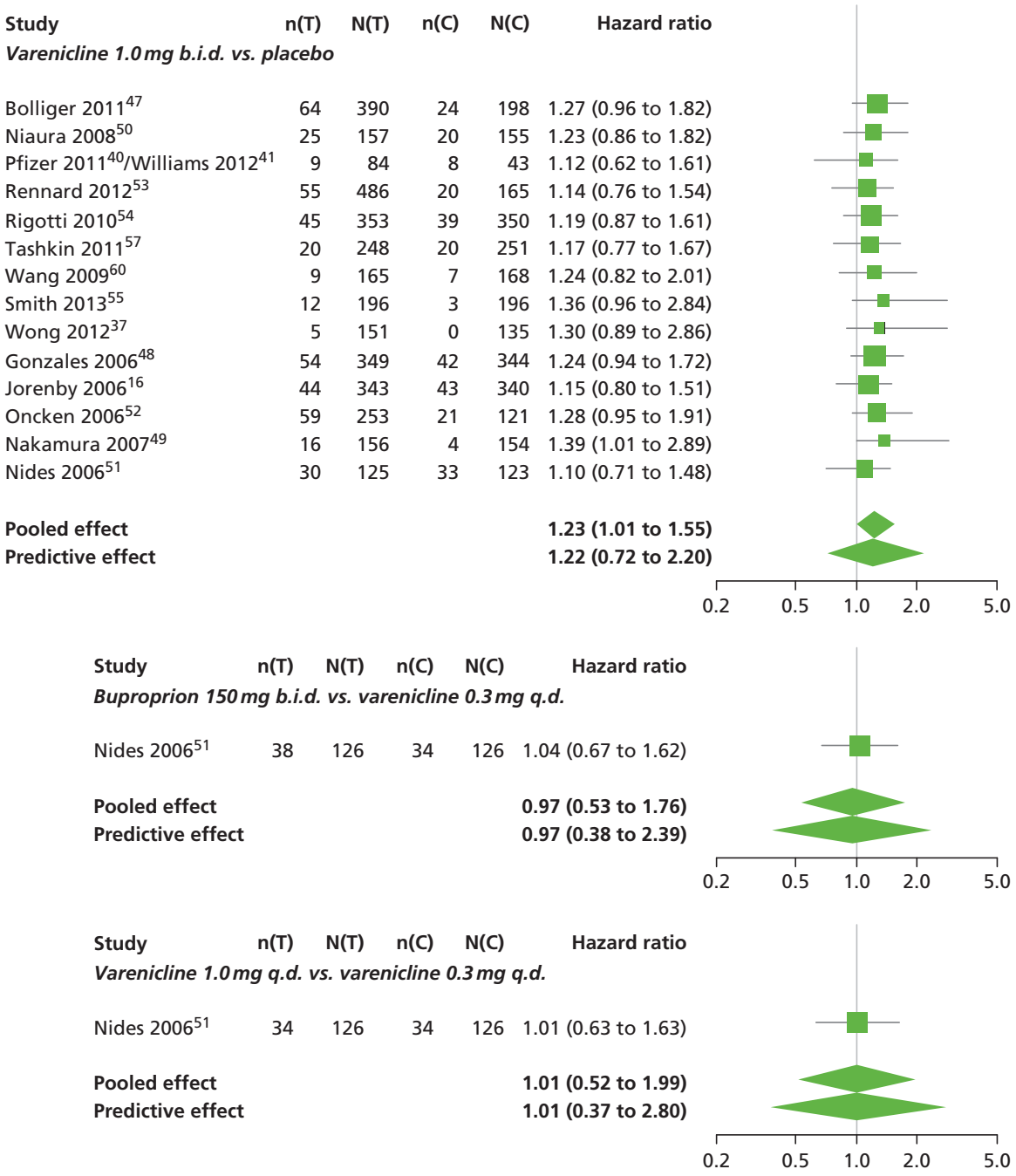
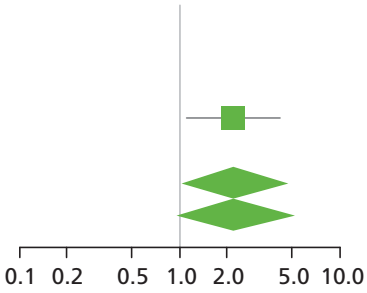
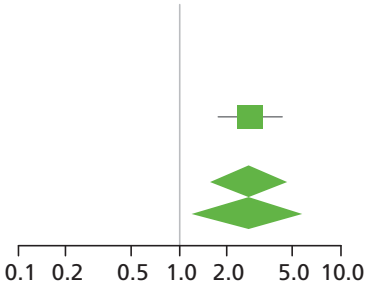


FIGURE 15 Headache: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details.

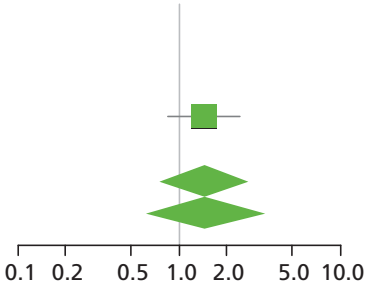
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. for 52 weeks vs. placebo					
Williams 2007[61]	48	251	12	126	2.17 (1.11 to 4.27)
Pooled effect					**2.16 (1.03 to 4.79)**
Predictive effect					**2.17 (0.95 to 5.34)**



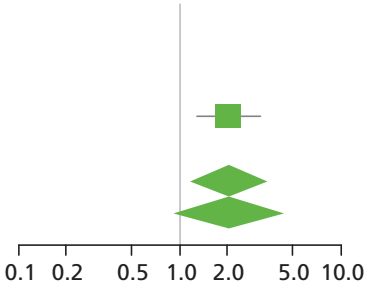
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 0.3 mg q.d.					
Nides 2006[51]	57	126	25	126	2.73 (1.76 to 4.40)
Pooled effect					**2.70 (1.55 to 4.75)**
Predictive effect					**2.70 (1.19 to 5.90)**



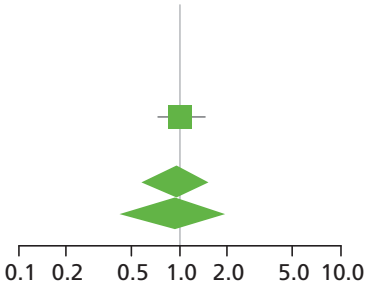
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg q.d. vs. varenicline 0.3 mg q.d.					
Nides 2006[51]	34	126	25	126	1.43 (0.86 to 2.41)
Pooled effect					**1.44 (0.76 to 2.72)**
Predictive effect					**1.43 (0.63 to 3.44)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.3 mg q.d.					
Nides 2006[51]	44	125	25	126	2.00 (1.28 to 3.22)
Pooled effect					**2.01 (1.16 to 3.51)**
Predictive effect					**2.01 (0.92 to 4.45)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.5 mg b.i.d.					
Oncken 2006[52]	75	253	69	253	1.02 (0.75 to 1.43)
Pooled effect					**0.95 (0.58 to 1.52)**
Predictive effect					**0.94 (0.43 to 1.95)**



