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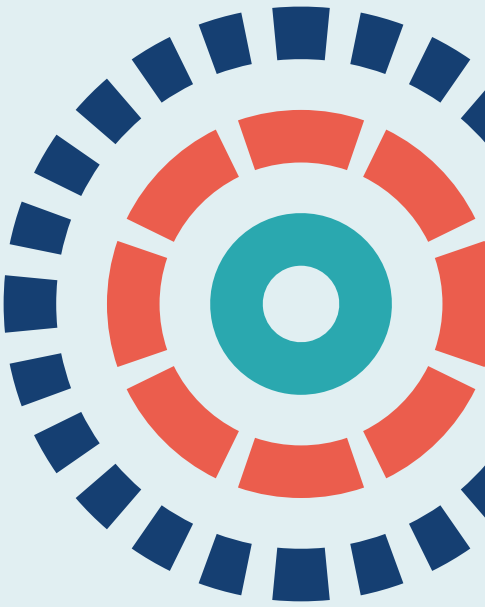

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This report

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Abstract

Smoking cessation medicines and e-cigarettes: a systematic review, network meta-analysis and cost-effectiveness analysis

Kyla H Thomas,[1*] Michael N Dalili,[1] José A López-López,[1] Edna Keeney,[1] David Phillippo,[1] Marcus R Munafò,[2,3,4] Matt Stevenson,[5] Deborah M Caldwell[1] and Nicky J Welton[1]

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Background: Cigarette smoking is one of the leading causes of early death. Varenicline [Champix (UK), Pfizer Europe MA EEIG, Brussels, Belgium; or Chantix (USA), Pfizer Inc., Mission, KS, USA], bupropion (Zyban; GlaxoSmithKline, Brentford, UK) and nicotine replacement therapy are licensed aids for quitting smoking in the UK. Although not licensed, e-cigarettes may also be used in English smoking cessation services. Concerns have been raised about the safety of these medicines and e-cigarettes.

Objectives: To determine the clinical effectiveness, safety and cost-effectiveness of smoking cessation medicines and e-cigarettes.

Design: Systematic reviews, network meta-analyses and cost-effectiveness analysis informed by the network meta-analysis results.

Setting: Primary care practices, hospitals, clinics, universities, workplaces, nursing or residential homes.

Participants: Smokers aged ≥ 18 years of all ethnicities using UK-licensed smoking cessation therapies and/or e-cigarettes.

Interventions: Varenicline, bupropion and nicotine replacement therapy as monotherapies and in combination treatments at standard, low or high dose, combination nicotine replacement therapy and e-cigarette monotherapies.

Main outcome measures: Effectiveness – continuous or sustained abstinence. Safety – serious adverse events, major adverse cardiovascular events and major adverse neuropsychiatric events.

Data sources: Ten databases, reference lists of relevant research articles and previous reviews. Searches were performed from inception until 16 March 2017 and updated on 19 February 2019.

Review methods: Three reviewers screened the search results. Data were extracted and risk of bias was assessed by one reviewer and checked by the other reviewers. Network meta-analyses were conducted for effectiveness and safety outcomes. Cost-effectiveness was evaluated using an amended version of the Benefits of Smoking Cessation on Outcomes model.

Results: Most monotherapies and combination treatments were more effective than placebo at achieving sustained abstinence. Varenicline standard plus nicotine replacement therapy standard (odds ratio 5.75, 95% credible interval 2.27 to 14.90) was ranked first for sustained abstinence, followed by e-cigarette low (odds ratio 3.22, 95% credible interval 0.97 to 12.60), although these estimates have high uncertainty. We found effect modification for counselling and dependence, with a higher proportion of smokers who received counselling achieving sustained abstinence than those who did not receive counselling, and higher odds of sustained abstinence among participants with higher average dependence scores. We found that bupropion standard increased odds of serious adverse events compared with placebo (odds ratio 1.27, 95% credible interval 1.04 to 1.58). There were no differences between interventions in terms of major adverse cardiovascular events. There was evidence of increased odds of major adverse neuropsychiatric events for smokers randomised to varenicline standard compared with those randomised to bupropion standard (odds ratio 1.43, 95% credible interval 1.02 to 2.09). There was a high level of uncertainty about the most cost-effective intervention, although all were cost-effective compared with nicotine replacement therapy low at the £20,000 per quality-adjusted life-year threshold. E-cigarette low appeared to be most cost-effective in the base case, followed by varenicline standard plus nicotine replacement therapy standard. When the impact of major adverse neuropsychiatric events was excluded, varenicline standard plus nicotine replacement therapy standard was most cost-effective, followed by varenicline low plus nicotine replacement therapy standard. When limited to licensed interventions in the UK, nicotine replacement therapy standard was most cost-effective, followed by varenicline standard.

Limitations: Comparisons between active interventions were informed almost exclusively by indirect evidence. Findings were imprecise because of the small numbers of adverse events identified.

Conclusions: Combined therapies of medicines are among the most clinically effective, safe and cost-effective treatment options for smokers. Although the combined therapy of nicotine replacement therapy and varenicline at standard doses was the most effective treatment, this is currently unlicensed for use in the UK.

Future work: Researchers should examine the use of these treatments alongside counselling and continue investigating the long-term effectiveness and safety of e-cigarettes for smoking cessation compared with active interventions such as nicotine replacement therapy.

Study registration: This study is registered as PROSPERO CRD42016041302.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta25590).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

AE	adverse event
BENESCO	Benefits of Smoking Cessation on Outcomes
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CrI	credible interval
DIC	deviance information criterion
EMA	European Medicines Agency
ENB	expected net benefit
ENDS	electronic nicotine delivery systems
EQ-5D	EuroQol-5 Dimensions
EVPI	expected value of perfect information
EVPPI	expected value of perfect partial information
FDA	Food and Drug Administration
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIQA	Health Information Quality Authority
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
MACE	major adverse cardiovascular event
MANE	major adverse neuropsychiatric event
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NRT	nicotine replacement therapy
ONS	Office for National Statistics
OR	odds ratio
PPA	point prevalence abstinence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
UKCTAS	UK Centre for Tobacco and Alcohol Studies

Plain English summary

Cigarette smoking is one of the main causes of early death both in the UK and worldwide. Three medicines, varenicline, bupropion and nicotine replacement therapy, are licensed in the UK to help people stop smoking. E-cigarettes can also be used as a stop smoking aid. We combined information from previous studies, including clinical trials, to determine which product was the safest, most effective and best value for money for the NHS. We compared treatments that were given alone as well as treatments that were combined with others, such as combination nicotine replacement therapy, varenicline combined with nicotine replacement therapy, varenicline combined with bupropion and bupropion combined with nicotine replacement therapy. The last three combined treatments are not currently licensed in the UK for smoking cessation. We also compared different treatment doses (low, high and standard doses). We found that most treatments were more effective than placebo in helping people to quit smoking. One of the combination treatments (varenicline at standard dose combined with nicotine replacement therapy at standard dose) was the most effective at getting people to quit smoking, followed by e-cigarette at low dose, varenicline at standard dose combined with bupropion at standard dose, and e-cigarette at high dose. We also found that smokers with higher tobacco dependence and smokers treated with counselling alongside medicines achieved a higher proportion of continuous quitting. We also found evidence that the standard dose of bupropion was associated with an increased risk of serious side effects compared with placebo. There was inconclusive evidence that any of the treatments increased the risk of major cardiovascular side effects. There was some evidence that smokers who received a standard dose of varenicline had an increased risk of major neurological and psychiatric side effects compared with those receiving a standard dose of bupropion. E-cigarette at low dose, varenicline standard plus nicotine replacement therapy standard and varenicline standard plus bupropion standard were the best value for money interventions, but further clinical trials comparing treatments against each other are needed to increase confidence in these findings.

Scientific summary

Background

Cigarette smoking is one of the leading causes of death in the UK and worldwide. In 2017, an estimated 77,800 deaths in England were attributable to smoking. Smoking costs the NHS between £2.6B and £5B per year. Varenicline, bupropion and nicotine replacement therapy are recommended by the National Institute for Health and Care Excellence and are licensed in the UK as medicines for smoking cessation. Although electronic cigarettes (e-cigarettes) are not licensed medicines, they may also be used in quit attempts in English smoking cessation services. All of the currently licensed smoking cessation medicines have been shown to be more effective than placebo in helping people quit smoking. However, concerns have been raised about the safety of smoking cessation medicines, particularly with respect to the neuropsychiatric safety of varenicline and the cardiovascular safety of varenicline and nicotine replacement therapy. There are also emerging concerns regarding the safety of e-cigarettes.

Objectives

The main research question addressed by this assessment is 'How do smoking cessation medicines compare with respect to their neuropsychiatric safety: a systematic review, network meta-analysis and cost effectiveness analysis?' The specific objectives of the assessment were:

- to perform a comprehensive systematic review and network meta-analysis of the clinical effectiveness and safety of varenicline, bupropion, nicotine replacement therapy and e-cigarettes as monotherapies and combination therapies in relation to each other, to placebo or to usual care
- to adapt a previously published economic model to incorporate the disutilities and costs resulting from adverse events in order to estimate the cost-effectiveness of monotherapies and combination therapies of smoking cessation medicines and e-cigarettes in the context of the NHS and primary care settings in the UK.

Methods

Clinical effectiveness and safety

Data sources

The data sources were MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands), PsycInfo® (American Psychological Association, Washington, DC, USA), Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA), ClinicalTrials.gov and Cochrane Databases including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE; updated until March 2015), the Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database, and reference lists of relevant research articles and previous reviews. The searches were performed from inception until 16 March 2017 and updated on 19 February 2019.

Study selection

For the review of studies reporting effectiveness, we included randomised controlled trials with durations of $\geq$ 6 months ($\geq$ 22 weeks) in any setting, including, but not limited to, primary care practices, hospitals, including inpatient and outpatient clinics, universities, workplace clinics, and nursing or residential homes. Trials with two or more study arms were included in the effectiveness

analyses, whereas crossover trials, non-randomised trials, quasi-randomised trials, large factorial studies and interrupted time series analyses were excluded.

For the review of studies examining safety, randomised controlled trials of any duration were included in addition to non-randomised (observational) studies with control groups. Uncontrolled observational studies (e.g. case reports and case series) were excluded, as were large factorial studies.

In both reviews, we included smokers aged ≥ 18 years of all ethnicities using UK-licensed smoking cessation therapies and/or electronic cigarettes. This included adult smokers accessing local authority stop smoking services. We also included smokeless-tobacco users. We excluded studies involving participants aged < 18 years, as varenicline, bupropion and electronic cigarettes are licensed for use only in adults in the UK. Non-smoking populations were excluded, as were pregnant and breastfeeding women, as varenicline and bupropion are not licensed for use in these groups in the UK.

Data extraction

Three reviewers screened the search results. Data were extracted and the risk of bias was assessed using the Cochrane risk-of-bias tool by one reviewer and checked by the other reviewers.

Outcomes

The main outcome measures were as follows:

- primary effectiveness outcome – continuous (or sustained abstinence)
- secondary effectiveness outcome – prolonged abstinence, any abstinence, 7-day point prevalence abstinence
- primary safety outcome – serious adverse events
- secondary safety outcome – major neuropsychiatric adverse events and major adverse cardiovascular events
- tertiary neuropsychiatric and cardiovascular outcomes
- other safety outcomes, including nausea, skin rash, headache and dry mouth.

Methods of data synthesis

Network meta-analyses were performed for the primary and secondary effectiveness and safety outcomes and the most frequently occurring other outcomes. The remaining outcomes were described narratively in tables. A sensitivity analysis was carried out to combine the safety outcomes from randomised and non-randomised evidence. Three different network meta-analysis models were considered: intervention effects defined by mode of delivery and dose (full interaction model), intervention effects defined by dose but assumed equal for different modes of delivery within an intervention and dose class (fixed-class model) and intervention effects defined by dose but effects of different modes of delivery assumed similar within an intervention and dose class (random-class model).

Cost-effectiveness

The model structure was based on the Sheffield model used in a previous Health Technology Assessment report on the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation. The Sheffield model was based on the Benefits of Smoking Cessation on Outcomes model. The population considered in the decision was adult smokers in the UK who were motivated to quit smoking. The perspective taken was that of the NHS for costs and health effects on the individual for outcomes, in line with National Institute for Health and Care Excellence guidance. A lifetime time horizon was taken, using a cohort simulation model to predict costs and utilities over a participant's lifetime.

Results

Results of the clinical effectiveness review

Three hundred and sixty-three trials reported on one or more effectiveness outcomes involving 201,045 participants across a range of settings. There was evidence that most monotherapies and combination treatments were more effective than placebo at helping participants achieve sustained (or continuous) abstinence. The three most effective treatments compared with placebo were varenicline standard plus nicotine replacement therapy standard (odds ratio 5.75, 95% credible interval 2.27 to 14.88), varenicline low plus nicotine replacement therapy standard (odds ratio 5.70, 95% credible interval 1.57 to 21.12) and e-cigarette low (odds ratio 3.22, 95% credible interval 0.97 to 12.55), although these estimates were very uncertain. Smokers randomised to varenicline standard plus nicotine replacement therapy standard were more likely to achieve sustained abstinence than participants receiving nicotine replacement therapy standard or bupropion standard. We also found that varenicline standard resulted in higher odds of sustained abstinence than nicotine replacement therapy standard or bupropion standard, and weak evidence that e-cigarette high may increase the odds of sustained abstinence compared with bupropion standard. Counselling delivered alongside medicines was associated with a higher proportion of smokers achieving sustained abstinence than medicines alone (additional log-odds ratio 0.86, 95% credible interval 0.45 to 1.27), and there was inconclusive evidence that this effect was synergistic (more effective than would be expected based on the sum of the pharmacological and counselling effects alone) (additional log-odds ratio 0.16, 95% credible interval −0.05 to 0.37). We also found a higher odds ratio of sustained abstinence among participants with higher average dependence scores (additional log-odds ratio 0.23, 95% credible interval 0.02 to 0.43).

The results for the secondary effectiveness outcomes were largely similar to those for sustained abstinence. Although reported in fewer studies and for fewer interventions, we found evidence that smokers treated with nicotine replacement therapy high, bupropion standard, varenicline standard and varenicline standard plus bupropion standard were more likely to achieve prolonged abstinence than those using placebo. Bioverified prolonged abstinence data at $\geq$ 6 months for e-cigarette or varenicline standard plus nicotine replacement therapy standard were not available. There was inconclusive evidence that bupropion standard, varenicline standard and varenicline standard plus bupropion standard differed from each other in the odds of achieving prolonged abstinence.

For our 'any abstinence' outcome, as for sustained abstinence, we found that most interventions were more effective than placebo at helping participants abstain from smoking, including e-cigarette at low and high doses. The three most effective treatments compared with placebo were bupropion low plus nicotine replacement therapy high, varenicline standard plus nicotine replacement therapy standard and varenicline not specified. Pairwise comparisons between interventions for 'any abstinence' indicated that smokers randomised to varenicline standard were more likely to achieve abstinence than those allocated to nicotine replacement therapy standard or bupropion standard. We also found that varenicline standard plus nicotine replacement therapy standard led to higher odds of abstinence than nicotine replacement therapy standard, bupropion standard, and bupropion standard plus nicotine replacement therapy standard, while varenicline standard plus bupropion standard led to higher odds of abstinence than bupropion standard alone.

Finally, there was evidence that a number of interventions were more effective than placebo at attaining 7-day point prevalence abstinence, including e-cigarette high. The three most effective treatments compared with placebo were bupropion low plus nicotine replacement therapy high, varenicline standard plus nicotine replacement therapy standard and varenicline not specified. In terms of 7-day point prevalence abstinence, our network meta-analysis indicated that smokers allocated to varenicline standard achieved abstinence more often than those using nicotine replacement therapy standard or bupropion standard. We also found that varenicline standard plus nicotine replacement therapy standard led to higher odds of abstinence than nicotine replacement therapy standard, bupropion standard or varenicline standard.

Ranking the interventions across primary and secondary effectiveness outcomes, varenicline standard plus nicotine replacement therapy standard showed a high probability of being ranked as the best or second-best intervention for all outcomes except prolonged abstinence, for which there were no data. Varenicline standard plus bupropion standard had the highest probability of being ranked as best for prolonged abstinence, but its rankings for other outcomes were less certain. Finally, varenicline standard showed high probabilities of being ranked second- to fourth-best across outcomes, while e-cigarette rankings were uncertain and placebo was consistently ranked last.

Results of the safety review

Three hundred and fifty-five trials reported on one or more safety outcomes involving 159,101 participants, and 53 observational studies involving 8,783,403 participants took place across a range of settings. There was evidence that, compared with placebo, bupropion standard increased the odds of experiencing serious adverse events (odds ratio 1.27, 95% credible interval 1.04 to 1.58).

Regarding secondary outcomes, we could not find any differences between interventions for major adverse cardiovascular events because of the rarity of events reported across studies, resulting in effect estimates with very wide confidence intervals. This did not change with the addition of 10 observational studies to our analyses; there was substantial uncertainty regarding the relative cardiovascular safety of the treatments. For major adverse neuropsychiatric events, there was evidence that smokers receiving nicotine replacement therapy not specified, bupropion standard, bupropion standard plus nicotine replacement therapy high or varenicline standard plus bupropion standard were less likely to report major adverse neuropsychiatric events than smokers treated with placebo. There was evidence of an increased odds of major adverse neuropsychiatric events for smokers randomised to varenicline standard compared with those using bupropion standard. Although 16 observational studies reported one or more major adverse neuropsychiatric events, our analyses incorporating these studies produced similar results to that of the randomised evidence. We found that bupropion standard, bupropion standard plus nicotine replacement therapy high and varenicline standard plus bupropion standard were associated with lower odds of experiencing a major adverse neuropsychiatric event than placebo. Intervention rankings have not been reported because they are unlikely to be robust as a result of the high levels of uncertainty associated with the safety outcomes.

Results of the cost-effectiveness review

There was a high level of uncertainty as to the most cost-effective intervention, although all of the interventions were cost-effective compared with nicotine replacement therapy low at the threshold for cost-effectiveness of £20,000 per quality-adjusted life-year. At this threshold, e-cigarette low appeared to be the most cost-effective intervention in the base case (expected net benefit £7085) followed by varenicline standard plus bupropion standard (expected net benefit £6756) and then varenicline standard plus nicotine replacement therapy standard (expected net benefit £6591). However, the probability of being the most cost-effective intervention was < 0.3 for all interventions. When the impact of major adverse neuropsychiatric events was excluded, varenicline standard plus nicotine replacement therapy standard was the most cost-effective intervention (expected net benefit £9895), followed by varenicline low plus nicotine replacement therapy standard (expected net benefit £9759). These results are also uncertain, with the probability of being the most cost-effective intervention being < 0.4 for all interventions. When the analysis was limited to interventions that are licensed in the UK, varenicline standard was the most cost-effective intervention (expected net benefit £3697), followed by nicotine replacement therapy standard (expected net benefit £3663).

The value-of-information analysis found that a large, adequately powered, randomised controlled trial of e-cigarettes against an active comparator such as varenicline standard plus nicotine replacement therapy standard or nicotine replacement therapy standard is likely to be a cost-effective use of research resources (population expected value of partial perfect information over a 5-year horizon = £3209M).

Conclusions

Our findings suggest that combined therapies of smoking cessation medicines are among the most clinically effective, safe and cost-effective treatment options for smokers. Although combination nicotine replacement therapy is commonly prescribed, combined therapy of nicotine replacement therapy delivered alongside varenicline at standard doses (currently unlicensed) was shown to be the most effective treatment for most cessation outcomes. Using combined therapies instead of monotherapy treatments may offer smokers a better chance of successfully quitting smoking over both short and long periods of time.

Although the use of bupropion standard may increase the odds of serious adverse events compared with placebo, we did not find strong evidence of any other negative associations between medicines and serious adverse events, major adverse cardiovascular events or major neuropsychiatric adverse events relative to placebo. Although e-cigarettes showed promise as cessation tools that are likely to be cost-effective, their safety profile remains uncertain and no existing model of the devices has been licensed as a medicine. This study has used the most up-to-date information to give an estimate of the most cost-effective intervention for smoking cessation in the UK today. This analysis showed that, in the base case, e-cigarette low, varenicline standard plus nicotine replacement therapy and varenicline standard plus bupropion standard appeared to be the most cost-effective interventions, although these results were uncertain. When the impact of the safety outcomes of depression and self-harm was excluded, varenicline standard plus nicotine replacement therapy standard was the most cost-effective intervention.

The research recommendations are as follows:

- Study authors should ensure complete and accurate reporting of their study methodology to reduce the number of domains identified as being at unclear risk of bias owing to a lack of detailed description of study motives.
- There should be improved reporting of safety data in studies. Consideration should be given to creating a core outcome set for safety outcomes in studies of smoking cessation to ensure the systematic recording and reporting of adverse events.
- A large randomised controlled trial comparing e-cigarettes with active comparators is needed, with long follow-up to enable the collection of sufficient safety data.

Study registration

This study is registered as PROSPERO CRD42016041302.

Funding

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Chapter 1 Background

Description of the health problem

Cigarette smoking is one of the leading causes of early death both in the UK and worldwide.[1,2] Although smoking is now down to fewer than 1 in 6 adults (14.4%) in the UK, this still equates to approximately 7.35 million people in the population.[3] In 2017, 77,800 deaths were estimated to be attributable to smoking in England, representing 16% of all deaths and 33% of deaths from conditions that can be caused by smoking.[3] The cost of smoking to the NHS has been estimated at between approximately £2.6B and £5B per year,[4,5] with the total cost to society in England estimated at approximately £12.9B per year.[6]

Description of the interventions under assessment

Smoking cessation medicines and electronic cigarettes

National Institute for Health and Care Excellence (NICE) public health guidance recommends the use of three medicines, varenicline, bupropion and nicotine replacement therapy (NRT), as aids to quitting smoking in the UK.[7] Varenicline is a partial agonist selective for alpha-4 beta-2 nicotinic receptor subtypes. It binds to these receptors, causing a dopamine release, albeit less than that from smoking, while simultaneously blocking the action of nicotine itself.[8,9] Therefore, it acts to both limit the reward experienced by smoking and counteract the withdrawal symptoms experienced during smoking cessation attempts that result from low dopamine release in the absence of nicotine. Varenicline was approved as a prescription smoking cessation aid in 2006 by the US Food and Drug Administration (FDA) as Chantix (Pfizer Inc., Mission, KS, USA), and by the European Medicines Agency (EMA) as Champix (Pfizer Europe MA EEIG, Brussels, Belgium). It was recommended by NICE in July 2007 as an option for smokers who had expressed a desire to quit smoking as part of a programme of behavioural support.[10,11]

Bupropion, or Zyban (GlaxoSmithKline, Brentford, UK), was licensed by the FDA in 1997 and by the Medicines and Healthcare products Regulatory Agency (MHRA) in June 2000 as a stop-smoking medicine. It is also used off-licence in the UK and in the USA as an antidepressant.[12] It has both dopaminergic and adrenergic actions and also appears to be an antagonist at the nicotinic acetylcholine receptor.[13] The drug promotes smoking cessation by blocking nicotine effects, relieving withdrawal symptoms,[14,15] or, in its antidepressant role, by blocking the neuronal reuptake of dopamine and noradrenaline, thereby reducing low mood.[16]

Nicotine replacement therapy (NRT) refers to products used to assist with a quit attempt by delivering nicotine to satisfy tobacco cravings and preventing withdrawal symptoms. NRT can come in fast-acting forms, such as gum, lozenge, spray, inhalator and tablet, or as slow-acting patches, and are often used in combination, to deliver varying doses of nicotine based on one's level of tobacco dependence, as standard care in the UK.

In late 2015, the MHRA approved the use of the first electronic cigarette, British American Tobacco's 'e-Voke', as a smoking cessation medicine.[17] Electronic cigarettes (also known as e-cigarettes, e-cigs, electronic nicotine delivery systems or vapes) are battery-powered devices that heat a liquid, typically containing nicotine, flavourings and additives, to generate an aerosol or a 'vapour', which the user then inhales.[18] However, e-Voke's development was terminated before the product could come to market. Although no e-cigarettes are currently licensed as medicines, NICE guidance recognises that e-cigarettes may help people to quit smoking cigarettes.[7,19] An independent expert review of e-cigarettes published

by Public Health England in 2015[20] advised that e-cigarettes should be considered as an option for smokers who have failed to quit smoking by other methods. The report's statement that e-cigarettes are 95% safer than tobacco smoking remains controversial. An updated report published in 2018 recommended improved access to e-cigarettes for people in disadvantaged groups and the importance of facilitating the regulation of some e-cigarettes as medicines via the MHRA.[21]

Changes in prescribing patterns

The number of prescriptions of all smoking cessation medicines has shown an overall reduction over the past 10 years, which may reflect the decrease in smoking prevalence and/or the increased use of e-cigarettes. Prescription data from 2018/19 show 740,000 total prescriptions of smoking cessation medicines, with 396,000 prescriptions of NRT (note that NRT is also available over the counter without a prescription), 24,000 prescriptions of bupropion and 320,000 prescriptions of varenicline.[3] In 2018, there were an estimated 3.2 million adult users of e-cigarettes in Great Britain.[22] Notably, the number of prescription items of varenicline dispensed in England decreased by 51% from a peak of 987,000 prescriptions in 2011 to 489,000 prescriptions in 2016,[23] possibly reflecting ongoing fears among prescribers and patients about varenicline's neuropsychiatric safety as a result of the safety warnings on varenicline's product labelling during that time (see *Adverse events*).

Effectiveness

All of the currently licensed smoking cessation medicines have been shown to improve people's chances of quitting smoking compared with placebo.[24–27] Varenicline has been shown to be the most clinically effective monotherapy for long-term smoking abstinence (i.e. > 6 months).[25] However, combination NRT has been shown to be just as effective as varenicline as an aid to quitting smoking.[25]

Adverse events

Concerns have been raised about the safety of smoking cessation medicines, particularly with respect to the neuropsychiatric safety of varenicline and the cardiovascular safety of varenicline and NRT. There are emerging concerns about the safety of e-cigarettes. Severe safety warnings about a potential increased risk of serious neuropsychiatric adverse events (AEs) (depression, suicidal ideation and suicidal behaviour) in patients prescribed varenicline have previously been issued by regulatory agencies.[28,29] A black-box warning, the FDA's most serious safety warning, was placed on varenicline's product labelling between 2009 and 2016.[30,31] These safety warnings were based on spontaneous reports to the MHRA's Yellow Card Scheme in the UK and the FDA's Adverse Events Reporting System in the USA.

Previous research into the neuropsychiatric safety of varenicline has provided inconsistent findings, adding to the debate.[32] In April 2016, the results of the EAGLES trial,[33] a randomised controlled trial (RCT), were published. This study randomised 8144 smokers to receive varenicline, transdermal NRT patch, bupropion or placebo. The trial's findings provided evidence suggesting that neither varenicline nor bupropion were associated with an increase in neuropsychiatric AEs relative to nicotine patch or placebo. Subsequently, the EMA lifted the warning about possible suicidal risks from varenicline in April 2016,[34] which was followed by the FDA's decision to remove the black-box warnings on varenicline's labelling in December 2016.[35] In terms of neuropsychiatric events, bupropion use has been specifically associated with an elevated risk of seizures.[36] However, a review by Hughes *et al.*[26] determined that, despite reported events, seizures remained rare, as the average rate was lower than the 1 : 1000 estimated risk reported in the product's safety information.

Previous systematic reviews comparing varenicline with placebo have reported inconsistent findings regarding varenicline's cardiovascular safety.[37,38] Mills *et al.*[39] conducted a network meta-analysis (NMA) to investigate the comparative safety of varenicline, bupropion and NRT for cardiovascular events, including major adverse cardiovascular events (MACEs) such as cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Although the authors found no clear evidence that varenicline or bupropion use was associated with an elevated risk of any cardiovascular events, NRT use was associated with an increased risk of events. This finding was driven by lower-risk events, typically tachycardia or arrhythmia.

However, NRT use was not associated with an increased risk of experiencing a MACE.[39] Similarly, based on the EAGLES trial and a 28-week extension that followed a subset of 4595 participants, Benowitz *et al.*[40] found inconclusive evidence that varenicline, bupropion or NRT increased the risk of MACEs.

Safety concerns about e-cigarettes include the risks associated with the devices being manufactured to variable standards, the risks of specific flavouring components, potentially harmful constituents found in the vapour and uncertainty about the long-term health impact on e-cigarette users.[41–43] More recently, there have been reports of an outbreak of lung injury associated with e-cigarette use in the USA, with seven confirmed deaths.[44] A similar outbreak has not been observed in the UK. However, in general, there is limited research and a lack of evidence regarding the safety of e-cigarettes compared with licensed smoking cessation medicines. Nonetheless, concerns about safety have led to a wide variety of regulatory decisions regarding the sale and use of e-cigarettes worldwide. Whereas e-cigarettes are widely available for sale as consumer products in the UK, their use is restricted in several countries.[45] Some countries (India, Uruguay, Jordan and Saudi Arabia) have banned the devices; in Thailand, possessing the devices can result in a 10-year prison conviction.[45,46]

Reasons for conducting this review

The ongoing debate regarding the safety of drugs for smoking cessation may be a result of the inconsistent research findings in this area.[32] Studies without control groups (those using AE reporting data and case studies)[47–49] have reported increased neuropsychiatric risks of varenicline and bupropion, whereas studies with control groups (observational cohort studies, RCTs, and systematic reviews of RCTs) have reported the opposite, and found inconclusive evidence of an increased risk of severe outcomes in patients prescribed these medicines.[50–56] Although large RCTs such as the EAGLES trial (the largest RCT comparing the neuropsychiatric safety of smoking cessation medicines) provide better evidence than non-randomised studies, even its sample size, and thereby its statistical power, was limited relative to that of much larger observational cohort studies.[53,57]

There have also been inconsistent findings regarding the cardiovascular safety of these medicines. A 2011 meta-analysis[38] of 14 trials reported an increased risk of serious adverse cardiovascular events. However, a larger meta-analysis[37] published the following year found no significant increase in serious cardiovascular AEs associated with varenicline use. The largest meta-analysis[39] of cardiovascular safety to date found no clear evidence that varenicline or NRT were associated with major adverse cardiovascular events. Bupropion was shown to be protective. However, NRT was associated with an elevated risk of less serious AEs, including tachycardia and palpitations.

To date, studies have focused mainly on comparing the safety of varenicline monotherapy with placebo.[50–52,58] However, making comparisons with other smoking cessation drugs is likely to be of greater relevance to patients, prescribers and regulators. Additionally, in the UK, although e-cigarettes are not licensed medicines, they are also used in smoking cessation, and, given their popularity, it is important to review their safety and effectiveness as smoking cessation aids.[22] Updated cost-effectiveness analyses of these medicines in UK settings will also be conducted to inform the overall risk–benefit evaluation of the different smoking cessation medicines and to determine which treatment represents the best 'value for money' to the NHS.

Clinical trials in this area have the following limitations:

- Relatively few smoking cessation trials compare medicines against each other or in combination, which can be addressed using NMA to estimate the comparative effectiveness and safety of medicines tested against a common comparator (placebo).
- Safety reporting varies greatly across trials.

The limitations of previous synthesis research in this area are as follows:

- There have been no comprehensive reviews of the neuropsychiatric safety of the smoking cessation medicines in relation to each other, as existing reviews mainly compare monotherapies with placebo.
- Previous reviews have failed to comprehensively investigate the safety of smoking cessation medicines in a NMA by not including data from all RCTs irrespective of their duration. As AEs may occur within hours or days of starting treatment,[59] the previous NMAs that excluded RCTs of < 6 months[58,60] may have failed to capture AEs reported in shorter-duration trials.
- There is a lack of sufficient data for nodes in the previous neuropsychiatric safety NMAs.[58,60]
- None of the previously published NMAs has examined combined therapies of smoking cessation medicines,[25,58,60] not currently licensed for use in the UK, although the effectiveness and safety of combined treatments are increasingly being examined in trials.
- No recent cost-effectiveness analyses have fully accounted for AEs in order to determine which UK-licensed smoking cessation medicine is estimated to be the most cost-effective in UK settings.

The limitations of previous cost-effectiveness analyses in this area are as follows:

- No previous cost-effectiveness analysis could be identified that compared the full range of available pharmacological interventions, comparing the standard licenced interventions with combination therapies and e-cigarettes.
- No previous cost-effectiveness analysis has incorporated safety outcomes.
- Only one previous study has compared the cost-effectiveness of e-cigarettes with that of NRT[61] but, to our knowledge, no previous study has assessed the cost-effectiveness of e-cigarettes compared with all other interventions available in the UK.

There is, therefore, a need for an updated and comprehensive review of the evidence for the safety and effectiveness of licensed smoking cessation medicines and electronic cigarettes to allow patients, prescribers and regulators to make informed decisions about treatment choice and to establish the cost-effectiveness of these treatments in UK settings.

Chapter 2 Research questions

Objectives of the evidence review

Our specific objectives were:

- to perform a comprehensive systematic review and NMA of the clinical effectiveness and safety of varenicline, bupropion, NRT and e-cigarettes as monotherapies and combination therapies in relation to each other, placebo or usual care
- to adapt a published economic model to incorporate the disutilities and costs resulting from AEs in order to estimate the cost-effectiveness of monotherapy and combination therapies of smoking cessation medicines and e-cigarettes in the context of the NHS and primary care settings in the UK
- where sufficient data are available, to explore the following subgroups in the NMA: those with psychiatric illness, those with comorbid conditions, heavy smokers (defined as people who smoke > 20 cigarettes per day), smokeless-tobacco users and smokers not willing to quit.

Chapter 3 Review methods: assessment of clinical effectiveness and safety

Introduction

We conducted systematic reviews with NMAs of:

- effectiveness of smoking cessation medicines and e-cigarettes using RCTs
- safety of smoking cessation medicines and e-cigarettes using RCTs and non-randomised (observational) studies.

We undertook these reviews in accordance with the Centre for Reviews and Dissemination (CRD) guidelines for undertaking systematic reviews[62] and the *Cochrane Handbook for Systematic Reviews of Interventions*[63] (as updated online during 2011: www.cochrane-handbook.org; accessed September 2019). We prospectively registered the reviews in the PROSPERO (international prospective register of systematic reviews) database (www.crd.york.ac.uk/prospero; accessed September 2019), with registration number CRD42016041302. A protocol of the review has also been published as a journal article.[64]

Eligibility criteria

Study designs

For the review of studies reporting effectiveness, we included RCTs with duration of ≥ 6 months (≥ 22 weeks) in any setting, including, but not limited to, primary care practices, hospitals, including inpatient and outpatient clinics, universities, workplace clinics, nursing or residential homes. Trials with two or more study arms were included in the effectiveness analyses, whereas crossover trials, non-randomised trials, quasi-randomised trials, large factorial studies and interrupted time series analyses were excluded.

For the review of studies examining safety, RCTs of any duration were included in addition to non-randomised (observational) studies with control groups. Uncontrolled observational studies (e.g. case reports and case series) were excluded, as were large factorial studies.

Participants

In both reviews, we included smokers aged ≥ 18 years of all ethnicities using UK-licensed smoking cessation therapies and/or electronic cigarettes. This included adult smokers accessing local authority stop-smoking services. We also included smokeless-tobacco users irrespective of whether or not they smoked. We excluded studies with participants aged < 18 years, as varenicline, bupropion and electronic cigarettes are licensed for use only in adults in the UK. Non-smoking populations were excluded, as were pregnant and breastfeeding women, as varenicline and bupropion are not licensed for use in these groups in the UK.

Interventions and comparators

Three smoking cessation medicines were the focus of all reviews, varenicline, bupropion and nicotine replacement therapy (NRT), as monotherapies as well as in combination treatments (e.g. varenicline combined with NRT, varenicline combined with bupropion and bupropion combined with NRT). We also assessed e-cigarette monotherapies as e-cigarettes are used in smoking cessation, although they are not licensed medicines in the UK. For NRT, combinations of different formulations given concurrently, for example patch and gum, were also included. Different dosages of treatments were also examined,

classified into low, standard and high, as described below. The dose categories for active interventions were determined using the *British National Formulary* (BNF)[65] and the MHRA public assessment report for the 'e-Voke'[66] (*Table 1*).

We also identified two additional NRT treatments: NRT combination, whereby two or more NRT products were administered in combination in a single arm, and NRT choice, whereby participants were given a choice of NRT products they could select to use. The dosage for NRT combination was indicated based on the highest dose among assigned products, while the dosage for NRT choice was indicated only when dosages for every offered product were reported.

We excluded trial arms of interventions in which patients could receive more than one intervention but where these were undefined (i.e. 'mixed' rather than 'combination' interventions). We also excluded alternative and complementary therapies (e.g. hypnotherapy, acupuncture, aromatherapy and herbal therapies).

As the reviews were conducted to inform NMAs, we determined the comparator interventions to ensure that they would provide information on the relative effectiveness/safety of the interventions of interest. Comparators were chosen based on the possibility of informing indirect evidence on the relative effectiveness of the interventions; and on the 'distance' of these comparators from our interventions of interest in the network, which relates to the likely increase in precision in the estimates of relative effectiveness and safety. We defined the following comparators:

- placebo (reference comparator for the NMAs)
- no drug treatment (including brief advice)
- usual care
- waitlist.

Where psychotherapies were included in each arm of a study (e.g. studies of a pharmacological treatment plus psychotherapy vs. psychotherapy alone), these studies were included and were analysed

TABLE 1 Interventions by formulation and dosage

Treatment (formulation)	Low dose	Standard dose	High dose
Bupropion (oral extended-release tablets)	< 150 mg b.i.d.	150 mg b.i.d.	> 150 mg b.i.d.
Varenicline (tablets)	< 1 mg b.i.d.	1 mg b.i.d.	> 1 mg b.i.d.
E-cigarette (electronic inhaler, five cartridges/day)	10 mg		15 mg
NRT			
NRT patch (16 hours)	< 15 mg	15 mg	> 15 mg
NRT patch (24 hours)	< 14 mg	14 mg	> 14 mg
NRT gum (15/day)		2 mg	4 mg
NRT nasal spray (2 sprays/hour, 64/day)		0.5 mg	
NRT mouth spray (4 sprays/hour, 64/day)		1 mg	
NRT lozenge (1 lozenge/1–2 hours, 15/day)	< 2 mg	2 mg	4 mg
NRT sublingual tablet (2 mg/tablet, 40/day)		1/hour	2/hour
NRT inhalator		10 mg (12/day)	15 mg (6/day)

b.i.d., twice a day.

as pharmacological treatment compared with no drug treatment, under the assumption of no interaction between pharmacological and psychotherapies when given together. Where psychotherapies were given as an adjunct to pharmacological treatments, but not in all arms of the study (e.g. studies of pharmacological treatment plus psychotherapy vs. usual care), these studies were included in the base case analysed as pharmacological treatment compared with no drug treatment, and the impact of the addition of psychotherapy was estimated using meta-regression. We assessed the sensitivity of our findings to excluding such studies in a sensitivity analysis. Although the efficacy of psychotherapies was not the focus of this review, studies in which psychotherapy was used as a comparator (e.g. studies of pharmacological treatment vs. psychotherapy) could potentially provide useful indirect evidence for estimates between pharmacological therapies. However, only four trials were identified in which this could have been possible and the psychotherapies used were very different across these studies, making such a comparison unreliable. We, therefore, did not include psychotherapy as a comparator in the NMA.

Outcomes of interest

Effectiveness

We only included bioverified events in our main analyses reported at $\geq$ 6 months' follow-up. We used Cochrane definitions for all outcomes.[68] Our primary effectiveness outcome was continuous (or sustained) abstinence defined as avoidance of all tobacco use since the quit day until the time the assessment was made, occasionally allowing for lapses where specified. Secondary effectiveness outcomes included:

- Prolonged abstinence – a measure of cessation that 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.
- Any abstinence – an outcome where we included abstinence by any definition reported at 6 months. Where studies reported more than one cessation outcome, we preferred continuous/sustained abstinence, followed by prolonged abstinence, 30-day point prevalence abstinence (PPA), 7-day PPA and any other abstinence.
- 7-day PPA – a measure of cessation based on behaviour over a 7-day period.

Safety

The primary composite safety outcome was serious adverse events (SAEs), defined as events that resulted in death, were life-threatening, required hospitalisation or resulted in significant disability.[69] We also recorded hospitalisation, treatment discontinuation and withdrawal from study as a result of AEs.

Furthermore, we sought data on the following outcome categories.

- Cardiovascular outcomes:
    - Secondary composite outcome – MACEs, including cardiovascular death, non-fatal myocardial infarction (excluding unstable angina), and fatal and non-fatal stroke.[70]
    - Tertiary outcomes – arrhythmias, congestive heart failure, unstable angina, palpitations, thromboembolism (deep-vein thrombosis or pulmonary embolism), and transient ischaemic attack.
- Neuropsychiatric outcomes:
    - Secondary composite outcome – major adverse neuropsychiatric events (MANEs), comprising suicide, attempted suicide, suicidal ideation, depression and seizures.[51]
    - Tertiary outcomes – abnormal dreams, aggression, anxiety, insomnia, irritability, sleep disorders and somnolence.
- Other outcomes: chronic obstructive pulmonary disease (COPD), dry mouth, fatigue, headache, nausea, pruritus, skin rash and all-cause death.

For the systematic review of RCTs, primary and secondary composite outcomes and the most frequent other outcomes were addressed in NMAs, whereas the remaining outcomes were reported in tables. Conversely, the systematic review of non-randomised studies retrieved a much smaller number of interventions; therefore, we decided to combine safety outcomes from randomised and non-randomised evidence in a sensitivity analysis. Outcomes reported in observational studies were presented in tables.

Identification of evidence

Search strategy

We searched the following databases: MEDLINE, EMBASE™ (Elsevier, Amsterdam, the Netherlands), PsycInfo® (American Psychological Association, Washington, DC, USA), Web of Science™ (Clarivate Analytics, Philadelphia, PA, USA), ClinicalTrials.gov and the Cochrane databases including the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects (DARE; updated until March 2015), the Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment (HTA) database. Searches were conducted with the help of information specialists and did not include any language restrictions. Non-English-language articles were reviewed by native speakers before a full translation was obtained. We also manually searched the reference lists of relevant research articles and previous reviews and communicated with authors to identify unpublished information.

To identify studies for the effectiveness NMAs, the search strategies from recent Cochrane reviews[24,26,71,72] were used to create an updated strategy to identify more recent trials for inclusion in the current study in addition to trials identified by past reviews. To identify studies for the safety NMAs, we built on the basic search strategy included in the cardiovascular NMA by Mills *et al.*[39] Searches for non-randomised studies were not date-limited. We completed our original searches on 16 March 2017 and our update searches were completed on 19 February 2019. For the search terms we used for our MEDLINE searches, see *Appendix 1*.

Assessing relevance and inclusion

Search results were uploaded to Covidence,[73] which we used to screen abstracts and full texts and to resolve disagreements. Three reviewers independently screened abstracts to determine whether or not full-text reports should be obtained. The same reviewers independently identified eligible full-text reports for inclusion. Each record was screened by at least two reviewers at each stage. Discrepancies were resolved by reaching consensus among reviewers.