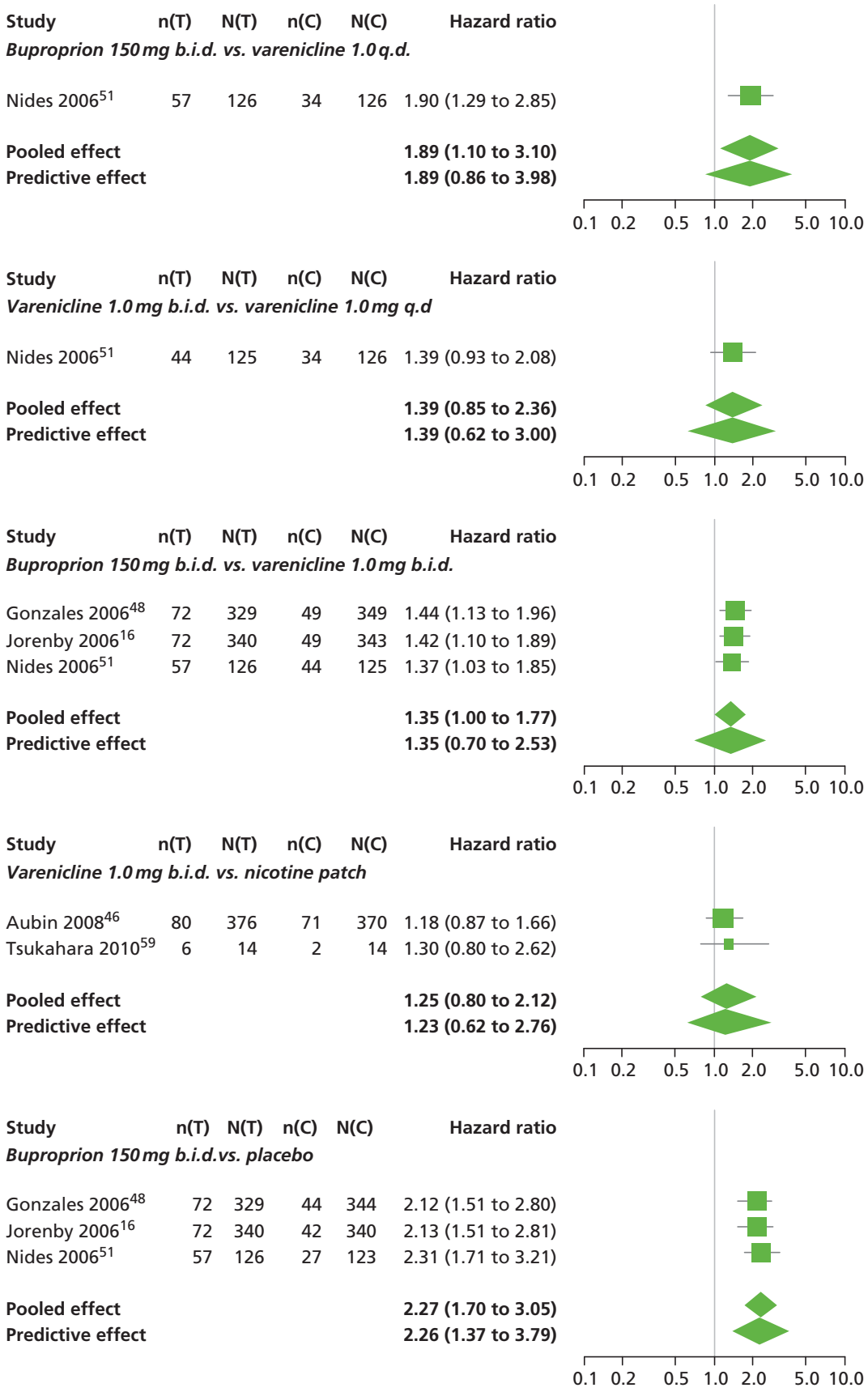


FIGURE 16 Insomnia: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. (*continued*)

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.3 mg q.d. vs. placebo					
Nides 2006[51]	25	126	27	123	0.85 (0.52 to 1.36)
Pooled effect					**0.84 (0.48 to 1.47)**
Predictive effect					**0.84 (0.42 to 1.66)**

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. placebo					
Oncken 2006[52]	69	253	14	121	1.86 (1.23 to 3.00)
Pooled effect					**1.76 (1.09 to 3.03)**
Predictive effect					**1.76 (0.96 to 3.60)**

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg q.d. vs. placebo					
Nides 2006[51]	34	126	27	123	1.22 (0.79 to 1.85)
Pooled effect					**1.22 (0.72 to 2.02)**
Predictive effect					**1.21 (0.64 to 2.39)**

Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. placebo					
Bolliger 2011[47]	50	390	13	198	1.74 (1.30 to 2.58)
Niaura 2008[50]	34	157	17	155	1.74 (1.32 to 2.61)
Pfizer 2011[40]/Williams 2012[41]	8	84	2	43	1.69 (1.15 to 2.71)
Rennard 2012[53]	43	486	6	165	1.75 (1.29 to 2.82)
Rigotti 2010[54]	42	353	23	350	1.71 (1.29 to 2.40)
Tashkin 2011[57]	24	248	15	251	1.68 (1.21 to 2.40)
Tsai 2007[58]	19	126	17	124	1.58 (1.04 to 2.11)
Wang 2009[60]	10	165	5	168	1.69 (1.19 to 2.69)
Smith 2013[55]	10	196	4	196	1.71 (1.21 to 2.82)
Gonzales 2006[48]	49	349	44	344	1.49 (0.99 to 1.93)
Jorenby 2006[16]	49	343	42	340	1.51 (1.03 to 1.96)
Oncken 2006[52]	75	253	14	121	1.86 (1.43 to 3.00)
Nides 2006[51]	44	125	27	123	1.68 (1.27 to 2.34)
Pooled effect					**1.68 (1.40 to 2.07)**
Predictive effect					**1.67 (1.09 to 2.67)**

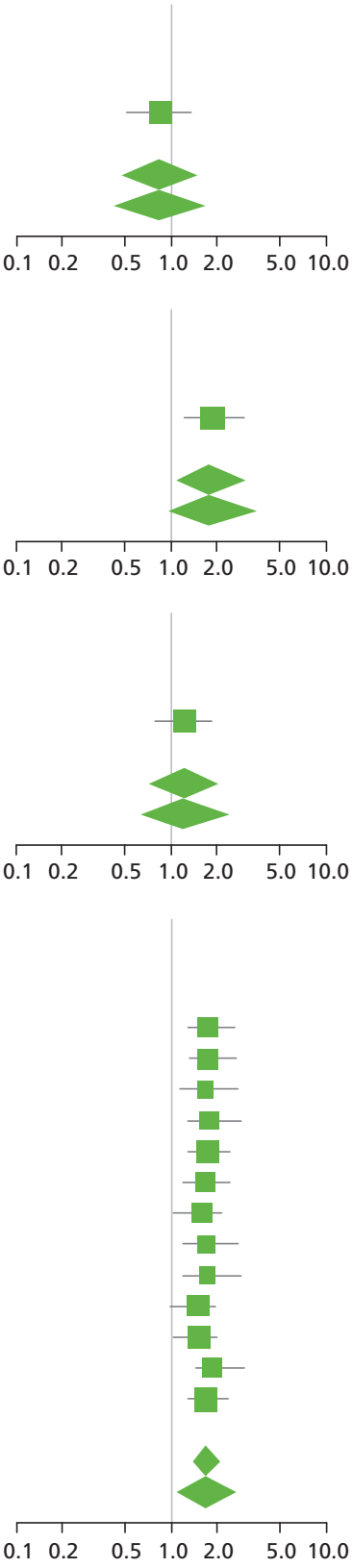


FIGURE 16 Insomnia: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate.