Data extraction

Data for included studies were extracted by one reviewer and checked by co-reviewers. Information was collected on study design (duration of treatment, description of allocation concealment and blinding), study participants (country, region and population studied), baseline characteristics (e.g. ethnicity, sex and smoking history), intervention and comparison groups (including the smoking cessation intervention, whether or not there was cotreatment, dosage and formulation), our predefined primary and secondary outcomes of interest including measures of effectiveness and safety outcomes, losses to follow-up and study sponsor. In the event of missing data, we contacted authors by e-mail to ask for original data. Authors of all identified studies with randomised controlled designs were contacted to verify the accuracy of the extracted data and/or to provide safety data.

Assessment of risk of bias in included trials

For all studies, the Cochrane tool for assessing the risk of bias[74] was used to determine whether there was a high, low or unclear risk of bias in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias. An overall risk of bias was also determined by selecting the highest rating of bias across domains, with the exception of selective outcome reporting. Reviewers independently assessed the risk of bias in each of the trials. Discrepancies were resolved by referring to the original publication and reaching consensus among reviewers. To aid with the risk-of-bias assessment, study authors of RCTs were contacted to obtain study protocols and additional information that may not have been published.

Selection of data for analysis

Intervention definitions

To perform NMAs, we had to allocate each intervention group in each trial to a category, with each intervention category forming a 'node' in the network. We defined intervention nodes according to the type and intensity of treatment and/or NRT received.

Quantitative synthesis (including network meta-analysis)

We performed a NMA for each outcome. NMA is a methodology that enables the quantitative integration of a collection of primary studies by pooling evidence from all intervention comparisons considered in those primary studies. Results for each pairwise comparison combine both the direct evidence, based on the head-to-head intervention comparisons made in primary studies, and the indirect evidence, which refers to the intervention comparisons inferred from the network via comparator interventions.[75,76] NMA thus enables an estimation of relative intervention effect estimates for every pair of interventions, regardless of whether or not they have been compared directly in a RCT. It also enables the inference of the ranking of treatments for a given outcome.

To be included in the analyses, studies were required to report the proportion of events for each arm (or enough information to calculate it manually), and to report at least one event in one of the arms for the outcome analysed. We considered three different NMA models:

1. Full interaction model – this is the standard NMA model in which each different combination of drug type, drug intensity, NRT type and NRT intensity is considered as a separate intervention.
2. Fixed-class model – this model assumes that the interventions can be grouped into classes, with treatment effects in the same class assumed to be identical.[77] We defined classes according to type of treatment and delivery.
3. Random-class model – this model also groups treatments into classes, but treatment effects in the same class are now assumed to be centred around a class mean effect with between-treatment variability within class.[77] This model yields both treatment and class effects. We defined classes according to type of treatment and delivery.

We chose between different models using the posterior mean deviance as an indicator of model fit and the deviance information criterion (DIC) as a measure of parsimony (with a preference for lower values of each). We created network plots to provide visual images of the data structure in each analysed outcome. The node sizes of the network plots are proportional to the number of patients randomised to each intervention, whereas the thickness of the edges (lines) is proportional to the number of patients contributing to that comparison. Therefore, the edges in the network plots connect interventions for which direct evidence was available. We plotted the networks to illustrate the data

structure for each analysed outcome. Interventions not included in the analysis have their names written between square brackets. Interventions were excluded if they were disconnected from the main network or if they caused convergence problems in the statistical estimation (typically owing to small numbers, with zero events in one or more arms of a study). Our NMAs treat data as binomial, modelling the number of events out of the total number of participants (number randomised) using a logistic model.[77] For each outcome, we defined the denominator for each group using the intention-to-treat principle (i.e. the number of randomised patients as the denominator of the formula, irrespective of attrition). Where outcome data were presented for multiple time points, we took the longest period of follow-up. For some effectiveness outcomes (sustained and prolonged abstinence), we included only observations with a minimum follow-up period of 24 weeks.

We excluded studies that had insufficient information about the numbers of events per arm (i.e. the number of events was not reported and it was not possible to calculate this using the available information in the paper) and we also excluded studies with no events in any arm from the analyses. Where there were events in at least one arm of a trial but no events in one or more other arms, we added 0.5 events to all cells in the 2×2 table for that trial.[78]

Owing to the anticipation of heterogeneity,[79] we took a random-effects approach to the meta-analyses, assuming a common heterogeneity variance across all comparisons.[75] We conducted the statistical analyses within a Bayesian framework using OpenBUGS (version 3.2.3; Andrew Thomas, OpenBUGS Foundation; Cambridge), simulating two Markov chains with 30,000 iterations for each chain (plus 15,000 burning iterations). We monitored the treatment effects, between-study and between-treatment (within-class) standard deviation (SD). Furthermore, we examined ranking of classes of monotherapies or combinations of therapies by estimating the probability that each intervention is best, second best, and so on, across safety and effectiveness outcomes. We included only standard doses, except for e-cigarettes.

We assessed convergence of the Markov chains by using the potential scale reduction factor[80] and examining the history and autocorrelation plots for each estimated parameter. We appraised goodness of fit by calculating the posterior mean residual deviance, whereby smaller values indicate better-fitting models and values close to the number of unconstrained parameters indicate a well-fitting model. Comparisons of models were made using the DIC.[81] The DIC penalises the posterior mean residual deviance (a measure of model fit) by the effective number of parameters in the model (as measure of complexity) and can, therefore, be viewed as a trade-off between the fit and complexity of the model. Smaller values are preferred, with differences of three or more considered meaningful. When two models fit the data similarly, we interpreted results from the most parsimonious model.

The validity of NMA depends on the assumption that there is no effect modification of the pairwise intervention effects or that the prevalence of effect modifiers is similar in the different studies. This key assumption has been referred to variously as exchangeability, transitivity, similarity and consistency.[80,82–84] We examined the tenability of the consistency assumption for different networks by comparing the posterior mean residual deviance, DIC, and between-study SD for the NMA model that assumes consistency with an inconsistency model that relaxes this assumption (an unrelated mean effects model).[85] When both direct and NMA effect estimates were available and differed (up to the second decimal place of the standard error), we used both to back-calculate the indirect estimates, while making the assumption that the NMA estimates (from the consistency model) are the result of a weighted average of normally distributed direct estimates (from the unrelated mean effects model) and the indirect estimates. A local measure of inconsistency for a specific comparison can be obtained by comparing the direct and indirect estimates for that comparison. Note that for many comparisons there was either only direct evidence or only indirect evidence, so that the NMA estimates correspond to one of these.

Further analyses

We performed meta-regression[86] to explore the influence of several covariates as potential effect modifiers for the primary effectiveness and safety outcomes, namely:

- Dependence – we combined average scores of several scales at the arm level with a hierarchy of preferred measurements. Specifically, we used scores on the Fagerström Test for Nicotine Dependence[87] in preference to the Fagerström Tolerance Questionnaire,[88] with Heaviness of Smoking Index[89] as a third alternative. The average scores from each arm were standardised to make the numbers comparable across different scales.
- Funding source – industry compared with non-industry sponsorship.
- Counselling – interventions that included pharmacological treatment plus counselling compared with pharmacological treatment alone.
- Type of placebo – for placebo arms, we examined the influence of including a drug placebo (alone or combined with NRT placebo) in comparison with NRT-only placebo arms.
- Duration of treatment in each arm (in weeks).
- Studies including samples in which all (or most) participants had one or more current psychiatric condition (e.g. depression, schizophrenia, bipolar disorder or substance misuse), compared with other studies.
- Studies including samples in which all (or most) participants had one or more of the 17 comorbidities specified by the Charlson Comorbidity Index,[90] compared with other studies.
- Studies in which patients were not required to make a quit attempt, compared with other studies.
- Studies focused on smokeless-tobacco consumers, compared with other studies.
- Studies in which patients were heavy smokers, compared with other studies. We defined samples of heavy smokers as those in which the average of smoked cigarettes was > 20 per day.
- Publication year.

Furthermore, we performed sensitivity analyses excluding different subsets of studies assessed as being at high risk of bias on any domain, and also a sensitivity analysis excluding studies that compared a pharmacological intervention plus counselling with control (where counselling was not given in each arm). Threshold analysis, a form of sensitivity analysis, was also performed to determine the robustness of our treatment recommendations for the primary effectiveness and safety outcomes to changes in the evidence provided by the individual studies.[91–93] Threshold analysis determines how much the evidence could change for any reason, such as bias or random error, before the treatment recommendation changes, and describes this using a set of thresholds. These thresholds can be compared with judgements of the plausible magnitude of potential biases and with estimates of uncertainty [e.g. confidence intervals (CIs)]. In this manner, we may have more confidence in conclusions that are shown to be robust, and can appropriately acknowledge where conclusions are shown to be sensitive to plausible biases or uncertainty in the evidence.

Chapter 4 Economic evaluation methods: assessment of cost-effectiveness

Introduction

The economic evaluation aimed to compare the cost-effectiveness of pharmacological treatments to aid smoking cessation, including NRT and e-cigarettes. The population considered in the decision was smokers in the UK aged ≥ 18 years who were motivated to quit smoking. The treatments compared were those included in the NMA on sustained abstinence (see *Chapter 5*). The NMA showed that it was important to distinguish between doses of the treatments (see *Table 1*), but that the mode of administration of NRT was not an effect modifier (based on model fit; see *Appendix 5*). We did not include treatments when the dose was not specified. The following treatments were included in the economic evaluation:

- NRT at low, standard and high dose
- bupropion at low and standard dose
- varenicline at low and standard dose
- e-cigarette at low and high dose
- bupropion standard dose plus NRT high dose
- varenicline low dose plus NRT standard dose
- varenicline standard dose plus NRT standard dose
- varenicline standard dose plus NRT high dose
- varenicline standard plus bupropion standard dose.

Combination treatments (varenicline or bupropion in combination with NRT at any dose) are not currently licensed as smoking cessation treatments in the UK. We include these in the base case but exclude them from a sensitivity analysis. Standard practice in the NHS is to offer smokers attempting to quit NRT a dose based on their level of cigarette use, including combinations of NRT modes of delivery (e.g. patch and gum). We use NRT standard dose as the reference treatment for comparison in the cost-effectiveness analysis. We do not include waitlist, no treatment, or placebo in the economic evaluation because these would not be used in standard care. Evidence from studies including those comparators is included in the NMA and contributes indirectly to the estimates between the active treatments that we include in our economic evaluation.

The perspective taken is that of the NHS for costs, and health effects on the individual for outcomes, in line with NICE guidance.[94] A lifetime time horizon was taken, using a cohort simulation model to predict costs and utilities over a participant's lifetime.

Methods

Model description

The model structure is based on the 'Sheffield model' used in a recent Health Technology Assessment report[58] on the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation. This in turn was based on the Benefits of Smoking Cessation on Outcomes (BENESCO) model, which was adapted from the Health Economic Consequences of Smoking (HECOS) model used by the World Health Organization European Partnership Project to reduce tobacco dependence.[95] The BENESCO model is an existing and widely used economic model that has previously

been applied to model the effects of smoking cessation interventions in the UK, the USA, Germany, France, Belgium, the Netherlands, Finland, Sweden and the Republic of Korea.[96–105]

A cohort simulation model is used for smokers making a one-time smoking cessation attempt. Smoking status, morbidity and mortality are simulated over a lifetime (until the age of 100 years) to calculate the costs and benefits of smoking cessation strategies from the perspective of the health-care payer. The model uses an annual cycle length. UK estimates are used to determine the percentage of the initial cohort that are male or female, their age (18–34, 35–64 or 65–100 years) and their underlying health conditions [lung cancer, COPD, coronary heart disease (CHD) and stroke].

Every cohort member begins in the smoker state and at the end of the first year a percentage of the cohort will have quit smoking, with this proportion dependent on the efficacy of the cessation aid treatment they receive. No further quit attempts are modelled. It is, therefore, assumed that those who fail to quit will remain smokers until death.

There is a possibility that quitters may relapse and start smoking again in future years. This possibility decreases as time since cessation increases, with the risk of relapse being highest in the four model cycles following cessation (recent quitters). After four cycles without relapse, recent quitters become long-run quitters and the annual relapse rate is lower in the next five cycles, and lower still in subsequent cycles, with this underlying relapse rate continuing for the duration of the model. It is assumed that the probability of relapse at any stage is the same regardless of which treatment is used to aid cessation.

At the end of each year, the cohort is distributed into smokers, quitters and relapsed smokers (*Figure 1*). Within these broad smoking states, cohort members can have no current morbidity or one of the following smoking-related morbidities: lung cancer, COPD, CHD, stroke or an asthma exacerbation. These health states correspond to the smoking-related diseases that cause the greatest morbidity, mortality and cost. It is assumed that a person can be in one of these health states at a time only. When a person dies, they are removed from the model. The probability of moving to a new health state at the end of each cycle depends on current health state, smoking status, age and sex.

It is assumed that a restricted hierarchy exists in which subjects can enter the CHD or stroke health state and subsequently transit to the COPD or lung cancer state. However, because of the irreversible nature of COPD and lung cancer, once subjects enter these health states, they stay there until they transition to death. An asthma exacerbation or exacerbations can occur from the no current morbidity health state only and are assumed to resolve within 1 year.

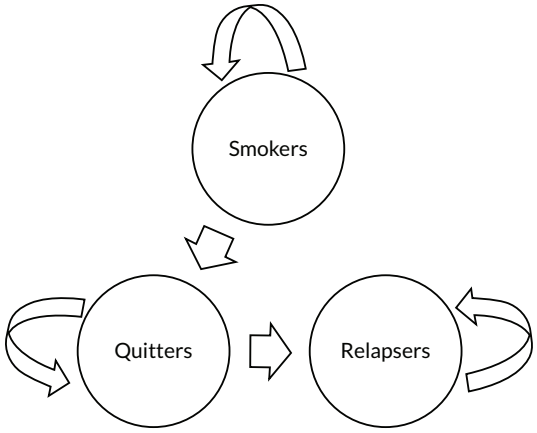

FIGURE 1 Transitions between smoking states. Note that death can occur from any state.

The original BENESCO model did not consider the AEs of treatment, but we have incorporated these as a probability of experiencing depression or fatal/non-fatal self-harm in the first year of treatment. We included these aspects of MANEs because we were able to identify cohort data sources for these outcomes with which to estimate the baseline probability of event on NRT standard. Depression and non-fatal self-harm are represented by a one-off disutility and cost, whereas fatal self-harm results in death. These are applied in the first year only because it is assumed that depression or self-harm would lead to discontinuation of treatment. We did not include cardiovascular treatment-related AEs in our model. This is because cardiovascular events are already included in the model as a consequence of smoking. Any differences observed between treatment groups in the RCTs in terms of cardiovascular events are more likely to be a result of having successfully quit or not (and subsequent reduction in risk), which is already captured in the model, or a side effect of the treatment. It is not possible to distinguish between these two causes from the RCT evidence, and we, therefore, could not estimate treatment-related adverse cardiovascular events.

All other health states are associated with utility and cost values, as detailed later. Therefore, cohort members accumulate costs and health outcomes each cycle until death. Future costs and benefits were discounted at a rate of 3.5% per annum.[94]

Model inputs

In this section, we describe the evidence sources used for each parameter in the model. Evidence sources were identified as follows. First, we looked for updates to the evidence sources used in the Sheffield model[58] by searching for studies that cited these sources and carrying out targeted searches on PubMed and EMBASE. Where alternative or more recent evidence sources were available, we considered these and made a decision about which evidence sources to use based on sample size and relevance to a contemporary UK population.

When searching for data on prevalence, we concentrated on large routine data sources such as the Health Survey for England. For incidence and relative risks (RRs), we searched for prospective cohorts (if RCT evidence was not available/not possible). Where no preferable evidence sources could be identified, we used the same data as used in the Sheffield model.

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. The proportion of male and female adults, and the mortality risk in each of the three age categories was determined from general population data.[106,107] Smoking prevalence data[108] were applied to these data to calculate the distribution across age and sex groups for a representative sample of 10,000 UK smokers (see *Appendix 2*, *Table 18*).

The prevalence of smoking-related diseases in the smoking cohort was estimated from various literature sources on the prevalence of each disease in the general UK population and risk ratios of these diseases in smokers (see *Table 19*). The most recent data source identified on the prevalence of COPD and asthma in the UK was an online report from the British Lung Foundation[109] based on data from 12.6 million patients in The Health Improvement Network (THIN) database, a UK general practice database that contains anonymised longitudinal patient records from over 500 practices (about 6% of the population). It reports the number of people ever diagnosed with COPD and asthma per 100,000 people, by age group, in 2012. This is updated from the estimate used in the Sheffield model, which was taken from a 2000 paper by Soriano *et al.*,[110] who used the General Practice Research Database to calculate the prevalence of COPD in the UK from January 1990 to December 1997. The British Lung Foundation reports an increased prevalence of COPD compared with Soriano *et al.* (e.g. new estimate of 7% in females aged > 65 years as opposed to 2%). This may be because of a difference in the number of elderly people included in the studies, although the British Lung Foundation estimate was thought to be a more representative estimate of COPD in the current population of those aged ≥ 65 years.[109,110]

The prevalence of lung cancer was taken from a paper by Maddams *et al.*,[111] who used data from cancer registries in the UK to provide prevalence estimates by sex and age for 2008. This was updated from a 2003 paper by Forman *et al.*,[112] who used UK cancer registries to provide estimates for 1992. The estimates were relatively similar (e.g. new estimate of 0.3% in females aged ≥ 65 years compared with 0.24%).

History of CHD prevalence was taken from the 2016 Health Survey for England,[113] which is one in a series of annual surveys designed to measure health and health-related behaviours in adults and children living in private households in England. In 2016, interviews were completed with 8011 adults. This was updated from an estimate taken from the 2005 Office for National Statistics (ONS) General Household Survey and was, again, higher (12% in females aged ≥ 65 years compared with 5.9%).

The source for prevalence of stroke history was Bhatnagar *et al.*,[114] who obtained 2013 prevalence data from the Clinical Practice Research Datalink Global Initiative for Chronic Obstructive Lung Disease (GOLD) database, which collates records from a widely used general practice software system and covers approximately 8.8% of the UK population. This was updated from a 2004 report from Asthma UK and was, again, higher (11% in females aged ≥ 65 years compared with 5.3%).

Relative risks for the prevalence of each disease in smokers relative to never-smokers were taken from the *Statistics on Smoking, England – 2017*[115] report for COPD, lung cancer, CHD and stroke (see *Table 37*), and from Cassino *et al.*[116] for asthma. These estimates were used to calculate the expected number of cases in the cohort of smokers using the formulae shown in *Appendix 3*. The data are reproduced in *Appendix 2*, *Table 20*.

Transition probabilities

The annual incidence of disease was estimated by age and sex categories for smokers, recent quitters and long-run quitters. These values relied on estimates used in the Sheffield model[58] (which, in turn, used estimates from a previous manufacturer's single technology assessment submission to NICE[117]) as no preferable evidence could be identified for COPD, CHD, stroke or asthma. For lung cancer, the 2016 ONS release (updating the 2005 release used in the Sheffield model) was identified,[118] which reports directly age-standardised rates per 100,000 population of newly diagnosed cases of cancer in England. These estimates showed that the incidence of lung cancer did not greatly increase between 2003 and 2016 (see *Table 21*). For simplicity, we, therefore, assumed that all incidence estimates were the same as those reported in the Sheffield model.

Appendix 2, *Tables 22–25* show the estimates of the annual incidences of diseases for the general population, smokers, recent quitters and long-run quitters, respectively. These were obtained using the same method as for prevalence (see *Appendix 3*), assuming that the RRs of incidence in smokers, short-run and recent quitters relative to never-smokers were the same as the RRs of prevalence (see *Table 37*).[115,116]

In accordance with previous BENESCO models, the RRs in recent quitters relative to never-smokers were assumed to be equal to the RRs for current smokers at year 1 for each disease. The RRs for COPD, stroke and asthma exacerbations are reduced when the smoker has quit for at least 1 year. The RRs in long-term quitters compared with never-smokers are assumed to be equal to the RRs in never-smokers after the smoker has quit smoking for > 5 years. Lung cancer has been approached differently: lung cancer risk for long-term quitters is kept equal to the risk in recent quitters. Although there is evidence that quitting smoking does reduce the risk of developing lung cancer, the risk does not return to that of non-smokers.[119]

Mortality

Annual mortality probability by condition, excluding asthma, was estimated using the British Heart Foundation's published total numbers of deaths in the UK in 2016 in each age group,[120] which are based on general population data. These numbers were used as the numerator, with the denominator as the number of prevalent cases in the UK calculated using the population and prevalence estimates for 2016 (see *Tables 18* and *19*).

It was assumed that no additional mortality was associated with asthma exacerbation. Mortality for chronic diseases, COPD and lung cancer is the probability of death from these diseases given the disease is present. Mortality from acute events, CHD and stroke is the probability of a fatal event that differs by smoking status, age and sex.

Appendix 2, *Tables 26–29* show the disease-specific mortality estimates for the general population, smokers, recent quitters and long-run quitters. The same RRs for smokers, short-run and recent quitters relative to never-smokers that were used for prevalence and incidence of diseases were also used to generate absolute probabilities of mortality. 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. The exception is lung cancer, for which the mortality risk is the same regardless of smoking status.

Relapse rates

Hawkins *et al.*[121] used British Household Panel Survey data to look at smokers who quit, but then relapsed. These data were used to calculate the annual relapse probability for short-run quitters (people for whom it had been < 5 years since they quit) and long-run quitters (people who had quit smoking for > 5 years but < 10 years). The annual relapse probability ≥ 10 years post cessation was based on a study by Krall *et al.*,[122] which followed 483 men for up to 35 years.

The probabilities of relapse that were used in the model are shown in *Appendix 2*, *Table 30*. Uncertainty around relapse rates is modelled as a beta distribution using event data from the original studies.

Costs

Costs included in the model related to health states and intervention costs. Owing to a lack of recent or relevant UK data, the mean costs of COPD and lung cancer estimated by the Irish Health Information and Quality Authority (HIQA) in its 2017 report on interventions for smoking cessation[123] were used in the model. This report used Irish data on the total annual spending divided by the total number of people with a diagnosis of each disease. The total direct costs to the Irish health service of inpatient and day-case treatment were estimated from the Hospital Inpatient Enquiry database for 2015, which is based on 2014 prices. The annual primary care and medication costs of COPD were estimated using 2014 Primary Care Reimbursement Service data from Ireland on the total costs of adrenergic and other drugs for obstructive airway diseases. The primary care and medication costs of lung cancer were estimated from a report on European cardiovascular disease statistics published by the European Society of Cardiology in 2012.[124] These costs were converted from euros to Great British pounds and inflated to 2019 prices using HM Revenue & Customs monthly exchange rates for February 2019.[125]

This resulted in a total annual cost of COPD of £1468, an increase from the £971 used in the Sheffield model based on a paper by Britton.[126] The annual cost of lung cancer (£5429) is lower than the estimate used in the Sheffield model (£6524), which was based on Flack *et al.*[127]

The cost of CHD was estimated from the British Heart Foundation's cardiovascular disease statistics reported in 2014.[128] These data are taken from analysis of commissioning expenditure in the UK (the programme budgeting data return). These estimates are based on the price paid for specific activities and services purchased from health-care providers for each region. The annual cost of CHD estimated (£1460) is higher than the £1163 used in the Sheffield model based on McMurray *et al.*[129]

The source used for the cost of stroke was Xu *et al.*,[130] who developed an individual patient simulation model to estimate health and social care costs at 1 and 5 years after stroke. The results were estimated using data on all patients with stroke included in Sentinel Stroke National Audit Programme (the national stroke register of England, Wales and Northern Ireland) from April 2015 to March 2016 ($n = 84{,}184$).

The annual cost of stroke estimated (£1460) is lower than the £5484 used in the Sheffield model based on Simpson *et al.*,[131] who calculated the cost of a dependent/independent state due to stroke using NHS reference costs for 'non-transient stroke or cerebrovascular accident, nervous system infections of encephalopathy' long-stay/short-stay non-elective inpatients.

Tan *et al.*[132] documented asthma costs over time for asthma patients who were enrolled in an asthma care programme in Singapore, using a 10-year longitudinal data set. The study population comprised different cohorts of 939 asthma patients entering the programme at different times during 2004–13. Ten-year average annual asthma costs were estimated as £341 per patient. The main drivers of costs were asthma medications and consultation fees. This is lower than the £1162 used in the Sheffield model based on Hoskins *et al.*,[133] which was a retrospective cohort analysis of a representative data set of 12,203 patients with asthma in the UK over a 1-year period. The estimate from Tan *et al.* was preferred as it was thought to be more reflective of mild asthma, which is what the majority of adults will have.

The cost associated with depression (£340) was taken from a paper by Hunter *et al.*[134] Here, a weighted average annual cost per UK patient to treat depression was calculated by multiplying the proportion of patients who access each type of treatment by the average annual cost of the treatment. The cost associated with self-harm was taken from a paper by Tsiachristas *et al.*,[135] who estimated hospital resource use and care costs for all patients presenting with self-harm to the John Radcliffe Hospital (Oxford, UK) between 1 April 2013 and 31 March 2014.

Uncertainty around cost estimates was incorporated into the probabilistic analysis. In the absence of data, the SDs for COPD and lung cancer were assumed to be 10% of the mean estimate, and the standard errors were calculated using this figure, along with the number of people on which the mean estimate was based. As it was not possible to identify the number of people on whom the depression and CHD cost estimates were based, the standard error in this case was assumed to be 10% of the mean. These data were assumed to follow a gamma distribution.[136] All costs have been inflated to 2019 prices using HM Revenue & Customs monthly exchange rates for February 2019.[125]

Appendix 2, *Table 31* details the source, summary estimates and distributions used for the health state costs employed in the model.

Intervention costs comprised the cost of the interventions alone. It was assumed that, although counselling and other health professional support are likely to occur, the cost of these is likely to be the same or very similar across interventions, thus not having an impact on the relative cost–utility. These costs were, therefore, excluded from the economic analysis.

Data from the BNF on dosage and pricing are used to calculate the costs of varenicline, bupropion and NRT.[137] For varenicline, 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), giving £163.80 in total. The cost of low-dose varenicline is assumed to be the same, as the BNF states the same price for both 1 mg and 0.5 mg (500 µg) tablets.

Bupropion was costed as 150 mg daily for 6 days and then 150 mg twice daily for 7–9 weeks at a cost of £83.52.[137] The cost of low-dose bupropion is assumed to be £62.54 based on a dose of one tablet per day for an average of 13 weeks.

Similarly, for NRT, standard treatment is assumed to be a high-strength patch daily for 6–8 weeks, followed by the medium-strength patch for 2 weeks and then the low-strength patch for the final 2 weeks, at a cost of £105.65.[137] The cost of NRT low is assumed to be £83.84, based on 4 weeks of 10-mg/16-hour patches and 4 weeks of 5-mg/16-hour patches. The cost of NRT high is estimated as

£77.46, based on a 4-week supply of 21 mg NicoDerm CQ (GlaxoSmithKline plc, Brentford, UK) transdermal patches followed by 2 weeks at 14 mg and 2 weeks at 7 mg.

E-cigarettes are not medically licensed in the UK.[138] The HIQA report[123] costed a 12-week supply of e-cigarettes (e-cigarette + 3.55 ml liquid per day, including a replacement atomiser in months 2 and 3) as €93.80, based on Liber *et al.*[139] This is equivalent to approximately £82.[125]

The costs of all interventions including combinations of interventions are shown in *Appendix 2, Table 32*.

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[140] using 2003 and 2006 Health Survey for England data (see *Table 33*). These data are a function of age and sex and are based on random samples of the population living in private households in England. A total of 26,679 participants were asked to complete the EuroQol-5 Dimensions (EQ-5D) questionnaire (a commonly used questionnaire to describe and value health), and preference-based health state utility values were estimated from the weights obtained using time trade-off valuations. Health state utility was determined by multiplying baseline utility by age by an estimate of the impact of the disease.

Disease-specific utility values for smoking-related diseases were estimated from the literature. For lung cancer utility, two sources were identified. Jang *et al.*[141] measured EQ-5D scores in 172 consecutive outpatients with non-small-cell lung cancer attending a major Canadian cancer centre outpatient clinic and estimated a mean utility of 0.76 (95% CI −0.7 to 0.78). A more recent paper by Bertranou *et al.*[142] derived a similar utility value for progressed non-small-cell lung cancer from EQ-5D patient-level data collected in two lung cancer treatment trials, AURA2 ($n = 199$) and IMPRESS ($n = 265$) (0.72, SD 0.029). The progressed disease utility was given by the mid-point of the two studies. The source used in our model is that estimated by Bertranou *et al.*[142] (0.72) owing to the larger sample size. This is higher than the estimate used in the Sheffield model (0.5), which was taken from Trippoli *et al.*,[143] who measured quality of life in 95 patients with non-small-cell lung cancer from 15 Italian hospitals.

For utility associated with COPD, the source was Pickard *et al.*,[144] who synthesised the literature on the validity and reliability of EQ-5D use in studies of asthma and COPD, and estimated EQ-5D utility scores associated with stage of disease. The authors found eight studies that recorded EQ-5D scores ranging from 0.52 (SD 0.16) to 0.84 (SD 0.15) for patients with COPD. Sufficient studies in COPD were available to calculate pooled mean utility scores according to GOLD stage, which categorises COPD severity in four stages, from very mild to very severe. The utilities estimated were 0.74 for stage I (95% CI 0.62 to 0.87), 0.74 for stage II (95% CI 0.66 to 0.83), 0.69 for stage III (95% CI 0.60 to 0.78) and 0.61 for stage IV (95% CI 0.44 to 0.77) (most severe). The utility used was that for stage II (moderate disease) as this should capture the mid-point of severities. This could have been estimated by calculating a weighted average based on patient numbers in each stage, but it was assumed that the utility for moderate disease would adequately reflect a mix of mild to severe. This is higher than the estimate used in the Sheffield model (0.63), which was based on Spencer *et al.*,[145] who derived utility values from 283 patients with COPD who took part in the 1996 Health Survey for England.

The source used for utility associated with CHD was Stevanović *et al.*[146] This estimate (0.76) was based on a multivariate meta-analysis of preference-based quality-of-life values from 40 studies representing over 30,575 patients with CHD. For this utility, the Sheffield model cited Hay and Sterling,[147] who sourced their utilities from the Beaver Dam Health Outcomes Study (a longitudinal cohort study of health status and health-related quality of life in a random sample of 1356 US adults). The average CHD utility (0.77) was a weighted average of myocardial infarction and angina utilities and was similar to that found in Stevanović *et al.*

Utility associated with stroke was estimated from Haacke *et al.*,[148] who assessed health-related quality of life (HRQoL) in 77 patients who had experienced an ischaemic stroke, a transient ischaemic attack or a haemorrhagic stroke. The mean EQ-5D value was 0.73 (SD 0.32). This replaces the estimate used in the Sheffield model (0.62), which was taken from Tengs and Lin,[149] who carried out a systematic search to identify 20 articles reporting 53 unique quality-of-life weights for stroke and pooled these using a hierarchical linear model. The estimate from Haacke *et al.*[148] was preferred as it was from a more recent study and was thought to more accurately reflect the specific disutility associated with stroke.[148]

For utility associated with second stroke, an estimate (0.48) was sourced from Ara and Brazier,[140] who looked at EQ-5D data collected in Health Survey for England from individuals who reported a history of more than one cardiovascular condition. For utility associated with second stroke, the Sheffield model cited Gage *et al.*,[150] who elicited preferences from 69 volunteers at the Veterans Affairs Palo Alto Health Care System and Stanford University who had atrial fibrillation. Twenty of the volunteers had previously had a stroke. This paper estimated a utility value of 0.12.

Lloyd *et al.*[151] reported the impact of asthma exacerbations on health-related quality of life and health utility in patients with moderate to severe asthma in the UK. Prospective data regarding health-related quality of life were collected from 112 patients at four asthma centres across the UK using the EQ-5D at two time points. The EQ-5D utility estimated was 0.57 (SD 0.27) for patients with an exacerbation that required oral steroids. For utility associated with asthma, the Sheffield model cited Szende *et al.*[152] In this study, 228 consecutive adult outpatients and inpatients at four sites in Hungary completed the EQ-5D questionnaire. Patients had to have been diagnosed and already treated for asthma, and were involved in the study at their outpatient visit or during their hospital stay. The utility value estimated for poorly controlled asthma is 0.52.

The utility associated with depression [0.58, standard error (SE) 0.015] was taken from a paper by Hunter *et al.*,[134] who calculated a score for depressed patients using a weighted average from four UK trials.[153–156] The utility associated with self-harm came from a paper by Byford *et al.*,[157] in which baseline EQ-5D was collected in 480 patients with a history of recurrent deliberate self-harm.

Intervention effectiveness

The absolute probabilities of cessation at 1 year for interventions were generated by combining the results of the NMA (see *Chapter 5*) on sustained abstinence with an estimate of response on NRT estimated from Taylor *et al.*[158] This was a prospective cohort study of electronic medical records from 654 general practices in England in the UK's Clinical Practice Research Datalink, including 287,079 patients who were prescribed smoking cessation medications during the study period. Of these, 149,526 patients prescribed NRT were eligible for analysis. At 1 year, 21.2% (31,695/149,526) of those prescribed NRT had quit smoking.

The mean probability of 1-year sustained abstinence with all treatments, and 95% credible intervals (CrIs), are shown in *Appendix 2*, *Table 34*. The results of the NMA suggested that varenicline low plus NRT standard and varenicline standard plus NRT standard have the highest absolute probability of sustained abstinence, followed by e-cigarette low/varenicline plus bupropion standard/e-cigarette high. Note that the absolute probabilities are derived from the NMA estimates, which are correlated because they are jointly estimated from a single model.

The absolute probabilities of depression at 1 year for interventions were generated by combining the results of the NMA on MANE (see *Chapter 6*) with an estimate of depression on NRT standard estimated from Kotz *et al.*[57] This was a retrospective cohort study using data from patients included in the validated QResearch database (www.qresearch.org), which holds data from 753 NHS general practices across England. Patients who were prescribed smoking cessation medications during the study period were identified and followed for 6 months. Of these, 106,759 patients prescribed NRT

were eligible for analysis and 8274 reported suffering from depression. This gave a probability of 7%. The mean probabilities of depression for all treatments and 95% CrIs are shown in *Appendix 2*, *Table 35*. As no data were available on the other interventions, assumptions had to be made about their relative level of harm. It was, therefore, assumed that NRT low and e-cigarette low have the same level of harm as NRT standard, e-cigarette high has the same level of harm as NRT high, bupropion low has the same level of harm as bupropion standard, and varenicline low plus NRT standard has the same level of harm as varenicline standard plus NRT standard.

The absolute probabilities of self-harm at 1 year for interventions were also generated by combining the results of the NMA on MANE with an estimate of self-harm on NRT estimated from Kotz *et al.*[57] A total of 540 of the patients in this study reported self-harm, giving a probability of 0.5%. The mean probability of self-harm for all treatments for which data were available is shown in *Appendix 2*, *Table 36*.

Cost-effectiveness analysis methods

We conduct a probabilistic analysis in which uncertainty in the model inputs is captured by simulating 5000 times from the assumed distributions described in the previous section, using Monte Carlo simulation performed in Microsoft Excel® version 1908 (Microsoft Corporation, Redmond, WA, USA). The absolute probabilities of abstinence, depression and self-harm were estimated using Bayesian inference, computed using Markov chain Monte Carlo simulation in OpenBUGS (URL: www.openbugs.net). Simulated samples for the model were drawn from 60,000 Markov chain Monte Carlo samples from the posterior distributions, taken from OpenBUGS and read into Microsoft Excel. Care was taken to preserve correlations from the Markov chain Monte Carlo.

We report mean lifetime costs and quality-adjusted life-years (QALYs) for each treatment option. Incremental cost-effectiveness ratios (ICERs), interpreted as the additional expected cost per additional unit gain in QALY for one treatment compared with another, are computed by first ordering treatments by increasing expected cost and then removing treatments that are dominated or extendedly dominated (i.e. have a higher expected cost and lower expected utility than another intervention). ICERs are then calculated for each non-dominated treatment relative to the previous (lower expected cost) non-dominated treatment, where:

$$\text{ICER} = \text{additional expected cost/additional expected utility.} \quad (1)$$

For each treatment we also computed net benefit for a given willingness to pay per additional QALY, λ (cost per QALY gained ratio), where net benefit is defined as:

$$\text{net benefit} = \text{utility} \times \lambda - \text{cost.} \quad (2)$$

'Net benefit' represents the value of a treatment in monetary terms by scaling both QALYs and use of resources to costs.[159] Averaging the net benefit over the probabilistic simulation samples gives the expected net benefit. The intervention with the highest expected net benefit (the optimal intervention) at any willingness-to-pay threshold, λ, can be calculated. We present the expected net benefit for λ = £20,000.

We also plot cost-effectiveness acceptability curves (CEACs), which present the uncertainty in the optimal treatment by plotting the probability that each treatment is the most cost-effective (has the highest net benefit) against the willingness to pay per QALY.

We also present uncertainty between these interventions using rank-o-grams that show the distribution of the probabilities that each treatment is optimal, second, third and so on for each of the 14 treatments, at a willingness-to-pay threshold of £20,000 per QALY. The *x*-axis reports each of the possible ranks, for which position 1 means that the intervention is optimal. The *y*-axis shows the probability that each treatment has been ranked at each of the possible positions and, therefore, fully encapsulates the

uncertainty in the intervention rankings. The peaks in the rank-o-gram plots show the most likely rank of a given treatment. Flat lines indicate a high degree of uncertainty for the ranking of that treatment type. We also explore how uncertainty in the model inputs impacts on the treatment considered to be optimal using value-of-information methods.[160] This method is also useful in guiding research recommendations as it can estimate the value of a future trial. The expected value of perfect information (EVPI) measures the value (in terms of net benefit) of eliminating all uncertainty in model inputs. The expected value of partial perfect information (EVPPI) measures the value (in terms of net benefit) of eliminating uncertainty in some of the model inputs. This allows us to identify which model inputs are the key drivers of decision uncertainty. Therefore, it follows that it is these areas in which further research might be most beneficial. EVPI and EVPPI are computed per person for the threshold of willingness to pay per QALY of £20,000. Population-level EVPI and EVPPI are also calculated, given an estimated number of smokers attempting to quit in England of 274,021.[3] The lifetime of a treatment represents the time until it becomes obsolete or goes out of use, for example by being superseded by a new intervention. We assume a lifetime of T = 1 year and 5 years, respectively, discounted at 3.5%. The Sheffield Accelerated Value of Information web application[161] was used to compute EVPPI for subsets of parameters.[162]

We also a present one sensitivity analysis in which the impact of depression and self-harm in the model is removed, so the results are driven by abstinence from smoking alone, and another limiting the analysis to UK-licensed treatments.

Chapter 5 Clinical results: effectiveness

Included studies

Study selection

The results of our search strategy are summarised in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram in *Figure 2*. Our original searches identified 345 studies for inclusion and our update searches identified an additional 18 studies for inclusion, resulting in a total of 363 studies reported on one or more effectiveness outcomes that are described below.[19,33,69,70,163–511] For the purpose of our analyses, the EAGLES study[33] was treated as two studies, where Anthenelli 2016a[33] included the four study arms from the non-psychiatric cohort and Athenelli 2016b[33] included the four arms from the psychiatric cohort. A list of records excluded at full-text screening (those that did not meet randomised or non-randomised inclusion criteria for effectiveness or safety analyses) and their reasons for exclusion are presented in *Report Supplementary Material 1*.

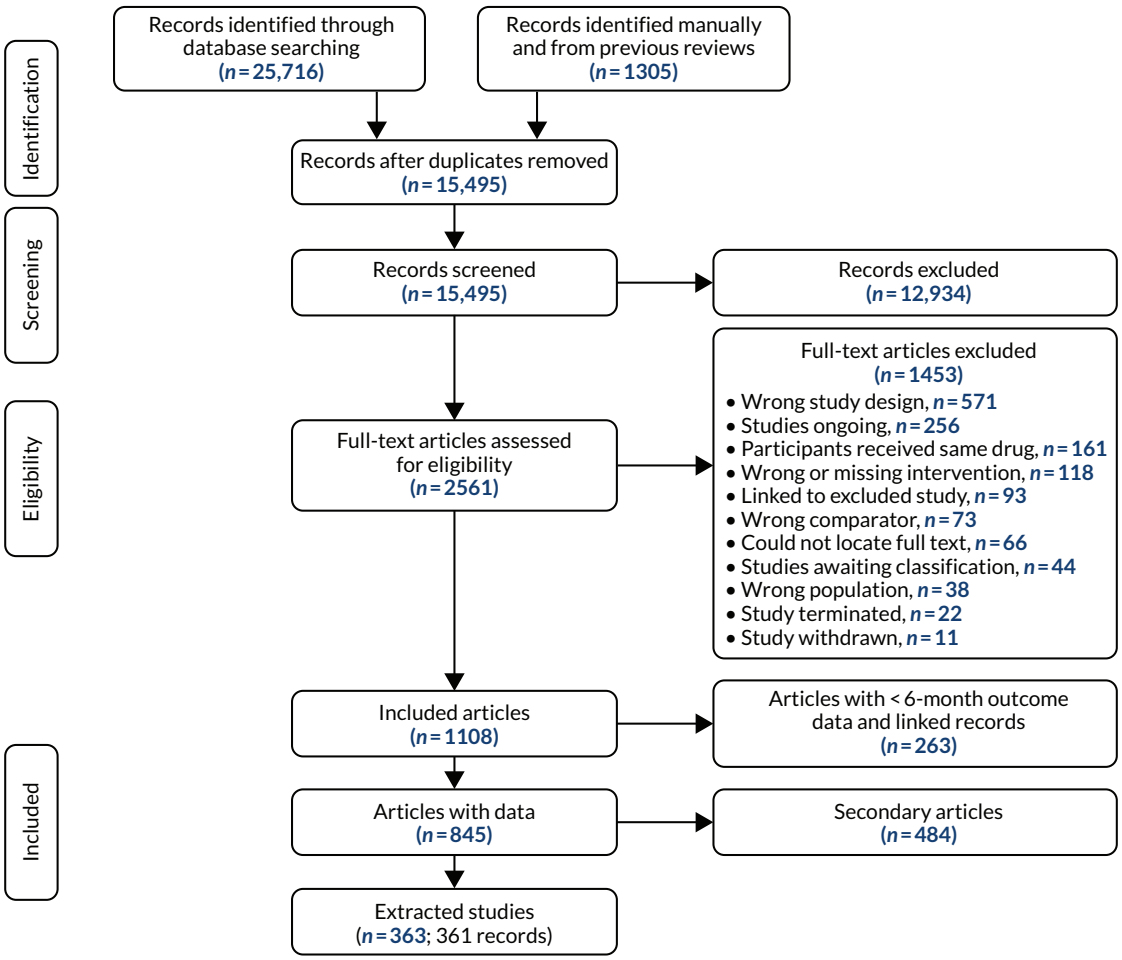

FIGURE 2 The PRISMA flow diagram for effectiveness study records. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Study characteristics

The number of participants randomised across the 363 trials ranged from 15 to 7354, with a total of 201,045 participants. Trials were conducted across six continents, with 208 trials in the USA, 29 trials in the UK, and 27 multicountry trials. Trials were conducted in several settings, including medical centres and facilities, academic and research centres, universities, community centres, low-income or subsidised housing neighbourhoods, hospitals, pharmacies, clinics (e.g. smoking cessation, dental, urology, methadone, surgical), primary care (general, family and private practices), over the counter, dispensaries, schools, companies and workplaces, Navy ships and over the telephone, by mail or online.