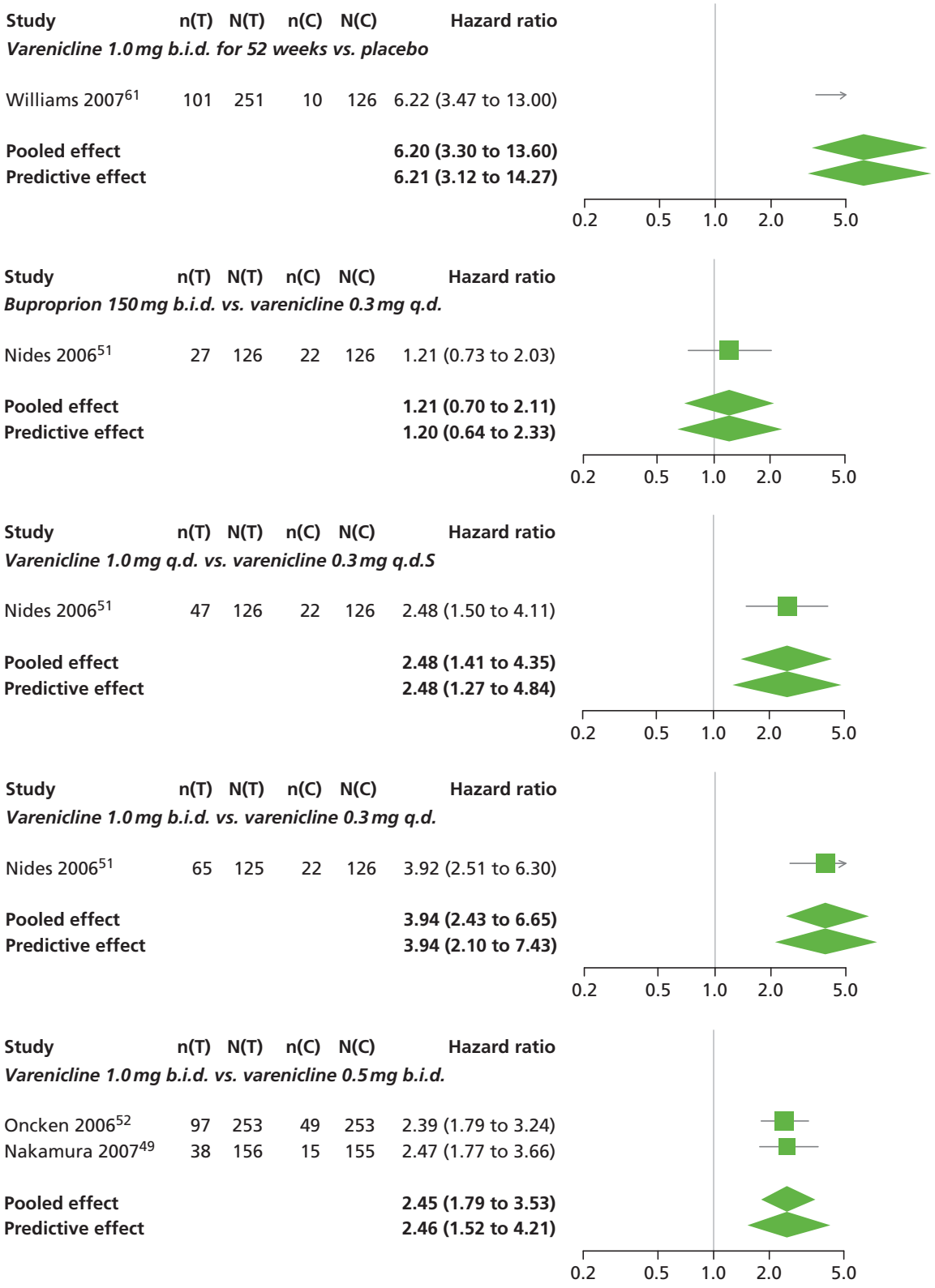
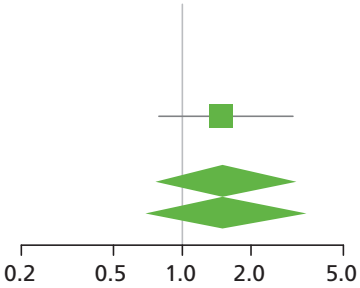
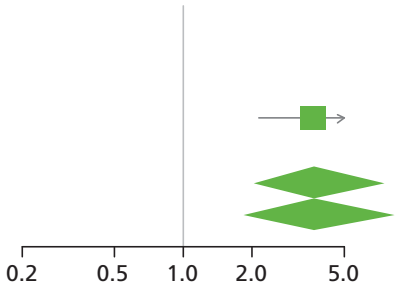


FIGURE 17 Nausea: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details. (*continued*)

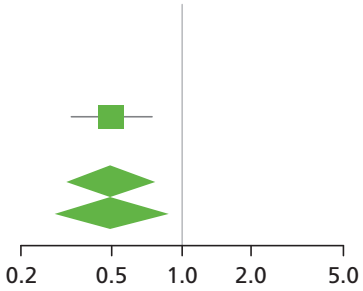
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	15	155	11	153	1.48 (0.78 to 3.03)
Pooled effect					**1.49 (0.76 to 3.12)**
Predictive effect					**1.49 (0.70 to 3.43)**



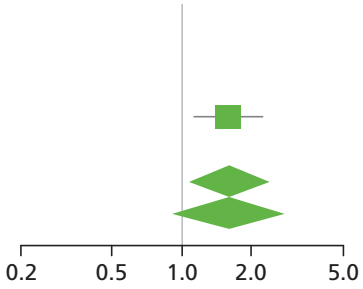
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	38	156	11	153	3.67 (2.11 to 7.25)
Pooled effect					**3.67 (2.03 to 7.46)**
Predictive effect					**3.67 (1.82 to 8.22)**



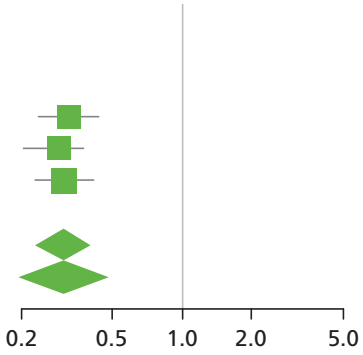
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[51]	27	126	47	126	0.50 (0.33 to 0.74)
Pooled effect					**0.49 (0.32 to 0.77)**
Predictive effect					**0.49 (0.28 to 0.88)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[51]	65	125	47	126	1.60 (1.13 to 2.26)
Pooled effect					**1.60 (1.08 to 2.42)**
Predictive effect					**1.60 (0.92 to 2.80)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg b.i.d.					
Gonzales 2006[48]	41	329	98	349	0.32 (0.24 to 0.44)
Jorenby 2006[16]	25	340	101	343	0.29 (0.21 to 0.38)
Nides 2006[51]	27	126	65	125	0.31 (0.23 to 0.41)
Pooled effect					**0.31 (0.23 to 0.40)**
Predictive effect					**0.31 (0.19 to 0.49)**