Study duration ranged from 24 to 754 weeks, with the duration of drug treatment ranging from 2 to 104 weeks. One hundred and twenty-one trials were industry sponsored and 122 trials were publicly registered online. We included 24 trials in which smokers were unwilling or not necessarily motivated to quit and 15 trials of smokeless-tobacco users. Twenty-six trials recruited smokers with comorbidities as specified by the Charlson Comorbidity Index,[90] 16 trials recruited smokers with current or a history of psychiatric conditions and 17 trials recruited smokers with current or a history of drug- or alcohol-related conditions.

The mean age of trial participants ranged from 27.1 to 62 years and the percentage of female participants (in studies that did not exclusively recruit male or female participants) ranged from 0.3% to 81%. Study populations ranged between ethnicities (e.g. white/Caucasian, African American, Latino/Hispanic, Asian, Indigenous Maori), types of tobacco use (e.g. smokeless tobacco, spit tobacco, cigars, waterpipes) and heaviness of smoking. Studies included smokers who were hospital inpatients or outpatients (including smokers scheduled for surgery), smokers with human immunodeficiency virus (HIV), smokers under criminal justice supervision, smokers with substance misuse, smokers with psychiatric conditions, smokers who were health-care professionals, smokers who were active or former armed forces and their family members (e.g. veterans, Navy, National Guard), smokers with prior quit attempts or who had recently relapsed, smokers who were cancer patients or prone to cancer or cancer survivors, female smokers concerned about weight, smokers from low-income or subsidised housing neighbourhoods, smokers with tuberculosis and smokers with asthma. Study-level characteristics of included trials can be found in tables in *Report Supplementary Material 2*.

Risk of bias in included studies

Ratings ranged from low to high risk of bias and an overall risk-of-bias domain was rated by selecting the highest rating of bias across domains, with the exception of selective outcome reporting (as this domain was usually rated as unclear as a result of inaccessibility of trial protocols and limited trial registration). Risk-of-bias ratings by trial and summarised across studies are presented in *Report Supplementary Material 3* and *Appendix 4*, *Figure 34*, respectively.

Random sequence generation

Few trials were rated as high risk of bias for random sequence generation, with 45% rated as being at low risk of bias, 53% rated as being at unclear risk of bias and only 2% rated as being at high risk of bias.

Allocation concealment

As was the case for random sequence generation, very few trials (3%) were rated as being at high risk of bias for allocation concealment; 38% of trials were rated as being at low risk of bias and 59% were rated as being at unclear risk of bias.

Blinding of participants and personnel

Blinding of participants and personnel saw nearly one-third of studies rated at each level; 31% of trials were rated as being at low risk of bias, 39% were rated as being at unclear risk of bias and 30% were rated as being at high risk of bias. This was because of a number of trials in which drugs were delivered open label without any blinding.

Blinding of outcome assessment

Nearly half of trials (48%) were rated as being at unclear risk of bias for blinding of outcome assessment domains, with 37% of the remaining trials rated as being at low risk of bias and 15% rated as being at high risk of bias.

Incomplete outcome data

More than half (62%) of trials were rated as being at low risk of bias for incomplete outcome data domain, as many studies used intention-to-treat analyses, and loss to follow-up was either low and/or similar among trial arms. Twenty-nine per cent of trials were rated as being at unclear risk of bias and only 9% were rated as being at high risk of bias.

Selective reporting

As previously mentioned, most (76%) trials were rated as being at unclear risk of bias for selective reporting due to a lack of study protocols or public trial registrations. Of the remaining 24%, 23% of trials were rated as being at low risk of bias and only 1% were rated as being at high risk of bias.

Other bias

Most trials (93%) were rated as being at low risk of bias for the other bias domain, with 4% rated as being at unclear risk of bias and 3% rated as being at high risk of bias.

Overall bias

Finally, ratings for our overall risk of bias domain indicated that 13% of trials were rated as being at low risk of bias, 47% of trials were rated as being at unclear risk of bias and 40% of trials as being at high risk of bias.

Results on clinical effectiveness

We performed NMA on four bioverified effectiveness outcomes: sustained (or continuous) abstinence, prolonged abstinence, any abstinence at 6 months, and 7-day PPA. We fitted a standard (full interaction) NMA model as well as fixed- and random-class NMA models for each outcome. Based on the model fit indices (see *Appendix 5*), we focused on fixed-class NMA models. A list of treatments delivered in the trials included in effectiveness analyses and their frequency is reported in *Appendix 3*, *Table 38*. In this chapter, we present results for each outcome based on a fixed-class NMA model, with additional results for other models provided in *Appendix 5*. The results are presented as median odds ratios (ORs) alongside 95% CrIs. A summary of results across outcomes is provided at the end of the effectiveness results in the form of a rank-o-gram.

Sustained abstinence

Our primary effectiveness outcome, sustained abstinence at a follow-up of at least 24 weeks, was reported in 171 studies with a total of 90,443 patients, of which 161 (86,884 patients) studies compared two or more of the treatment classes of interest. The network of treatments for this outcome is displayed in *Figure 3*, where thicker edges represent comparisons with a larger number of randomised patients. Similarly, interventions with a larger number of randomised patients have larger circles. Most interventions were compared with placebo in the primary studies, although arms with no drug treatment or with usual care were also used as comparators in some studies, and some direct comparisons between different drug types are also available. One study comparing varenicline standard plus NRT gum standard (114/245 patients quit) with varenicline low plus NRT gum standard (111/240 patients quit) was disconnected from the network at the treatment level (see *Figure 37*) but not at the class level (see *Figure 3*); hence, we excluded that study when comparing the different models (see *Table 39*) but were able to include it in the analyses discussed in this section (which report results at the class level).

Figure 4 displays the results for the fixed-class NMA model based on 161 studies with placebo as a comparator. There was evidence that smokers randomised to usual care were less likely to quit than

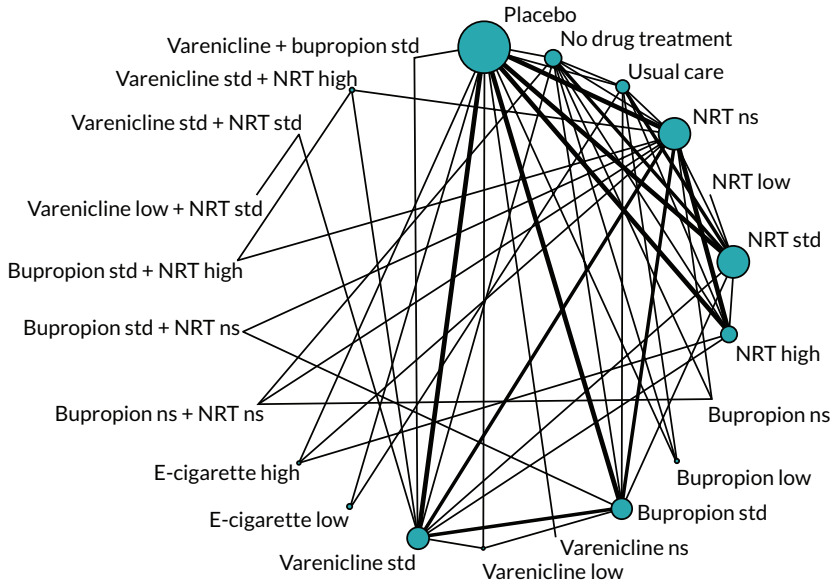

FIGURE 3 Network plot for sustained abstinence at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

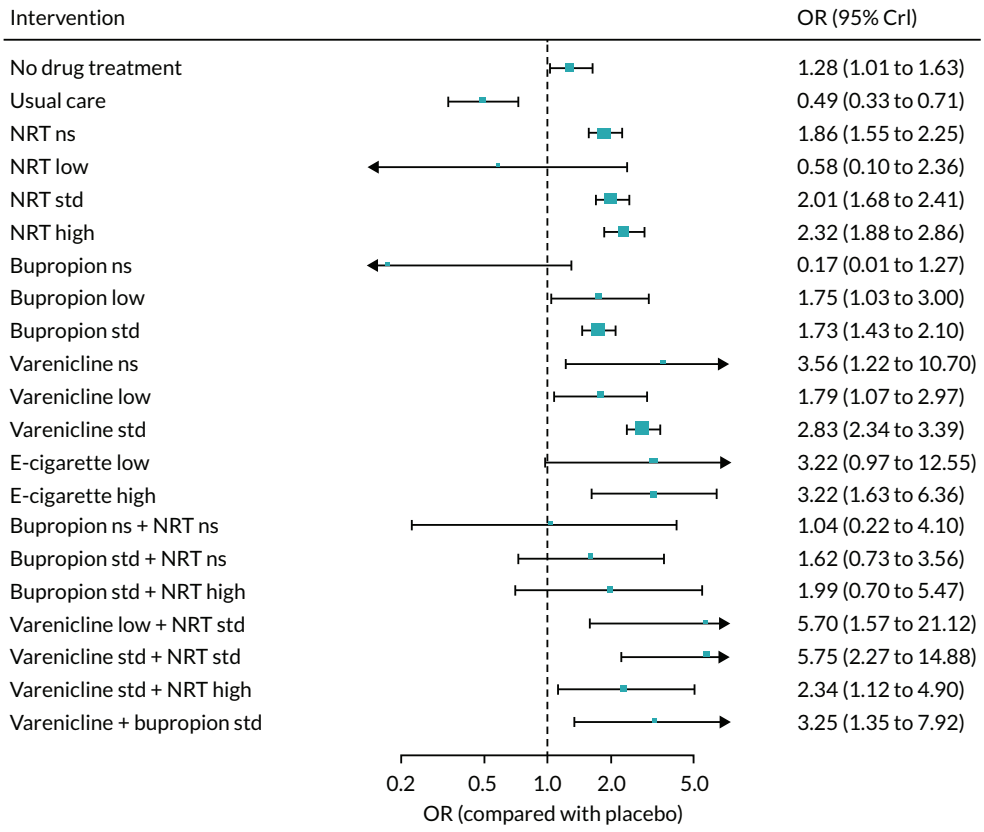

FIGURE 4 Forest plot with results of the fixed-class NMA model for sustained abstinence. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

those who received placebo (OR 0.49, 95% CrI 0.33 to 0.71), whereas smokers randomised to no drug treatment were more likely to quit than those who received placebo (OR 1.28, 95% CrI 1.01 to 1.83). Moreover, there was evidence that smokers receiving NRT standard (OR 2.01, 95% CrI 1.68 to 2.41) and NRT high (OR 2.32, 95% CrI 1.88 to 2.86) were more likely to quit than those randomised to placebo. Most interventions were more effective than placebo, including bupropion low (OR 1.75, 95% CrI 1.03 to 3.00), bupropion standard (OR 1.73, 95% CrI 1.43 to 2.10), varenicline low (OR 1.79, 95% CrI 1.07 to 2.97), varenicline standard (OR 2.83, 95% CrI 2.34 to 3.39), e-cigarette high (OR 3.22, 95% CrI 1.63 to 6.36), varenicline low plus NRT standard (OR 5.70, 95% CrI 1.57 to 21.12), varenicline standard plus NRT standard (OR 5.75, 95% CrI 2.27 to 14.88), varenicline standard plus NRT high (OR 2.34, 95% CrI 1.12 to 4.90) and varenicline standard plus bupropion standard (OR 3.25, 95% CrI 1.35 to 7.92). There was weak evidence for the effectiveness of e-cigarette low compared with placebo (OR 3.22, 95% CrI 0.97 to 12.55).

Table 2 presents the class effect estimates with placebo as comparator obtained from the NMA (last column) alongside the estimates obtained from direct and indirect evidence. Direct evidence was available for most monotherapies, whereas comparisons of combinations of interventions with placebo largely relied on indirect evidence only. Most effect estimates are above 1, suggesting that the interventions helped smokers to reach sustained abstinence more frequently than placebo. Where there was enough information to back-calculate indirect evidence and compare it with direct evidence,

TABLE 2 Results for sustained abstinence: comparisons with placebo

	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	0.70 (0.08 to 4.01)	1.30 (1.02 to 1.64)	1.28 (1.01 to 1.63)
Usual care	0.81 (0.38 to 1.72)	0.41 (0.27 to 0.63)	0.49 (0.33 to 0.71)
NRT not specified	1.86 (1.55 to 2.25)	–	1.86 (1.55 to 2.25)
NRT low	–	0.58 (0.10 to 2.36)	0.58 (0.10 to 2.36)
NRT standard	2.01 (1.68 to 2.41)	–	2.01 (1.68 to 2.41)
NRT high	2.32 (1.88 to 2.86)	–	2.32 (1.88 to 2.86)
Bupropion not specified	–	0.17 (0.01 to 1.27)	0.17 (0.01 to 1.27)
Bupropion low	0.96 (0.44 to 2.05)	3.04 (1.46 to 6.33)	1.75 (1.03 to 3.00)
Bupropion standard	1.73 (1.43 to 2.10)	–	1.73 (1.43 to 2.10)
Varenicline not specified	3.56 (1.22 to 10.7)	–	3.56 (1.22 to 10.7)
Varenicline low	1.79 (1.07 to 2.97)	–	1.79 (1.07 to 2.97)
Varenicline standard	2.83 (2.34 to 3.39)	–	2.83 (2.34 to 3.39)
E-cigarette low	3.22 (0.97 to 12.6)	–	3.22 (0.97 to 12.6)
E-cigarette high	2.46 (0.86 to 7.03)	3.89 (1.63 to 9.28)	3.22 (1.63 to 6.36)
Bupropion not specified plus NRT not specified	–	1.04 (0.22 to 4.10)	1.04 (0.22 to 4.10)
Bupropion standard plus NRT not specified	–	1.62 (0.73 to 3.56)	1.62 (0.73 to 3.56)
Bupropion standard plus NRT high	–	1.99 (0.70 to 5.47)	1.99 (0.70 to 5.47)
Varenicline low plus NRT standard	–	5.70 (1.57 to 21.1)	5.70 (1.57 to 21.1)
Varenicline standard plus NRT standard	–	5.75 (2.27 to 14.9)	5.75 (2.27 to 14.9)
Varenicline standard plus NRT high	–	2.34 (1.12 to 4.90)	2.34 (1.12 to 4.90)
Varenicline standard plus bupropion standard	3.42 (1.39 to 8.67)	1.88 (0.09 to 39.9)	3.25 (1.35 to 7.92)

the results show some potentially inconsistent results, with examples where direct evidence shows a less beneficial effect for the experimental drug than the indirect evidence (e.g. bupropion low vs. placebo) and also the opposite (e.g. varenicline standard plus bupropion standard vs. placebo).

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 5*, *Table 39*). The pairwise comparisons between interventions for this outcome are presented in *Table 3*. Most of the effect estimates were informed by indirect evidence only, and the results were consistent when both direct and indirect evidence were available. There was evidence that smokers randomised to varenicline standard plus NRT standard were more likely to achieve sustained abstinence than those receiving NRT standard (OR 2.87, 95% CrI 1.11 to 7.49) or bupropion standard (OR 3.34, 95% CrI 1.28 to 8.65). The results also suggest higher odds of abstinence with varenicline standard compared with NRT

TABLE 3 Results for sustained abstinence: pairwise comparisons of interventions

	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	0.70 (0.17 to 2.83)	0.87 (0.67 to 1.12)	0.86 (0.67 to 1.11)
Varenicline standard vs. NRT standard	–	1.40 (1.10 to 1.78)	1.40 (1.10 to 1.78)
E-cigarette low vs. NRT standard	–	1.60 (0.48 to 6.30)	1.60 (0.48 to 6.30)
E-cigarette high vs. NRT standard	–	1.60 (0.80 to 3.20)	1.60 (0.80 to 3.20)
Varenicline standard plus NRT standard vs. NRT standard	–	2.87 (1.11 to 7.49)	2.87 (1.11 to 7.49)
Varenicline standard plus bupropion standard vs. NRT standard	–	1.61 (0.66 to 3.98)	1.61 (0.66 to 3.98)
Varenicline standard vs. bupropion standard	–	1.63 (1.27 to 2.07)	1.63 (1.27 to 2.07)
E-cigarette low vs. bupropion standard	–	1.85 (0.55 to 7.29)	1.85 (0.55 to 7.29)
E-cigarette high vs. bupropion standard	–	1.86 (0.92 to 3.73)	1.86 (0.92 to 3.73)
Varenicline standard plus NRT standard vs. bupropion standard	–	3.34 (1.28 to 8.65)	3.34 (1.28 to 8.65)
Varenicline standard plus bupropion standard vs. bupropion standard	–	1.87 (0.76 to 4.59)	1.87 (0.76 to 4.59)
E-cigarette low vs. varenicline standard	–	1.14 (0.34 to 4.47)	1.14 (0.34 to 4.47)
E-cigarette high vs. varenicline standard	–	1.14 (0.57 to 2.30)	1.14 (0.57 to 2.30)
Varenicline standard plus NRT standard vs. varenicline standard	2.05 (0.82 to 5.17)	–	2.05 (0.82 to 5.17)
Varenicline standard plus bupropion standard vs. varenicline standard	–	1.15 (0.48 to 2.76)	1.15 (0.48 to 2.76)
E-cigarette high vs. e-cigarette low	–	1.00 (0.22 to 4.03)	1.00 (0.22 to 4.03)
Varenicline standard plus NRT standard vs. e-cigarette low	–	1.80 (0.34 to 8.39)	1.80 (0.34 to 8.39)
Varenicline standard plus bupropion standard vs. e-cigarette low	–	1.01 (0.20 to 4.41)	1.01 (0.20 to 4.41)
Varenicline standard plus NRT standard vs. e-cigarette high	–	1.79 (0.57 to 5.71)	1.79 (0.57 to 5.71)
Varenicline standard plus bupropion standard vs. e-cigarette high	–	1.00 (0.33 to 3.08)	1.00 (0.33 to 3.08)
Varenicline standard plus bupropion standard vs. varenicline standard plus NRT standard	–	0.56 (0.16 to 1.98)	0.56 (0.16 to 1.98)

standard (OR 1.40, 95% CrI 1.10 to 1.78) or bupropion standard (OR 1.63, 95% CrI 1.27 to 2.07). Furthermore, there was weak evidence that e-cigarette high might increase the odds of sustained abstinence compared with bupropion standard (OR 1.86, 95% CrI 0.92 to 3.73).

Estimates of absolute probabilities of sustained abstinence for each intervention can be obtained by applying the relative effects in *Table 3* to an assumed cessation rate on NRT standard (estimates shown in *Appendix 2*, *Table 34*).

With regard to effect modifiers, there was evidence of effect modification as a function of counselling, with interventions that included counselling being associated with a higher proportion of smokers achieving sustained abstinence (additional log-OR was 0.86, 95% CrI 0.45 to 1.27; see *Figure 45*). We also found evidence of effect modification as a function of dependence, with higher odds of sustained abstinence among participants with higher average dependence scores (additional log-OR 0.23, 95% CrI 0.02 to 0.43; see *Figure 47*). We found inconclusive evidence of effect modification according to industry sponsorship, type of placebo, treatment duration, comorbidities, willingness to quit, smokeless tobacco, smoking level or publication year (see *Figures 42*, *44*, *48* and *53*). A sensitivity analysis excluding studies at high risk of bias yielded the same findings reported in this section for active interventions, although with wider intervals for most effect estimates, and particularly for e-cigarettes and treatment combinations (see *Appendix 5*, *Figure 40*). However, the results from this analysis suggested no difference between usual care and placebo (OR 1.16, 95% CrI 0.64 to 2.12). We observed the same trends in a further sensitivity analysis where we excluded studies comparing pharmacological with non-pharmacological interventions (the estimate of the OR comparing usual care with placebo was 1.03, 95% CrI 0.57 to 1.86; see *Figure 41*). Within this sensitivity analysis, we found inconclusive evidence of effect modification when pharmacological interventions were given with counselling, with a trend towards a synergistic effect (more effective than would be expected based on the sum of the pharmacological and counselling effects alone) (additional log-OR of 0.16, 95% CrI −0.05 to 0.37; see *Figure 46*).

Threshold analysis

Varenicline standard plus NRT standard had the highest estimated odds of sustained abstinence and was the first-ranked treatment in our analyses. *Figure 5* shows the results of the threshold analysis for sustained abstinence, focusing on a selection of the eight treatment classes considered most relevant (and examined in the rank-o-grams presented later in this chapter). Threshold analysis determines how much the evidence could change before the first-ranked treatment changes. Each row in *Figure 5* corresponds to a single study estimate, and displays the estimate (log-OR) and 95% CI from that study, along with the invariant interval (shaded bar). Any changes to the study estimate that lie within the invariant interval will not affect the first-ranked treatment. Changes that pass the thresholds at either end of the invariant interval will result in a new first-ranked treatment, which are shown as numeric treatment codes at either side of the invariant interval.

Figure 5 also shows the risk-of-bias judgements (see *Report Supplementary Material 3*). The smallest threshold is 0.44 (on the log-odds scale) for the Cinciripini *et al.*[207] study estimate of varenicline standard plus bupropion standard versus placebo; if the log-OR of this estimate changed from 1.63 to 2.07 (= 1.63 + 0.44) or higher in favour of varenicline standard plus bupropion standard, then varenicline standard plus bupropion standard would become the first-ranked treatment. This study was rated as being at low risk of bias; however, the upper end of the 95% CI for the study estimate crosses this threshold, meaning that the first-place ranking is sensitive to the level of uncertainty in this study estimate. The second smallest threshold is −0.47 (on the log-odds scale) for the Koegelenberg *et al.*[351] estimate of varenicline standard plus NRT standard versus varenicline standard; if the log-OR of this estimate changes from 0.71 to 0.24 (= 0.71 − 0.47) or lower, in favour of varenicline standard, then e-cigarette low would become the first-ranked treatment. This study was rated as being at unclear risk of bias, and it may be judged whether or not any bias due to inadequate random sequence generation or allocation concealment would lead to such an overestimation of treatment effects.