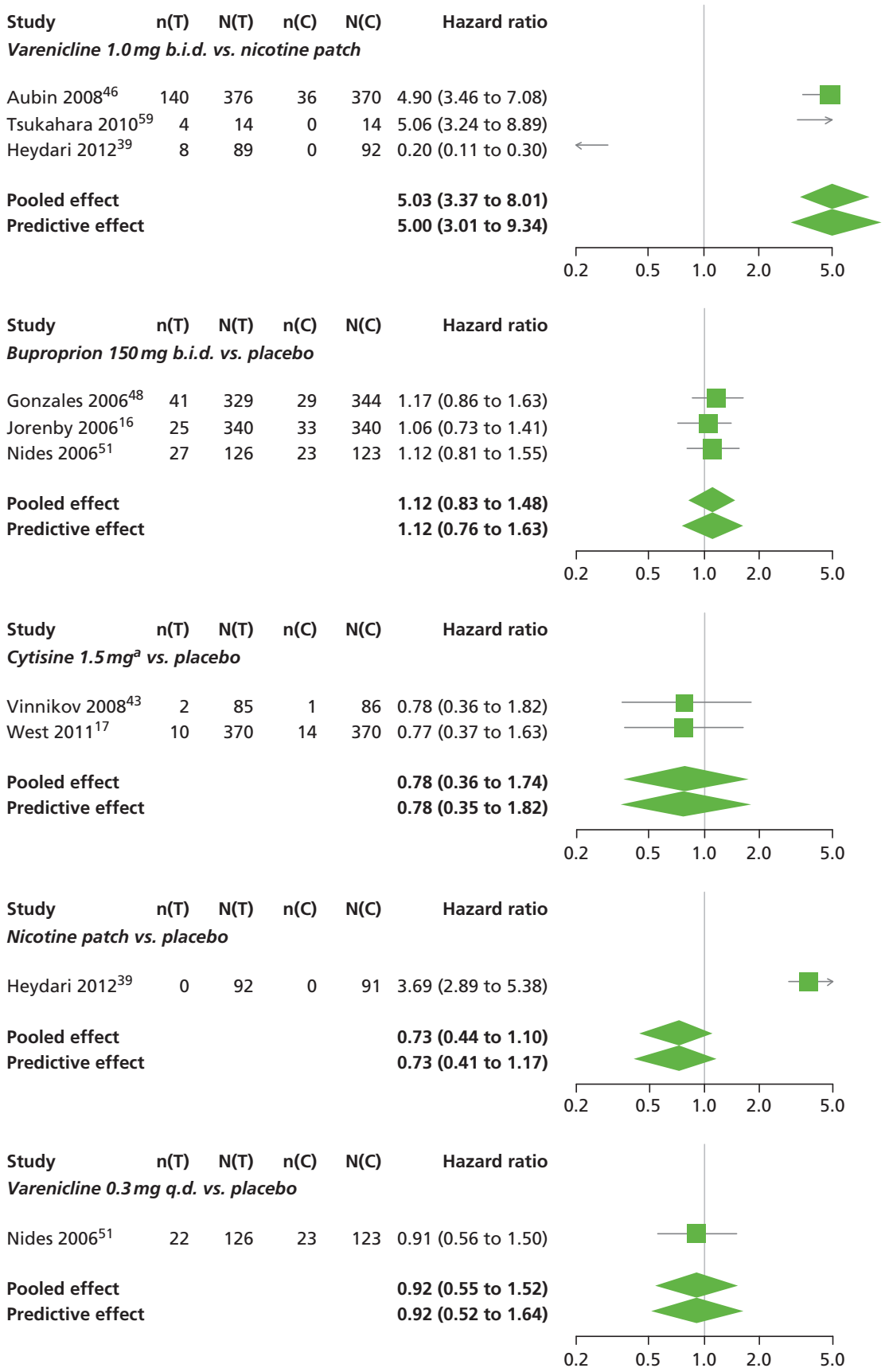
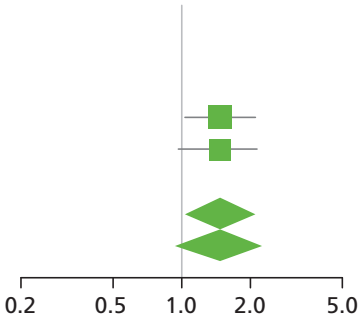
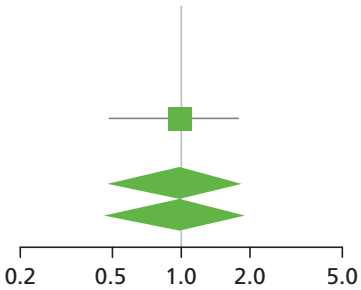


FIGURE 17 Nausea: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details. (*continued*)

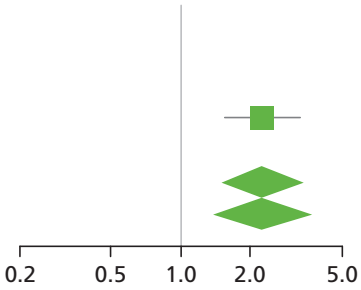
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. placebo					
Oncken 2006[52]	49	253	18	121	1.47 (1.03 to 2.08)
Nakamura 2007[49]	15	155	12	154	1.46 (0.97 to 2.14)
Pooled effect					**1.48 (1.03 to 2.10)**
Predictive effect					**1.47 (0.93 to 2.25)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.25 mg b.i.d. vs. placebo					
Nakamura 2007[49]	11	153	12	154	0.98 (0.48 to 1.77)
Pooled effect					**0.98 (0.48 to 1.82)**
Predictive effect					**0.98 (0.46 to 1.90)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg q.d. vs. placebo					
Nides 2006[51]	47	126	23	123	2.26 (1.55 to 3.31)
Pooled effect					**2.26 (1.50 to 3.44)**
Predictive effect					**2.27 (1.39 to 3.70)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. placebo					
Bolliger 2011[47]	103	390	16	198	3.62 (2.82 to 4.69)
Niaura 2008[50]	21	157	8	155	3.58 (2.63 to 4.68)
Pfizer 2011[40]/Williams 2012[41]	20	84	6	43	3.55 (2.45 to 4.53)
Rennard 2012[53]	142	486	15	165	3.63 (2.84 to 4.72)
Rigotti 2010[54]	104	353	30	350	3.67 (2.97 to 4.72)
Steinberg 2011[56]	10	38	2	37	3.65 (2.78 to 5.07)
Tashkin 2011[57]	67	248	20	251	3.65 (2.89 to 4.74)
Tsai 2007[58]	55	126	14	124	3.71 (2.98 to 5.08)
Wang 2009[63]	48	165	20	168	3.54 (2.58 to 4.40)
Smith 2013[55]	32	196	3	196	3.78 (3.03 to 5.78)
Wong 2012[37]	20	151	5	135	3.64 (2.78 to 4.87)
Gonzales 2006[48]	98	349	29	344	3.62 (2.90 to 4.52)
Jorenby 2006[16]	101	343	33	340	3.63 (2.90 to 4.57)
Oncken 2006[52]	97	253	18	121	3.56 (2.68 to 4.41)
Heydari 2012[39]	8	89	0	91	0.73 (0.42 to 1.17)
Nakamura 2007[49]	38	156	12	154	3.63 (2.77 to 4.70)
Nides 2006[51]	65	125	23	123	3.61 (2.85 to 4.64)
Pooled effect					**3.63 (3.10 to 4.27)**
Predictive effect					**3.63 (2.68 to 5.06)**

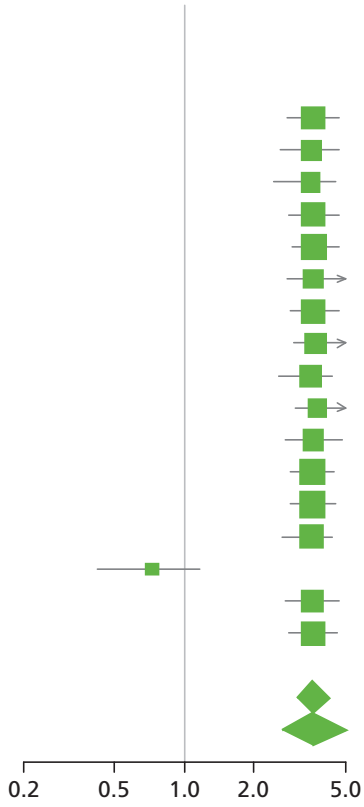


FIGURE 17 Nausea: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details.

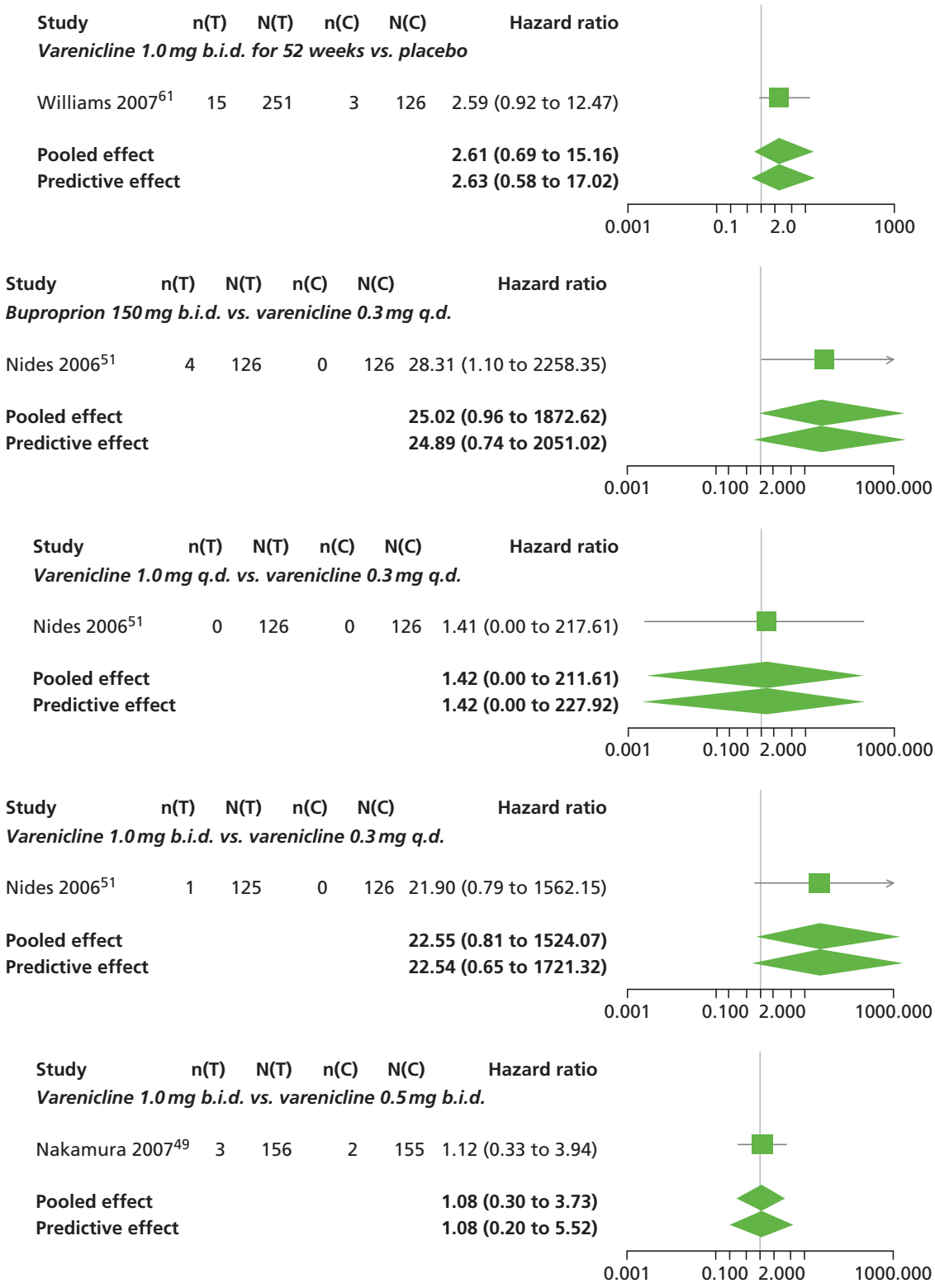
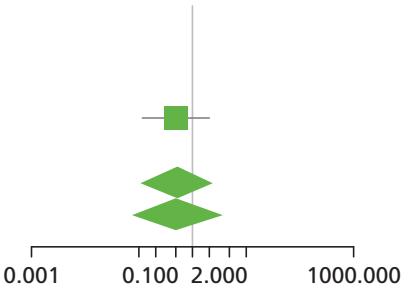
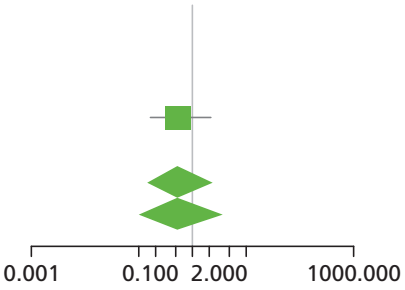


FIGURE 18 Serious adverse events: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details. (*continued*)

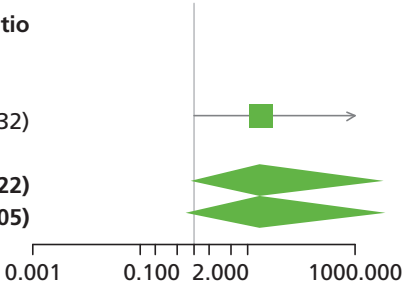
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 0.5 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	2	155	5	153	0.49 (0.12 to 2.03)
Pooled effect					**0.51 (0.11 to 2.34)**
Predictive effect					**0.50 (0.08 to 3.53)**



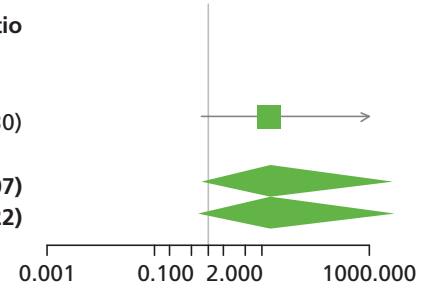
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 0.25 mg b.i.d.					
Nakamura 2007[49]	3	156	5	153	0.54 (0.17 to 2.16)
Pooled effect					**0.53 (0.14 to 2.43)**
Predictive effect					**0.53 (0.10 to 3.55)**



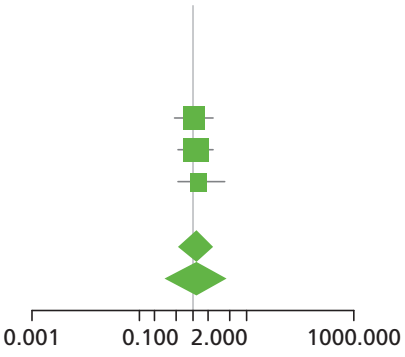
Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[51]	4	126	0	126	18.68 (1.06 to 3905.32)
Pooled effect					**16.84 (0.90 to 3484.22)**
Predictive effect					**16.90 (0.74 to 3720.05)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Varenicline 1.0 mg b.i.d. vs. varenicline 1.0 mg q.d.					
Nides 2006[51]	1	125	0	126	14.07 (0.78 to 2870.30)
Pooled effect					**14.52 (0.79 to 2839.07)**
Predictive effect					**14.58 (0.65 to 3044.22)**