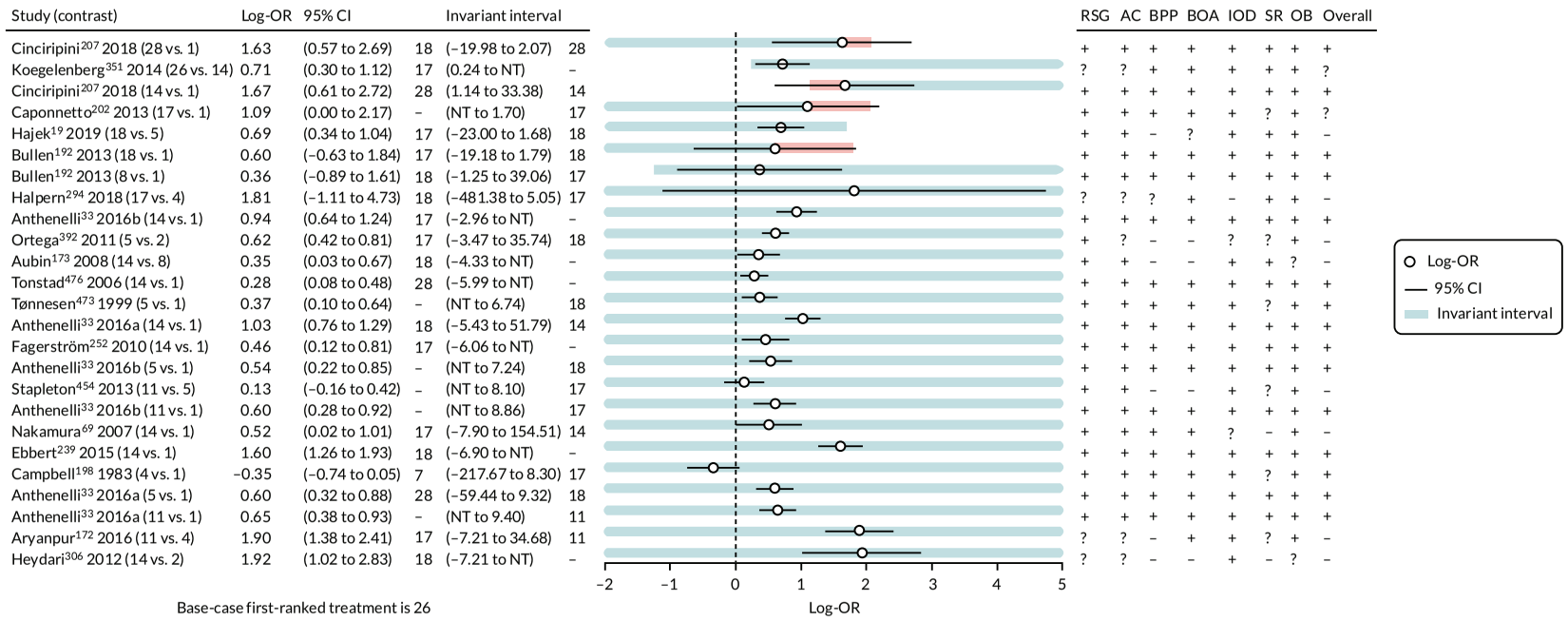

FIGURE 5 Threshold analysis results for sustained abstinence, sorted by size of threshold (smallest to largest). Only studies with thresholds of < 10 log-OR are shown, for brevity. Treatment codes are (1) placebo, (7) NRT standard, (11) bupropion standard, (14) varenicline standard, (17) e-cigarette low, (18) e-cigarette high, (26) varenicline standard plus NRT Standard and (28) varenicline plus bupropion standard. For a full list, see *Appendix 6*. Bold study labels and red shaded invariant intervals show where a 95% CI crosses the corresponding threshold, indicating sensitivity to the level of uncertainty in this estimate. AC, allocation concealment; BOA, blinding of outcome assessment; BPP, blinding of participants and personnel; IOD, incomplete outcome data; NT, no threshold; OB, other bias; RSG, random sequence generation; SR, selective reporting. '+', low risk of bias; '?', unclear risk of bias; '–', high risk of bias.[19,33,69,172,173,192,198,202,207,239,252,294,306,351,392,454,473,476] This figure is reproduced with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

There is no threshold in the other direction for this study estimate, indicated by 'NT' in the invariant interval; no amount of change to this estimate in favour of varenicline standard plus NRT would change the first-ranked treatment. Only one other study (Caponnetto *et al.*;[202] e-cigarette low vs. placebo) has a threshold < 0.7 log-OR (equivalent to a factor of 2 on the OR scale); the threshold is 0.61 in the direction favouring e-cigarette low, at which point e-cigarette low would be the first-ranked treatment. The upper end of the 95% CI for the study estimate crosses this threshold, meaning that the first-place ranking is sensitive to the level of uncertainty in this study estimate. Only another two studies[19,192] have thresholds < 3 log-OR (equivalent to a factor of 20 on the OR scale). Bullen *et al.*[192] is rated as being at low risk of bias, but Hajek *et al.*[19] is rated as being at high or unclear risk of bias for blinding. To change the first-ranked treatment (to e-cigarette high), the Hajek *et al.*[19] estimate of e-cigarette high versus NRT not specified would have to underestimate the true OR by a factor of 2.6. The remaining 212 study estimates have even larger thresholds, and it is unlikely that any potential biases could plausibly change these estimates by such an amount to affect the first-place ranking.

Overall, the first-place ranking of varenicline standard plus NRT standard appears relatively robust. However, there is some sensitivity to the level of uncertainty and potential biases in the evidence, which could lead to varenicline plus bupropion standard, e-cigarette low or e-cigarette high being ranked first for sustained abstinence.

Prolonged abstinence

Prolonged abstinence was also restricted to measurements with a follow-up of at least 24 weeks. It was reported in 19 studies (4434 patients), with 17 studies (3512 patients) including at least one relevant comparison. *Appendix 5*, *Figure 54* presents the structure of this network, sparser than the previous one but still connected both at (a) the treatment and (b) the class level. Placebo was, again, the main comparator across studies, although some direct comparisons between different drug types are also available. We excluded one study comparing NRT gum standard (8/79 patients quit) with no drug treatment (2/82 patients quit), which was disconnected from the main network both at the treatment and at the class levels, and one study comparing bupropion low (1/9 patients quit) with placebo (0/9 patients quit) because of small numbers that caused convergence problems in the models.

Therefore, the NMA for this outcome was based on 15 studies. Results with placebo as a comparator are presented in *Appendix 5*, *Figure 55*. There was evidence that smokers treated with bupropion standard (OR 2.34, 95% CrI 1.46 to 3.86), varenicline standard (OR 3.63, 95% CrI 2.23 to 6.36) and varenicline standard plus bupropion standard (OR 4.76, 95% CrI 2.48 to 10.10) were more likely to achieve prolonged abstinence than those who received placebo.

Appendix 5, *Table 40* gives the NMA results with placebo as comparator alongside effect estimates from direct and/or indirect evidence, where available. Most estimates are above 1, which suggests that smokers assigned to each of the drugs examined were more likely to achieve prolonged abstinence than those receiving placebo. As would be expected, CrIs around the NMA effect estimates are typically narrower than those obtained using either direct or indirect evidence in isolation.

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 5*, *Table 42* and *Figures 55* and *56*). Pairwise comparisons between active interventions, mostly obtained through indirect evidence, are displayed in *Appendix 5*, *Table 41*. There was inconclusive evidence that bupropion standard, varenicline standard, and varenicline standard plus bupropion standard differed from each other in the odds of achieving prolonged abstinence.

Any abstinence

Any abstinence was restricted to measurements with a follow-up of at least 22 weeks. A total of 216 studies (99,630 smokers) reported on it, with 196 (91,667 smokers) including at least one relevant comparison. The structure of the network at the treatment level is displayed in *Appendix 5*, *Figure 58* and at the class level in *Figure 6*.

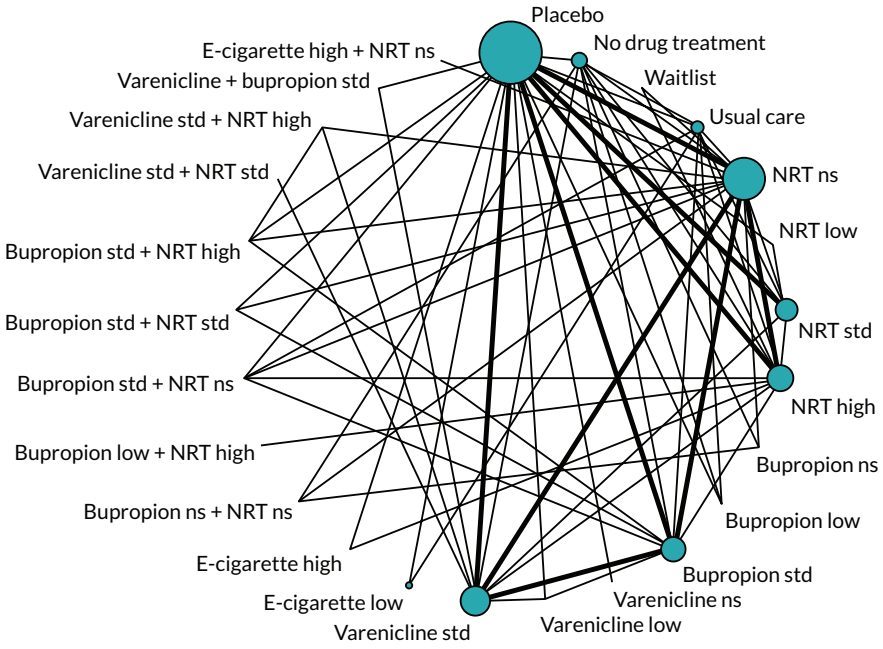

FIGURE 6 Network plot for any abstinence at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Results for the fixed-class random-effects NMA with placebo as a comparator are presented in *Figure 7*. Compared with placebo, there was evidence that smokers randomised to no drug treatment were more likely to achieve any abstinence (OR 1.48, 95% CrI 1.19 to 1.86), whereas smokers receiving usual care were less likely to do so (OR 0.66, 95% CrI 0.46 to 0.96). With regard to active interventions, smokers allocated to NRT not specified (OR 1.86, 95% CrI 1.57 to 2.20), NRT standard (OR 2.03, 95% CrI 1.72 to 2.44), NRT high (OR 2.46, 95% CrI 2.03 to 2.94), bupropion low (OR 2.89, 95% CrI 1.34 to 6.23), bupropion standard (OR 1.84, 95% CrI 1.57 to 2.16), varenicline not specified (OR 4.06, 95% CrI 1.04 to 11.90), varenicline standard (OR 2.69, 95% CrI 2.27 to 3.19), e-cigarette low (OR 3.29, 95% CrI 1.13 to 10.80), e-cigarette high (OR 2.77, 95% CrI 1.01 to 7.69), bupropion low plus NRT high (OR 5.75, 95% CrI 1.79 to 19.10), bupropion standard plus NRT not specified (OR 2.10, 95% CrI 1.22 to 3.60), bupropion standard plus NRT high (OR 2.56, 95% CrI 1.60 to 4.14), varenicline standard plus NRT standard (OR 5.53, 95% CrI 2.12 to 14.40), varenicline standard plus NRT high (OR 2.36, 95% CrI 1.12 to 4.90), and varenicline standard plus bupropion standard (OR 3.56, 95% CrI 1.84 to 6.89) had higher odds of any abstinence than those receiving placebo.

Appendix 5, *Table 43* presents the class effect estimates with placebo as comparator obtained from the NMA and direct and indirect evidence. Direct evidence was available for most monotherapies, whereas comparisons of combinations of interventions compared with placebo largely relied on indirect evidence only. Most effect estimates are above 1, suggesting that the interventions helped smokers to reach sustained abstinence more frequently than placebo.

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 5*, *Table 45* and *Figures 59* and *60*). Where there was enough information to back-calculate indirect evidence and compare it with direct evidence, the results were largely consistent, although there were instances when direct evidence showed a less beneficial effect for the experimental drug than the indirect evidence (e.g. e-cigarette low vs. placebo).

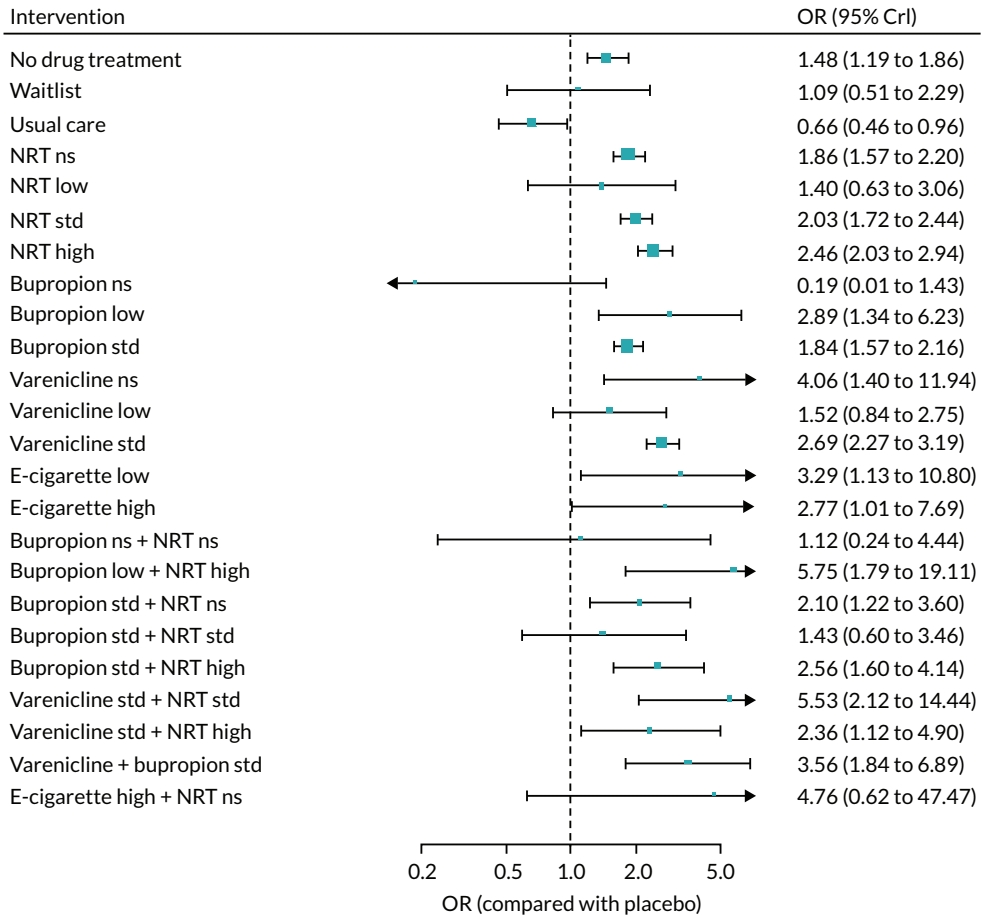

FIGURE 7 Forest plot with results of the fixed-class NMA model for any abstinence. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

The pairwise comparisons between experimental interventions for this outcome are presented in *Appendix 5*, *Table 44*. Most effect estimates were informed by indirect evidence only, and the results were consistent when both direct and indirect evidence were available. There was evidence that smokers randomised to varenicline standard were more likely to achieve any abstinence than those allocated to NRT standard (OR 1.32, 95% CrI 1.05 to 1.65) and bupropion standard (OR 1.46, 95% CrI 1.18 to 1.81). Furthermore, varenicline standard plus NRT standard led to higher odds of abstinence than NRT standard alone (OR 2.70, 95% CrI 1.02 to 7.13), bupropion standard (OR 2.99, 95% CrI 1.13 to 7.88) and standard doses of bupropion and NRT combined (OR 3.83, 95% CrI 1.05 to 14.00). Last, there was weak evidence that the combination of varenicline standard plus bupropion standard was more effective than bupropion standard alone (OR 1.93, 95% CrI 0.98 to 3.79).

Seven-day point prevalence abstinence

Point prevalence abstinence at 1 week was reported in 139 studies (55,724 patients), with 122 studies (48,110 patients) including at least one relevant comparison. *Appendix 5*, *Figure 61* presents the structure of this network at the treatment level and *Figure 8* presents the structure of this network at the class level.

The NMA for this outcome was based on 122 studies. Results with placebo as a comparator are presented in *Figure 9*. There was evidence that smokers randomised to NRT not specified (OR 1.75, 95% CrI 1.48 to 2.08), NRT standard (OR 1.58, 95% CrI 1.21 to 2.12) and NRT high (OR 1.99, 95% CrI

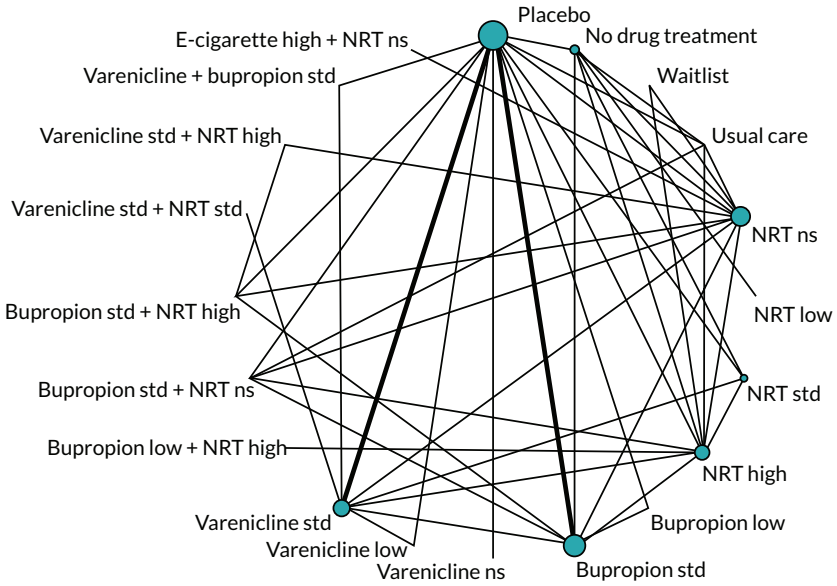

FIGURE 8 Network plot for 7-day PPA at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

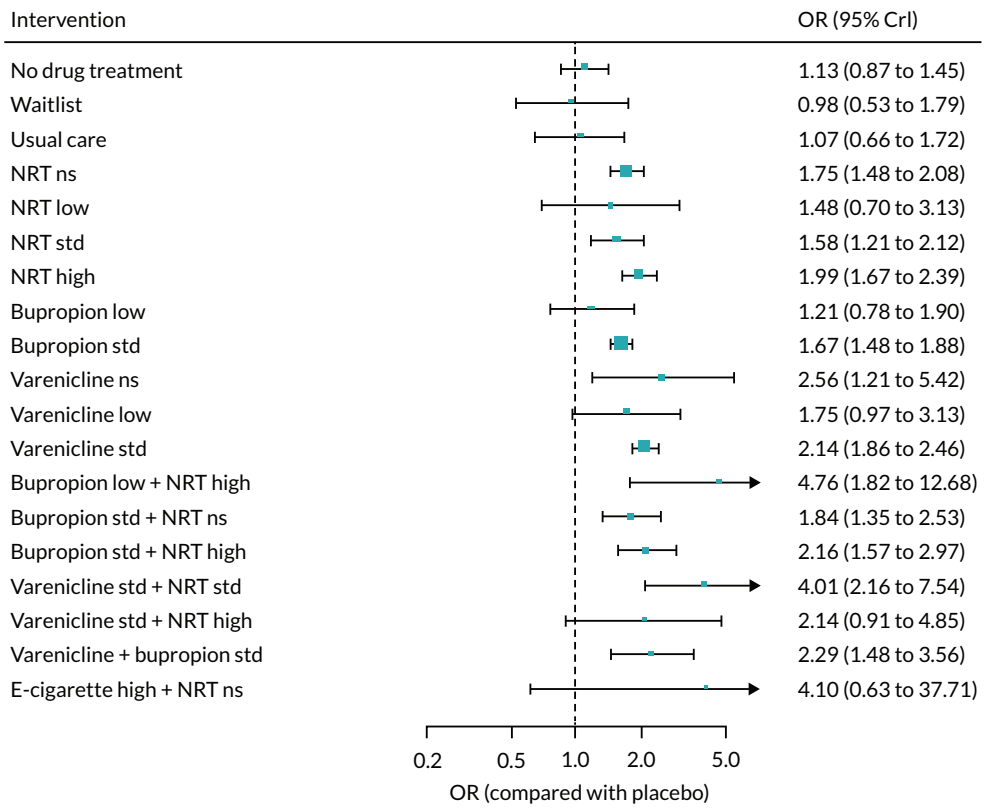

FIGURE 9 Forest plot with results of the fixed-class NMA model for PPA. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

1.67 to 2.39) were more likely to remain abstinent for a full week than those receiving placebo. Similarly, smokers treated with bupropion standard (OR 1.67, 95% CrI 1.48 to 1.88), varenicline not specified (OR 2.56, 95% CrI 1.21 to 5.42), varenicline standard (OR 2.14, 95% CrI 1.86 to 2.46), bupropion low plus NRT high (OR 4.76, 95% CrI 1.82 to 12.70), bupropion standard plus NRT high (OR 2.16, 95% CrI 1.57 to 2.97), varenicline standard plus NRT standard (OR 4.01, 95% CrI 2.16 to 7.54) and varenicline standard plus bupropion standard (OR 2.29, 95% CrI 1.48 to 3.56) reached 7-day PPA more often than those taking placebo. There was weak evidence that varenicline low was more effective than placebo (OR 1.75, 95% CrI 0.97 to 3.13).

Appendix 5, *Table 46* presents the NMA results with placebo as comparator alongside effect estimates from direct and/or indirect evidence, where available. Most estimates are above 1, which suggests that smokers assigned to each of the drugs examined were more likely to remain abstinent for a full week than those receiving placebo. Nonetheless, intervals around effect estimates obtained from direct and indirect evidence tend to be wider than those obtained when integrating both in the NMA, which reflects the gain in precision when using the latter approach. A comparison between direct and indirect evidence reveals largely consistent results, although examples can be found where direct evidence suggests a less beneficial effect of the experimental intervention (e.g. varenicline low vs. placebo) and also the opposite (NRT high vs. placebo).

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 5*, *Table 48* and *Figures 62* and *63*). Pairwise comparisons between active interventions, mostly obtained through indirect evidence, are displayed in *Appendix 5*, *Table 47*. Smokers allocated to varenicline standard achieved the target more often than those treated with NRT standard (OR 1.35, 95% CrI 0.99 to 1.82) or bupropion standard (OR 1.28, 95% CrI 1.08 to 1.53). Furthermore, there was strong evidence that the combination of varenicline standard plus NRT standard led to higher odds of abstinence than NRT standard alone (OR 2.54, 95% CrI 1.28 to 4.98), bupropion standard (OR 2.42, 95% CrI 1.28 to 4.57) and varenicline standard alone (OR 1.88, 95% CrI 1.02 to 3.46).

Ranking of interventions

Table 4 presents ranks for a selection of classes according to the primary effectiveness outcome, namely sustained abstinence. Varenicline standard plus NRT standard yielded the highest probability of being the most effective intervention (0.61, mean rank 1.67), followed by e-cigarette low (0.19, mean rank 3.61), varenicline standard plus bupropion standard (0.12, mean rank 3.42) and e-cigarette high (0.08, mean rank 3.32). Conversely, there was strong evidence that placebo had the lowest rank among the eight shortlisted interventions, with a mean rank of 7.97.

TABLE 4 Mean ranking of interventions for sustained abstinence

Intervention	Pr(best)	Mean rank
Placebo	0	7.97
NRT standard	0	5.64
Bupropion standard	0	6.57
Varenicline standard	0	3.80
E-cigarette low	0.19	3.61
E-cigarette high	0.08	3.32
Varenicline standard plus NRT standard	0.61	1.67
Varenicline standard plus bupropion standard	0.12	3.42

Figure 10 is a rank-o-gram displaying the ranking of the same interventions across the four effectiveness outcomes examined in our NMA models. Varenicline standard plus NRT standard showed a high probability to be ranked best or second-best intervention for all of them (note that there was no information for the effect of this drug combination on prolonged abstinence). Furthermore, varenicline standard plus bupropion standard yielded the highest probability to be ranked as the best intervention for prolonged abstinence, although there was higher uncertainty about its ranking for the other outcomes. Moreover, varenicline standard showed highest probabilities of being ranked second to fourth best for the different outcomes, whereas e-cigarettes presented a more uncertain ranking profile. Last, placebo was ranked as the least effective intervention for all outcomes.

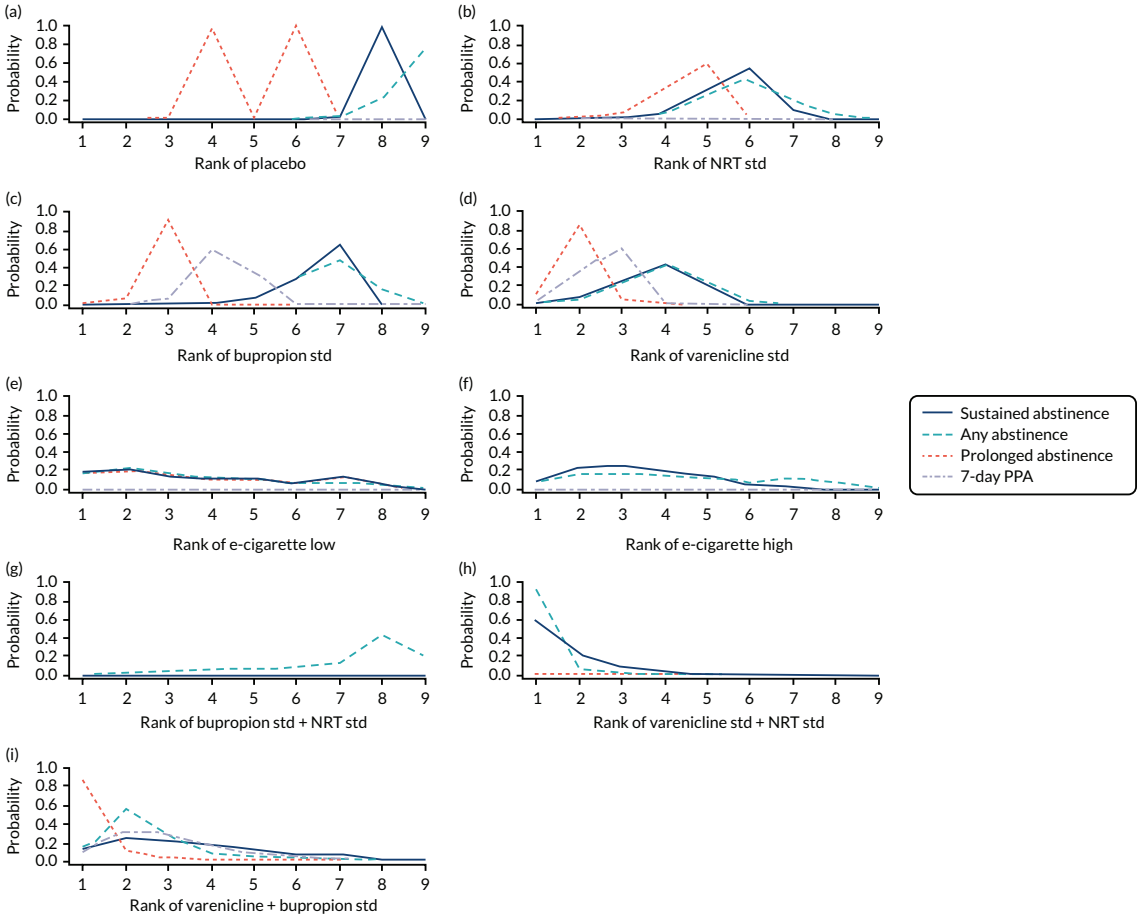

FIGURE 10 Rank-o-gram of interventions across effectiveness outcomes. Rank of (a) placebo; (b) NRT standard; (c) bupropion standard; (d) varenicline standard; (e) e-cigarette low; (f) e-cigarette high; (g) bupropion standard plus NRT standard; (h) varenicline standard plus NRT standard; and (i) varenicline standard plus bupropion standard. Std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Chapter 6 Clinical results: safety

Included studies

Randomised evidence

Study selection

The results of our search strategy are summarised in *Figure 11*. Our original searches identified 335 studies for inclusion and our update searches identified an additional 20 studies for inclusion, resulting in a total of 355 studies[19,33,40,69,70,164–166,169–171,173–180,184–186,190,192,193,196–198,200–203,205–208,212,216–218,220,221,223–226,228–231,233–252,255,257–259,261–263,265–268,271–275,277–279,281–283,286–288,295–297,300–303,307–311,313,315,318–331,336–340,343–345,347,349–352,354,356,357,359,361–366,371,373–378,380,381,385–387,390,391,393,395–397,399,401,403,404,406,408,410,411,413–416,418–422,424–427,429–436,438–440,442–450,453–458,460,463–476,478–482,484,487,488,490–495,497–506,509,511–604] that reported on one or more safety outcomes; these are described in the following sections. For the purpose of our analyses, the EAGLES study[33] was treated as two studies, where Anthenelli 2016a[33] included the four study arms from the non-psychiatric cohort

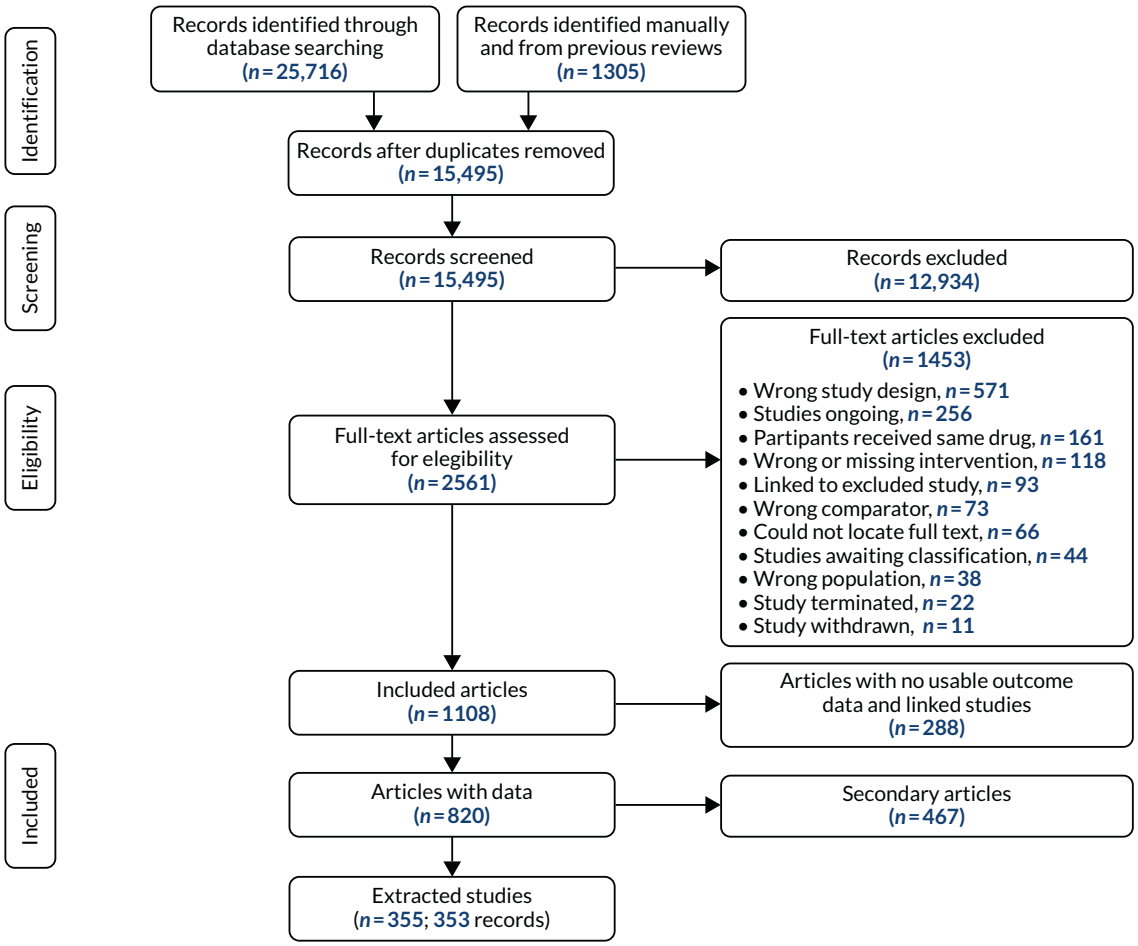

FIGURE 11 The PRISMA flow diagram for randomised safety study records. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

and Anthenelli 2016b[33] included the four arms from the psychiatric cohort. A list of records excluded at full-text screening (that did not meet randomised or non-randomised inclusion criteria for effectiveness or safety analyses) and the reasons for their exclusion are presented in *Report Supplementary Material 1*.

Study characteristics

The number of participants randomised across the 355 trials ranged from 5 to 5887, with a total of 159,101 participants. Trials were conducted across six continents, with 211 trials in the USA, 34 trials in the UK, and 31 multicountry trials. Trials were conducted in several settings, including medical centres and facilities, academic and research centres, universities, community centres, subsidised housing neighbourhoods, hospitals, pharmacies, clinics (e.g. smoking cessation, dental, substance misuse, HIV), primary care (general, family and private practices), over-the-counter, companies and workplaces, over the telephone and by mail.

Trial duration ranged from 0.14 (1 day/single session) to 754 weeks and duration of drug treatment ranged from 0.07 (half a day) to 104 weeks. One hundred and forty trials were industry sponsored and 154 trials were publicly registered online. We included 48 trials in which smokers were unwilling or not necessarily motivated to quit and 13 trials of smokeless-tobacco users. Twenty-three trials recruited smokers with comorbidities as specified by the Charlson Comorbidity Index,[90] 29 trials recruited smokers with current or a history of psychiatric conditions and 25 trials recruited smokers with current or a history of drug- or alcohol-related conditions.

The mean age of trial participants ranged from 28.4 to 62.8 years and the percentage of female participants (in studies that did not exclusively recruit male or female participants) ranged from 0.3% to 79%. Study populations ranged between ethnicities (e.g. white/Caucasian, African American, Asian, Indigenous Maori), types of tobacco use (e.g. smokeless tobacco, spit tobacco, cigars, waterpipes) and heaviness of smoking. Studies included smokers who were hospital inpatients or outpatients (including smokers scheduled for surgery), smokers with HIV, smokers with substance misuse, smokers with psychiatric conditions, smokers who were health-care professionals, smokers who were active or former armed forces and their family members (e.g. veterans, National Guard), smokers with previous quit attempts or who had recently relapsed, smokers who were cancer patients or survivors, female smokers concerned about weight, smokers from low-income or subsidised housing neighbourhoods, smokers with tuberculosis and smokers with asthma. Study-level characteristics can be found in tables in *Report Supplementary Material 4*.

Non-randomised evidence

Study selection

The results of our search strategy are summarised in *Figure 12*. Our original searches identified 48 studies for inclusion and our update searches identified an additional five studies for inclusion, resulting in a total of 53 studies[53–55,57,605–653] that reported on one or more safety outcomes; these are described in the following sections. A list of records excluded at full-text screening (i.e. they did not meet randomised or non-randomised inclusion criteria for effectiveness or safety analyses) and the reasons for their exclusion are presented in *Report Supplementary Material 1*.

Study characteristics

The number of participants randomised across the 53 studies ranged from 32 to 7,917,436, with a total of 8,783,403 participants. Study designs included case–control, population cohort, retrospective cohort, prospective cohort and quasi-randomised. Studies were conducted across five continents, with 19 studies in the USA, seven studies in the UK, and no multicountry studies. Studies were conducted in several settings, including hospitals, primary care (e.g. GP practices), clinics (e.g. community, smoking cessation, tobacco dependence, surgical preoperative), academic, drug monitoring and medical centres. Observational studies used a range of databases, including the Clinical Practice Research Datalink (CPRD) (formerly the General Practice Research Database), New York City Fire Department, Bureau

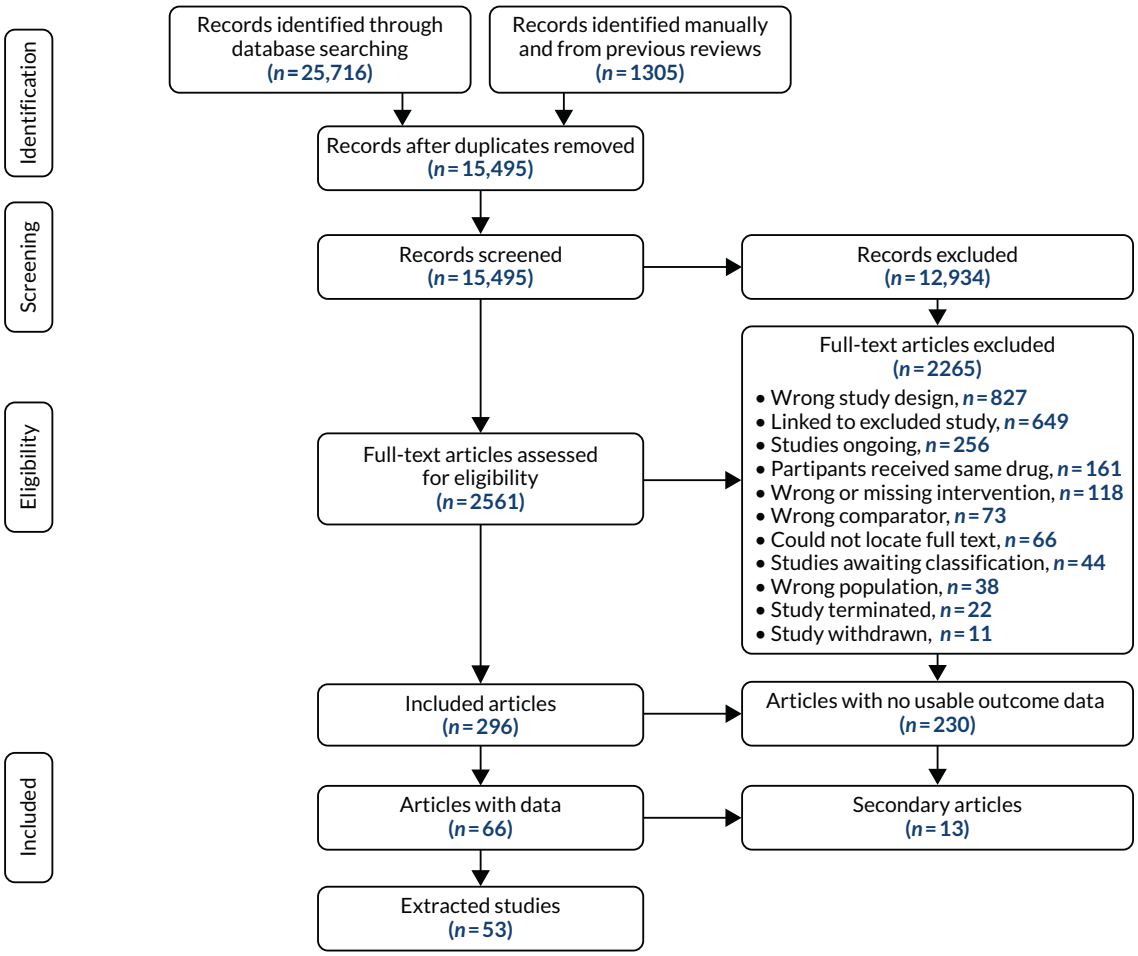

FIGURE 12 The PRISMA flow diagram for non-randomised safety study records.

of Medical Services, Medicaid, Military Health System Data Repository, nationwide registries (National Prescription Registry, National Patient Registry), and were conducted over the telephone and online.

Study duration ranged from 4 to 208 weeks and the duration of drug treatment ranged from 1.26 to 208 weeks. Three studies were industry sponsored and three studies were publicly registered online. We included two studies in which smokers were not necessarily motivated to quit and no studies of smokeless-tobacco users. Five studies recruited smokers with comorbidities as specified by the Charlson Comorbidity Index,[90] five studies recruited smokers with current or a history of psychiatric conditions and two studies recruited smokers with current or a history of drug- or alcohol-related conditions.

The mean age of study participants ranged from 37.9 to 58.3 years and the percentage of female participants (in studies that did not exclusively recruit male or female participants) ranged from 1% to 61.6%. Studies included smokers who were hospital inpatients or outpatients (including smokers scheduled for surgery), smokers with HIV, smokers with substance misuse, smokers with psychiatric conditions, smokers who were veterans, New York City Fire Department employees and their household family members who smoked, smokers with previous quit attempts, smokers who were critically ill and smokers who were Medicare patients. Study-level characteristics can be found in tables in *Report Supplementary Material 6*.

Risk of bias in included studies

Randomised evidence

Ratings ranged from low to high risk of bias, and an overall risk of bias domain was rated by selecting the highest rating of bias across domains, with the exception of selective outcome reporting (as this domain was usually rated as unclear owing to inaccessibility of study protocols and limited trial registration). Risk-of-bias ratings by study and summarised across studies are presented in *Report Supplementary Material 5* and *Appendix 4*, *Figure 35*, respectively.

Random sequence generation

Few trials were rated as being at high risk of bias for random sequence generation, with only 1% rated as being at high risk of bias. Conversely, over half (52%) of trials were rated as being at low risk of bias and the remaining 47% of trials were rated as being at unclear risk of bias.

Allocation concealment

As with random sequence generation, only 2% of trials were rated as being at high risk of bias for allocation concealment, whereas 42% were rated as being at low risk of bias and over half (56%) of trials were rated as being at unclear risk of bias.

Blinding of participants and personnel

Blinding of participants and personnel was rated as being at high risk of bias in 22% of trials, largely as a result of trials where drugs were delivered open label without any blinding. Ratings for the remaining trials were similarly split between low risk of bias (39%) and unclear risk of bias (39%).

Blinding of outcome assessment

Almost half (45%) of trials were rated as being at unclear risk of bias for blinding of outcome assessment domains, with 43% of trials rated as being at low risk of bias and 12% of trials rated as being at unclear risk of bias.

Incomplete outcome data

More than half (69%) of the trials were rated as being at low risk of bias for the incomplete outcome data domain, as loss to follow-up was either low or similar among trial arms. The remining trials were rated as being at unclear risk of bias (21%) or high risk of bias (10%).

Selective reporting

As previously mentioned, most (66%) of trials were rated as being at unclear risk of bias for selective reporting owing to a lack of study protocols or public trial registrations. One-third of studies (33%) were rated as being at low risk of bias and only 1% of trials were rated as being at high risk of bias.

Other bias

Nearly all (95%) trials were rated as being at low risk of bias for the other bias domain, with only 3% rated as being at unclear risk of bias and 2% rated as being at high risk of bias.

Overall bias

Finally, ratings for our overall risk of bias domain indicated that 16% of trials were rated as being at low risk of bias, 51% of trials were rated as being at unclear risk of bias and 33% of trials as being at high risk of bias.

Non-randomised evidence

Ratings ranged from low to high risk of bias and an overall risk-of-bias domain was rated by selecting the highest rating of bias across domains, with the exception of selective outcome reporting (as this domain was usually rated as unclear owing to inaccessibility of study protocols and limited study registration).

Risk-of-bias ratings by study and summarised across studies are presented in *Report Supplementary Material 7* and *Appendix 4*, *Figure 36*, respectively.