Study	n(T)	N(T)	n(C)	N(C)	Hazard ratio
Buproprion 150 mg b.i.d. vs. varenicline 1.0 mg b.i.d.					
Gonzales 2006[48]	3	329	4	349	1.11 (0.47 to 2.38)
Jorenby 2006[16]	9	340	8	344	1.16 (0.55 to 2.39)
Nides 2006[51]	4	126	1	125	1.29 (0.55 to 4.17)
Pooled effect					**1.16 (0.54 to 2.50)**
Predictive effect					**1.15 (0.31 to 4.37)**



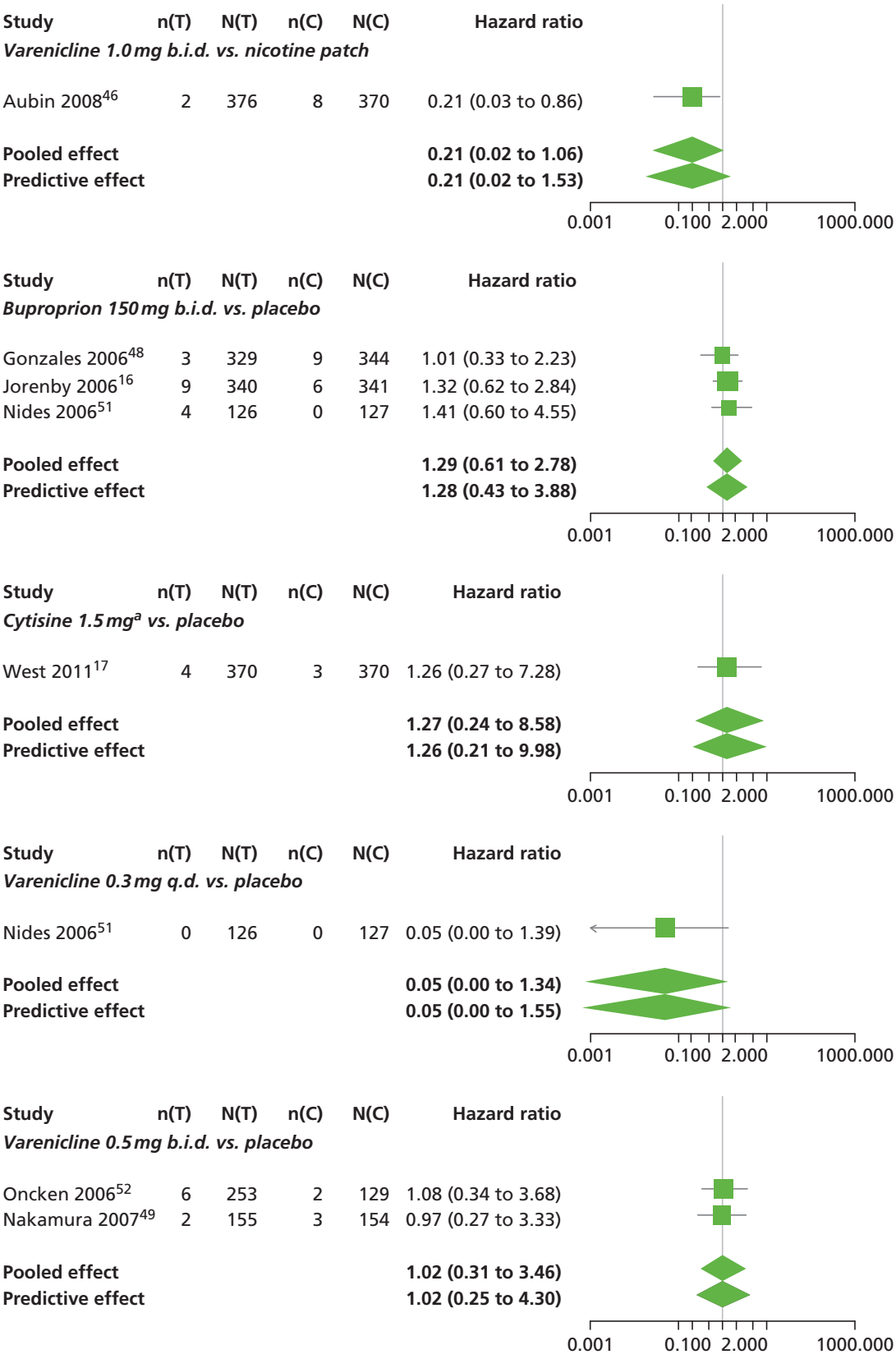


FIGURE 18 Serious adverse events: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details. (*continued*)

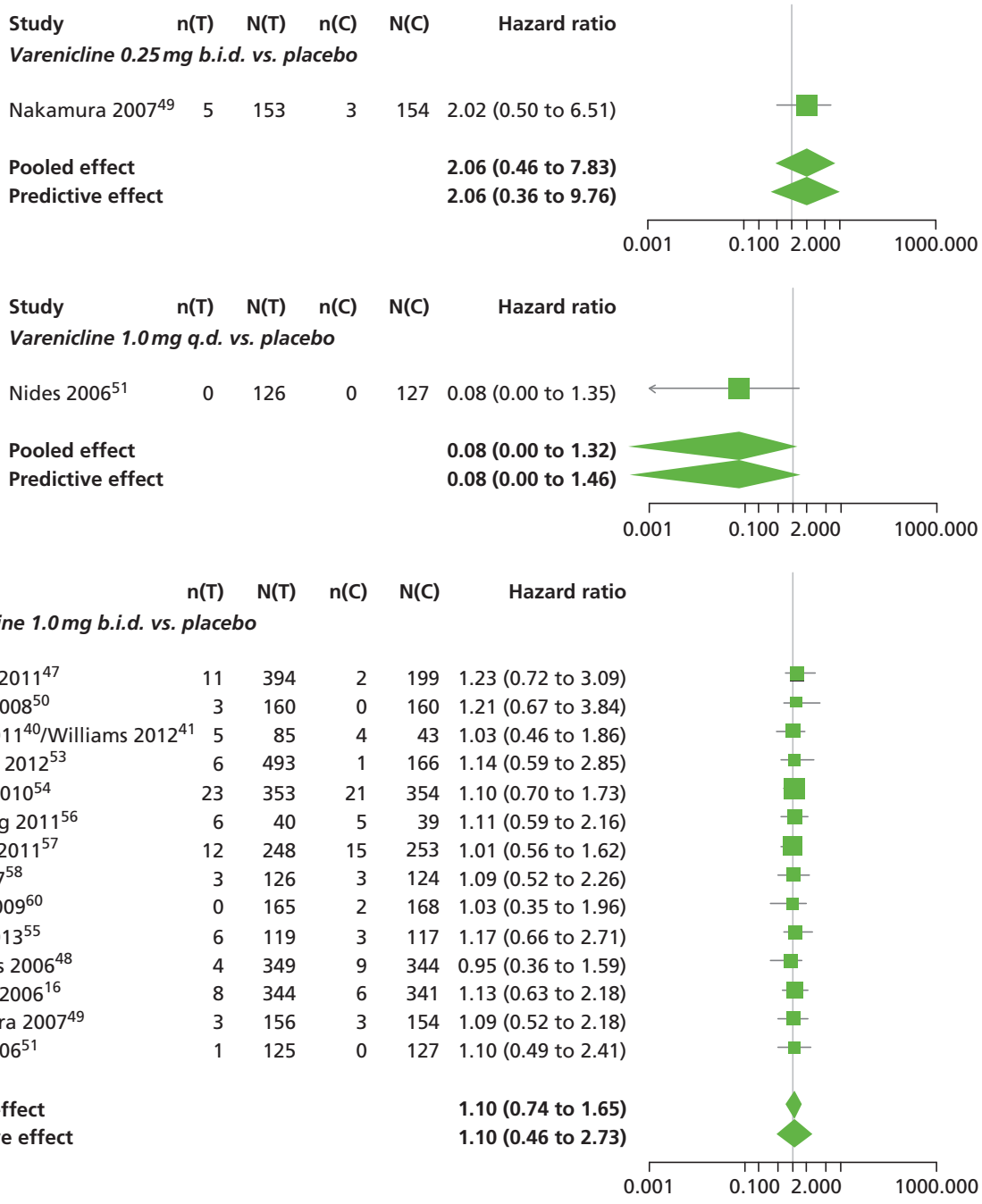


FIGURE 18 Serious adverse events: forest plots of study-specific treatment effects and population mean treatment effects, where median is used as the best estimate. a See *Table 1* for regime details.

Appendix 6 Results of the sensitivity analysis of the efficacy data using studies measured either continuous abstinence or repeated 7-day point prevalence abstinence

A sensitivity analysis was carried out including all studies measured using either continuous abstinence or repeated 7-day point prevalence abstinence. A total of 21 studies comparing pairs, triplets or quintuplets of interventions provided information at various study durations. The varenicline 0.25 mg b.i.d. arm in study Nakamura *et al.*[49] was removed from the data because the number of events was not reported for this particular arm.

A summary of all the trials (data) included in the network meta-analysis for continuous abstinence including repeated 7-day point prevalence abstinence is presented in *Table 44*. *Figure 19* presents the network of evidence.

The network meta-analysis model fitted the data not very well, with a total residual deviance not very close to the total number of data points included in the analysis. The total residual deviance was 58.72, which compared favourably with the 51 data points being analysed.

TABLE 44 Summary of the trials included in the base-case network meta-analysis on continuous abstinence data including repeated 7-day point prevalence abstinence data for all treatments, where 1 = placebo, 2 = nicotine patch, 3 = cytisine 1.5 mg, 4 = varenicline 0.3 mg q.d., 5 = varenicline 1.0 mg q.d., 6 = varenicline 0.5 mg b.i.d., 7 = varenicline 1.0 mg b.i.d., 8 = bupropion hydrochloride 150 mg b.i.d.

Author, year	Study duration (years)	Treatments					Number of events					Number of patients				
		Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Vinnikov 2008[43]	0.50	1	3	–	–	–	1	9	–	–	–	97	100	–	–	–
West 2011[17]	1.00	1	3	–	–	–	9	31	–	–	–	370	370	–	–	–
Bolliger 2011[47]	0.46	1	7	–	–	–	26	157	–	–	–	199	394	–	–	–
Niaura 2008[50]	1.00	1	7	–	–	–	12	35	–	–	–	160	160	–	–	–
Rennard 2012[53]	0.46	1	7	–	–	–	21	171	–	–	–	166	493	–	–	–
Rigotti 2010[54]	1.00	1	7	–	–	–	26	68	–	–	–	359	355	–	–	–
Tashkin 2011[57]	1.00	1	7	–	–	–	14	47	–	–	–	254	250	–	–	–
Tsai 2007[58]	0.46	1	7	–	–	–	27	59	–	–	–	124	126	–	–	–
Smith 2013[55]	1.00	1	7	–	–	–	42	61	–	–	–	196	196	–	–	–
Aubin 2008[46]	1.00	2	7	–	–	–	75	98	–	–	–	379	378	–	–	–
Steinberg 2011[62]	0.46	1	7	–	–	–	12	9	–	–	–	39	40	–	–	–
Wang 2009[60]	0.46	1	7	–	–	–	42	63	–	–	–	168	165	–	–	–
Wong 2012[37]	1.00	1	7	–	–	–	34	55	–	–	–	135	151	–	–	–
Pfizer 2011[40]/ Williams 2012[41]	0.46	1	7	–	–	–	1	10	–	–	–	43	85	–	–	–
Gonzales 2006[48]	1.00	1	7	8	–	–	29	77	53	–	–	344	352	329	–	–
Jorenby 2006[16]	1.00	1	7	8	–	–	35	79	50	–	–	341	344	342	–	–
Oncken 2006[52]	1.00	1	6	7	–	–	5	48	58	–	–	129	259	259	–	–
Heydari 2012[39]	1.00	1	2	7	–	–	6	23	29	–	–	91	92	89	–	–
de Dios 2012[38]	0.46	1	2	7	–	–	0	0	3	–	–	11	11	10	–	–
Nakamura 2007[49]	1.00	1	6	7	–	–	35	51	56	–	–	154	156	156	–	–
Nides 2006[51]	1.00	1	4	5	7	8	6	10	7	18	8	127	128	128	127	128

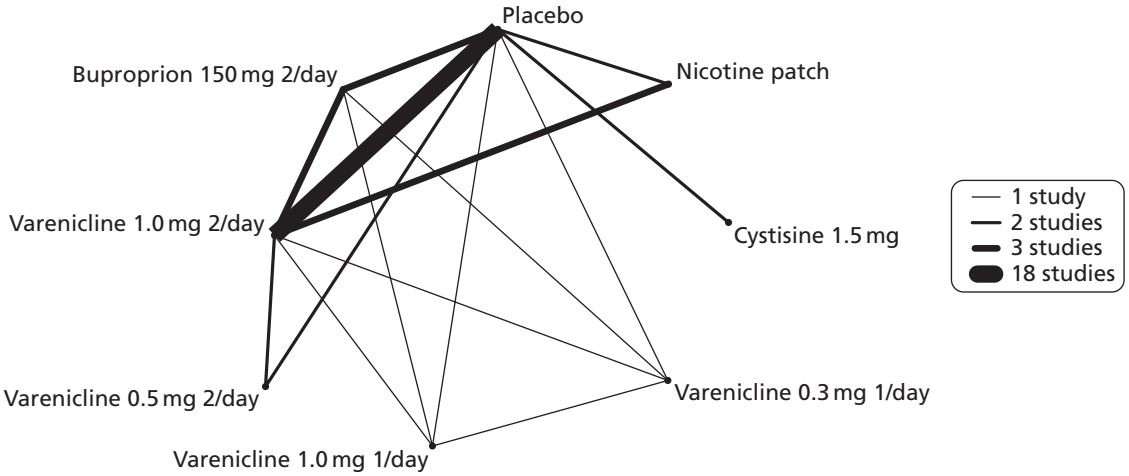


FIGURE 19 Network diagram of different interventions compared with placebo for continuous abstinence including repeated 7-day point prevalence abstinence. The nodes represent the interventions. Lines between nodes indicate when interventions have been compared. Different thicknesses of the lines represent the number of times that each pair of interventions has been compared.

There was evidence of mild heterogeneity in treatment effects between studies, 0.28 with 95% CrI (0.098 to 0.53). All interventions apart from varenicline 0.3 mg q.d. and 1.0 mg q.d. were associated with a statistically significant effect on continuous abstinence at a conventional 5% level relative to placebo. Cytisine 1.5 mg produced the greatest effect [4.35 with 95% CrI (1.91 to 11.75) relative to placebo] (see *Table 39*). Cytisine 1.5 mg was the intervention with the highest probability of being the most effective intervention (probability = 0.84) (see *Table 40*).

TABLE 45 Continuous abstinence including repeated 7-day point prevalence abstinence: estimates of treatment-specific effect relevant to placebo and estimates of between-study SD from the posterior distribution

Intervention	Hazard ratio (95% CrI)
Nicotine patch	1.94 (1.14 to 3.40)
Cytisine 1.5 mg[a]	4.35 (1.91 to 11.75)
Varenicline 0.3 mg q.d.	1.58 (0.62 to 3.89)
Varenicline 1.0 mg q.d.	1.10 (0.37 to 2.86)
Varenicline 0.5 mg b.i.d.	2.17 (1.35 to 3.61)
Varenicline 1.0 mg b.i.d.	2.54 (2.09 to 3.14)
Bupropion hydrochloride 150 mg b.i.d.	1.58 (1.02 to 2.38)
Between-study standard deviation	0.28 (0.098 to 0.53)

a See *Table 1* for regime details.

TABLE 46 The probability of each treatment to achieve each one of the eight possible ranks P(j = b)

	Treatment j							
Rank b	Placebo	Nicotine patch	Cytisine 1.5 mg	Varenicline 0.3 mg q.d.	Varenicline 1.0 mg q.d.	Varenicline 0.5 mg b.i.d.	Varenicline 1.0 mg b.i.d.	Bupropion hydrochloride 150 mg b.i.d.
1	0.00	0.03	0.84	0.03	0.01	0.03	0.06	0.00
2	0.00	0.08	0.07	0.09	0.02	0.19	0.53	0.00
3	0.00	0.18	0.04	0.09	0.03	0.30	0.32	0.04
4	0.00	0.31	0.02	0.14	0.05	0.26	0.07	0.15
5	0.01	0.21	0.02	0.17	0.10	0.13	0.01	0.36
6	0.10	0.14	0.00	0.22	0.15	0.07	0.00	0.32
7	0.40	0.05	0.00	0.16	0.26	0.01	0.00	0.12
8	0.49	0.00	0.00	0.10	0.39	0.00	0.00	0.01

TABLE 47 Nature of SAEs reported for all studies

Study	Serious adverse events
Aubin 2008[46]	*Varenicline*: seven nausea; five headache; and five insomnia *NRT*: one insomnia
Bolliger 2011[47]	*Varenicline*: abortion; hypersensitivity; overdose; bronchitis and asthma; nasal septum deviation; suicidal ideation and depressed mood; suicidal ideation; tachycardia, bradycardia, and dyspnoea; panic attack; injury; and appendicitis *Placebo*: thyroid neoplasm; peritonitis, appendicitis and diverticulitis
de Dios 2012[38]	Not reported
Gonzales 2006[48]	*Varenicline*: abdominal pain, atrial fibrillation, pneumonia and possible stroke (one attributed to study drug) *Bupropion*: cholecystitis and septic shock, headache and grand mal seizure (one attributed to study drug) *Placebo*: lung cancer, acute myocardial infarction, schizophrenia (acute exacerbation), chest pain, urinary tract infection, atrial fibrillation and chest pain (under arms)
Heydari 2012[39]	Not reported
Jorenby 2006[16]	*Varenicline*, during treatment: cancer (lung or brain); acute coronary syndrome; chest pain; dehydration, periorbital cellulitis; acute psychosis, emotional lability; worsening vertigo, elevated blood pressure, chest pain (judged to be related to study medication) *Varenicline, during follow-up*: right-arm staphylococcal cellulitis and acute psychosis (same participant as in the treatment phase) *Bupropion, during treatment*: ectopic pregnancy, angiooedema (judged to be related to study medication), gun shot wound to left shoulder, postoperative bleeding, right leg pain below knee and breast cancer (female) *Bupropion, during follow-up*: occlusion coronary artery, a fatal motorcycle accident and a miscarriage Specific SAEs not reported for placebo

TABLE 47 Nature of SAEs reported for all studies (*continued*)

Study	Serious adverse events
Nakamura 2007[49]	*Varenicline (considered treatment related)*: one case of cholecystitis in the varenicline 0.25 mg b.i.d. group, which resolved after laparoscopic cholecystectomy, and one case of angina pectoris in the 1 mg b.i.d. group, which resolved after discontinuation of treatment
	Placebo: nature of SAEs not specified for placebo group
Niaura 2008[50]	*Varenicline*: myocardial infarction, ventricular fibrillation and spontaneous abortion (not considered related to treatment)
	Placebo: none reported
Nides 2006[51]	*Varenicline*: transient ischemic attacks in a subject with mild stenosis of the ipsilateral common carotid artery (considered possibly related to the study drug
	Bupropion: persistent intermittent bloody diarrhoea, syncope, and convulsion (two subjects) (considered possibly related to the study drug)
	Placebo: nature of SAEs not specified for placebo group
Oncken 2006[52]	*Varenicline, within 30 days of last study medication dose*: one subject in the 0.5 mg b.i.d. non-titrated group had a syncopal episode; four SAEs occurred in the 0.5 mg b.i.d. titrated group (one duodenal ulcer, one right ear cholesteatoma, one unstable angina, and one seizure following a car crash) and four SAEs occurred in the 1.0 mg b.i.d. group (one paroxysmal supraventricular tachycardia, one aseptic meningitis, one multiple sclerosis and one carcinoid colon cancer)
	Varenicline, more than 30 days after last study medication dose: diabetes mellitus in the 0.5 mg b.i.d. titrated group and cholelithiasis in the 1 mg b.i.d. non-titrated group
	Placebo: one syncope and one suicide attempt
Pfizer 2011[40]/ Williams 2012[41]	*Varenicline*: one chest pain; one convulsion; one depression; one psychiatric symptom; one suicidal ideation; one suicide attempt; and one asthma
	Placebo: one hyperglycaemia; one breast cancer; one aggression; and one suicidal ideation
Rennard 2012[53]	*Varenicline*: two intervertebral disc protrusion; one caratoid artery stenosis; one syncope; one peripheral arterial occlusive disease and one ureteric calculus with obstruction
	Placebo: one suicidal ideation
Rigotti 2010[54]	Nature of SAEs not specified
Smith 2013[55]	*Varenicline*: six deaths all non-related to study medication (patients had co-existing morbidities). One atrial fibrillation; four depressive episodes; and one aggression
	Counselling: seven deaths, all patients had underlying comorbidities
Steinberg 2011[56]	*Varenicline*: 15 SAEs defined as requiring or prolonging hospitalisation, but not further defined
	Placebo: 13 SAEs defined as requiring or prolonging hospitalisation, but not further defined
Tashkin 2011[57]	Nature of SAEs not specified
Tsai 2007[58]	*Varenicline*: one unstable angina, one peritonitis, one acute pyelonephritis
	Placebo: three traffic accidents
Tsukahara 2010[59]	Nature of SAEs not specified
Vinnikov 2008[43]	None reported
Wang 2009[60]	Placebo: one ulcer, one other not specified.
West 2011[17]	Not listed
Williams 2007[61]	Nature of all SAEs not specified
Wong 2012[37]	No severe adverse events reported

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