Given the non-randomised study designs, nearly all studies were rated as at high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment domains. This was as a result of the studies not randomising participants and commonly not concealing the allocation to study arms, and in most studies blinding was not used. Most studies (81%) of studies were rated as unclear for the incomplete outcome data domain, as the number of participants followed up was either not reported or not applicable in the study design. As previously mentioned, most (94%) of the studies were rated as unclear for selective reporting and 92% of studies were rated as low for the other bias domain. Finally, ratings for our overall risk of bias domain indicated that 100% of studies were rated as being at high risk as a result of the ratings for most studies across the first four domains.

Results on safety

We performed NMA on three safety outcomes: SAEs, MACEs and MANEs. We fitted a standard (full interaction) NMA model as well as fixed- and random-class NMA models for each outcome. Based on the model fit indices (see *Appendix 7*), we focused on fixed-class NMA models. *Appendix 7*, *Tables 49* and *50* provide a list of the treatments delivered in the randomised trials and non-randomised studies included in safety analyses and their frequency, respectively. In this chapter we present results for each outcome based on a fixed-class NMA model; for additional results using other models, see *Appendix 7*. Results are presented as median ORs alongside 95% CrIs. A summary of results across outcomes is provided at the end of this chapter in the form of a rank-o-gram.

Serious adverse events

Randomised evidence only

Our primary safety outcome, SAEs, was reported in 111 studies with a total of 63,927 patients, of which 101 studies (58,318 patients) compared two or more of the treatment classes of interest. We excluded one study from all analyses [varenicline not specified (3/160 patients with event) vs. placebo (0/160 patients with event)] because of small event numbers causing convergence problems. Furthermore, two studies (bupropion standard plus NRT inhalator vs. usual care, and varenicline standard plus NRT gum standard vs. varenicline low plus NRT gum standard) were disconnected at the treatment level (see *Figure 64*), but connected to the main network at the class level (*Figure 13*). We excluded both studies when comparing the different models (see *Table 51*), but we were able to include them in the analyses discussed in this section (which report results at the class level).

Figure 14 displays results for the fixed-class NMA model based on 100 studies with placebo as a comparator. There was evidence that bupropion standard (OR 1.27, 95% CrI 1.04 to 1.58) increased the odds of SAEs compared with placebo.

Table 5 presents the class effect estimates with placebo as comparator obtained from the NMA (final column) alongside the estimates obtained from direct and indirect evidence. Direct evidence was available for most monotherapies, whereas comparisons of most combinations of interventions with placebo were obtained largely through indirect evidence only. Evidence for some of the main interventions (e.g. bupropion standard and varenicline standard) was informed by large trials that compared these drugs against placebo, so that indirect evidence did not add anything to the NMA results. When both direct and indirect evidence was available, results were mostly consistent, although there were some instances in which direct evidence suggested a larger increase in the odds of a SAE for the experimental drug (e.g. e-cigarette high vs. placebo).

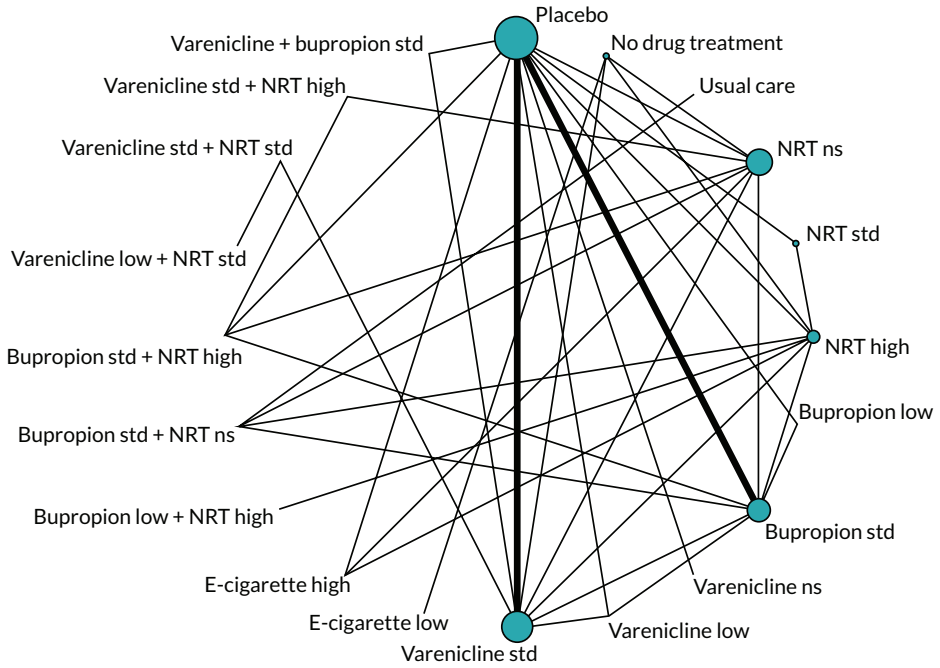

FIGURE 13 Network plot for SAEs at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

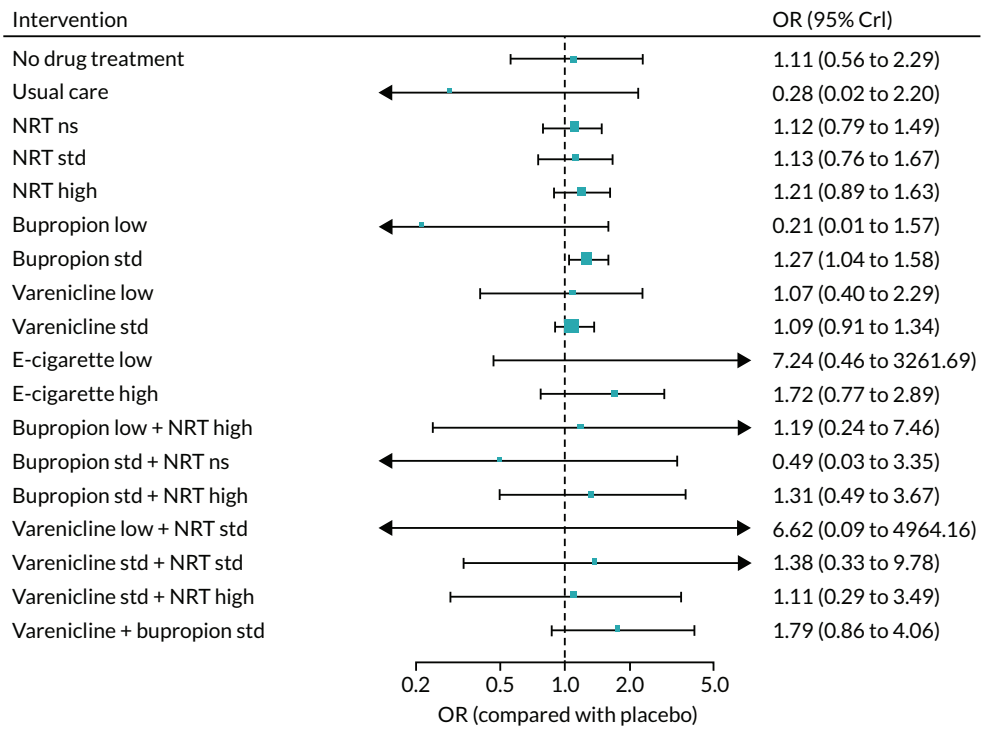

FIGURE 14 Forest plot with results of the fixed-class NMA model for SAEs. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 5 Results for SAEs: comparisons with placebo

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	–	1.11 (0.56 to 2.29)	1.11 (0.56 to 2.29)
Usual care	–	0.28 (0.02 to 2.20)	0.28 (0.02 to 2.20)
NRT not specified	1.19 (0.86 to 1.62)	0.72 (0.31 to 1.68)	1.12 (0.79 to 1.49)
NRT standard	1.11 (0.74 to 1.68)	1.37 (0.38 to 4.96)	1.13 (0.76 to 1.67)
NRT high	1.11 (0.77 to 1.58)	1.40 (0.87 to 2.27)	1.21 (0.89 to 1.63)
Bupropion low	0.26 (0.03 to 1.52)	0.37 (0.01 to 9.36)	0.21 (0.01 to 1.57)
Bupropion standard	1.27 (1.04 to 1.58)	–	1.27 (1.04 to 1.58)
Varenicline low	1.12 (0.54 to 2.29)	1.62 (0.15 to 17.6)	1.07 (0.40 to 2.29)
Varenicline standard	1.09 (0.91 to 1.34)	–	1.09 (0.91 to 1.34)
E-cigarette low	–	7.24 (0.46 to 3262)	7.24 (0.46 to 3262)
E-cigarette high	1.99 (0.90 to 4.44)	1.44 (0.61 to 3.42)	1.72 (0.77 to 2.89)
Bupropion low plus NRT high	–	1.19 (0.24 to 7.46)	1.19 (0.24 to 7.46)
Bupropion standard plus NRT not specified	–	0.49 (0.03 to 3.35)	0.49 (0.03 to 3.35)
Bupropion standard plus NRT high	0.73 (0.05 to 4.18)	1.57 (0.47 to 5.28)	1.31 (0.49 to 3.67)
Varenicline low plus NRT standard	–	6.62 (0.09 to 4964)	6.62 (0.09 to 4964)
Varenicline standard plus NRT standard	–	1.38 (0.33 to 9.78)	1.38 (0.33 to 9.78)
Varenicline standard plus NRT high	–	1.11 (0.29 to 3.49)	1.11 (0.29 to 3.49)
Varenicline standard plus bupropion standard	2.51 (0.73 to 9.49)	1.48 (0.57 to 3.84)	1.79 (0.86 to 4.06)

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 7*, *Table 51* and *Figures 66* and *67*). The pairwise comparisons between active interventions for this outcome are presented in *Table 6*. Most effect estimates were informed by indirect evidence only. As a consequence of this, and also the small event rates reported, effects were imprecisely estimated and all intervals included the null.

With regard to effect modifiers, there was inconclusive evidence of effect modification according to industry sponsorship, type of placebo, treatment duration, counselling, dependence score, comorbid samples, studies in which patients were not required to be willing to quit, smokeless-tobacco users, analyses restricted to samples of heavy smokers, and publication year (see *Figures 69–80*); sensitivity analysis excluding studies at high risk of bias yielded the same findings reported in this section, although with wider intervals for most effect estimates (see *Figure 68*; full results provided in *Appendix 7*). A sensitivity analysis excluding studies that compared pharmacological interventions with psychological interventions (that were not given on all arms of the study) was very similar to that in the main analysis (*see Appendix 7*).

Threshold analysis

The results of the threshold analyses for the first- and last-ranked treatments for SAEs are shown in *Figures 15* and *16*. The first-ranked treatment is placebo and the last-ranked is e-cigarette low. Both figures also include the risk-of-bias judgements from *Report Supplementary Material 5*.

TABLE 6 Results for SAEs: pairwise comparisons of interventions

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	–	1.12 (0.72 to 1.80)	1.12 (0.72 to 1.80)
Varenicline standard vs. NRT standard	–	0.98 (0.62 to 1.50)	0.98 (0.62 to 1.50)
E-cigarette low vs. NRT standard	–	6.48 (0.39 to 3087)	6.48 (0.39 to 3087)
E-cigarette high vs. NRT standard	–	1.54 (0.58 to 2.90)	1.54 (0.58 to 2.90)
Varenicline standard plus NRT standard vs. NRT standard	–	1.23 (0.28 to 8.39)	1.23 (0.28 to 8.39)
Varenicline standard plus bupropion standard vs. NRT standard	–	1.60 (0.69 to 3.82)	1.60 (0.69 to 3.82)
Varenicline standard vs. bupropion standard	–	0.86 (0.67 to 1.11)	0.86 (0.67 to 1.11)
E-cigarette low vs. bupropion standard	–	5.75 (0.37 to 2419)	5.75 (0.37 to 2419)
E-cigarette high vs. bupropion standard	–	1.34 (0.69 to 2.28)	1.34 (0.69 to 2.28)
Varenicline standard plus NRT standard vs. bupropion standard	–	1.10 (0.25 to 8.09)	1.10 (0.25 to 8.09)
Varenicline standard plus bupropion standard vs. bupropion standard	–	1.39 (0.67 to 3.20)	1.39 (0.67 to 3.20)
E-cigarette low vs. varenicline standard	–	6.36 (0.42 to 2879)	6.36 (0.42 to 2879)
E-cigarette high vs. varenicline standard	–	1.56 (0.74 to 2.67)	1.56 (0.74 to 2.67)
Varenicline standard plus NRT standard vs. varenicline standard	1.28 (0.30 to 7.77)	–	1.28 (0.30 to 7.77)
Varenicline standard plus bupropion standard vs. varenicline standard	1.24 (0.49 to 3.34)	2.55 (0.78 to 8.31)	1.64 (0.80 to 3.59)
E-cigarette high vs. e-cigarette low	–	0.23 (0.00 to 3.47)	0.23 (0.00 to 3.47)
Varenicline standard plus NRT standard vs. e-cigarette low	–	0.21 (0.00 to 5.40)	0.21 (0.00 to 5.40)
Varenicline standard plus bupropion standard vs. e-cigarette low	–	0.27 (0.00 to 4.28)	0.27 (0.00 to 4.28)
Varenicline standard plus NRT standard vs. e-cigarette high	–	0.83 (0.17 to 5.52)	0.83 (0.17 to 5.52)
Varenicline standard plus bupropion standard vs. e-cigarette high	–	1.07 (0.42 to 3.31)	1.07 (0.42 to 3.31)
Varenicline standard plus bupropion standard vs. varenicline standard plus NRT standard	–	1.33 (0.19 to 6.31)	1.33 (0.19 to 6.31)

The first-place ranking (of placebo) is very sensitive to the level of uncertainty in the evidence, as shown by the number of study estimates with 95% CIs that cross the corresponding threshold. At each of these thresholds, the new first-ranked treatment is NRT standard, varenicline standard plus NRT standard, e-cigarette high, e-cigarette low, or varenicline plus bupropion standard. Five studies[351,386,415,444,468] have thresholds < 0.7 log-OR (equivalent to a factor of 2 on the OR scale), and, of these, only one[468] is rated as being at low risk of bias.

The last-place ranking (of e-cigarette low) is sensitive to the level of uncertainty from only one study[525] (e-cigarette low vs. no drug treatment). The first-place ranking is also sensitive to the level of uncertainty in this study estimate. If the estimate were to change by –0.80 log-OR from 1.32 to 0.52 in favour

FIGURE 15 Threshold analysis results for SAEs (first-ranked treatment), sorted by size of threshold (smallest to largest). Only studies with thresholds < 3 log-OR are shown, for brevity. Treatment codes are (1) placebo, (7) NRT standard, (11) bupropion standard, (14) varenicline standard, (17) e-cigarette low, (18) e-cigarette high, (26) varenicline standard plus NRT standard and (28) varenicline plus bupropion standard (for a full list, see *Appendix 6*). Bold study labels and red shaded invariant intervals show where a 95% CI crosses the corresponding threshold, indicating sensitivity to the level of uncertainty in this estimate. AC, allocation concealment; BOA, blinding of outcome assessment; BPP, blinding of participants and personnel; IOD, incomplete outcome data; OB, other bias; RSG, random sequence generation; SR, selective reporting. '+', low risk of bias; '−', high risk of bias; '?', unclear risk of bias. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

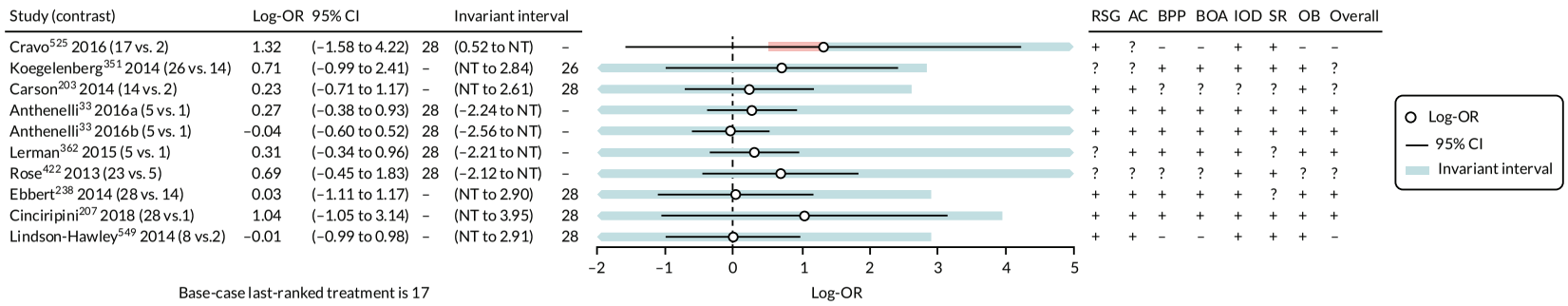

FIGURE 16 Threshold analysis results for SAEs (last-ranked treatment), sorted by size of threshold (smallest to largest). Only studies with thresholds < 3 log-OR are shown, for brevity. Treatment codes are (1) placebo, (7) NRT standard, (11) bupropion standard, (14) varenicline standard, (17) e-cigarette low, (18) e-cigarette high, (26) varenicline standard plus NRT standard and (28) varenicline plus bupropion standard (for a full list, see *Appendix 6*). Bold study labels and red shaded invariant intervals show where a 95% CI crosses the corresponding threshold, indicating sensitivity to the level of uncertainty in this estimate. AC, allocation concealment; BOA, blinding of outcome assessment; BPP, blinding of participants and personnel; IOD, incomplete outcome data; OB, other bias; NT, no threshold; RSG, random sequence generation; SR, selective reporting. '+', low risk of bias; '–', high risk of bias; '?', unclear risk of bias. This figure is reproduced with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

of e-cigarette low, then e-cigarette low would no longer be ranked last (replaced by varenicline plus bupropion standard), and if the estimate were to change only a little more to 0.24, then e-cigarette low would be ranked first for SAEs. Owing to the high level of uncertainty in this study estimate and the resulting wide CI, both of these are plausible owing to sampling error. Cravo *et al.*[525] has the smallest threshold for the last-place ranking (–0.80 log-OR, equivalent to a factor of 2.2 on the OR scale) and was judged to be at high risk of bias owing to inadequate blinding and other bias. The remaining thresholds for the other 122 study estimates are equivalent to a factor of ≥ 8 on the OR scale, which may be larger than any plausible biases.

Overall, the first- and last-place rankings for SAEs are not very robust: both are sensitive to the level of uncertainty in the data, and there may be plausible biases in studies at high or unclear risk of bias that could result in a change of first- or last-place ranking. The Cravo *et al.*[525] study is notably influential for both first- and last-place rankings, displays high levels of uncertainty and is rated as being at high risk of bias. The last-place ranking is likely to be robust to plausible biases in all other studies.

Incorporating non-randomised evidence

Only one non-randomised study[632] reported one or more SAEs. This was a three-arm study comparing e-cigarette standard (14 events in 343 patients), dual smoking (10 events in 319 patients) and no drug treatment (14 events in 693 patients). The network plots at the treatment level and at the class level, combining randomised and non-randomised evidence for this outcome, are presented in *Appendix 7*, *Figure 65* and *Figure 17*, respectively.

The statistical integration was identical to that restricted to randomised evidence, except for the addition of the non-randomised study. The results for the fixed-class random-effects NMA, based on 102 studies and 59,673 smokers, are displayed in *Figure 18*. Comparison with *Figure 14* suggests that, although only one study was added, the effect estimates changed substantially, now suggesting that varenicline

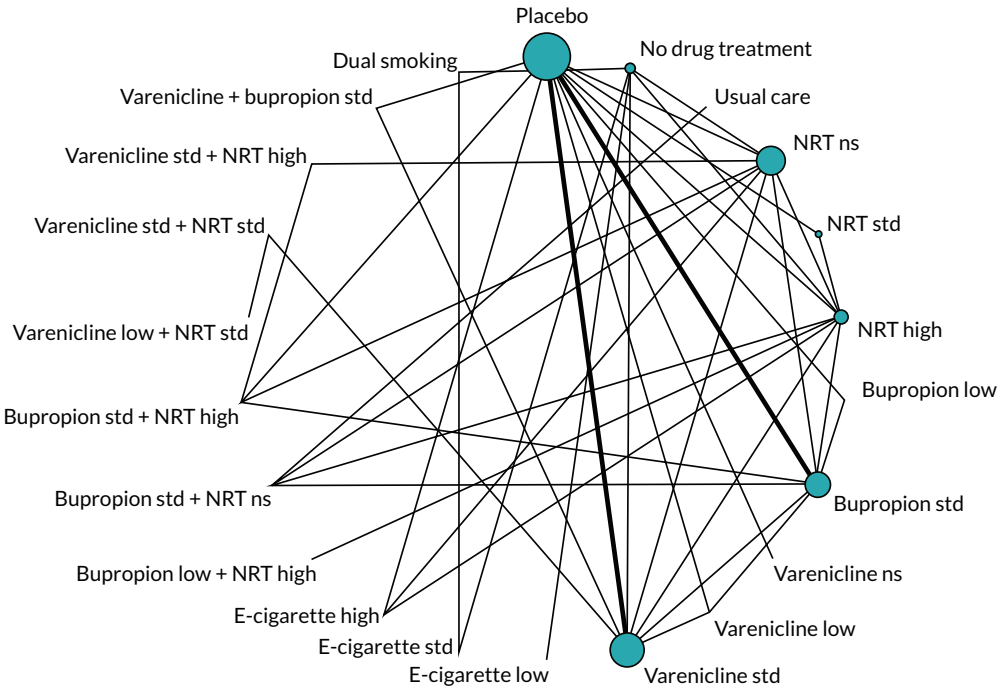

FIGURE 17 Network plot for SAEs, incorporating non-randomised evidence at class level. Ns, not specified; std, standard.

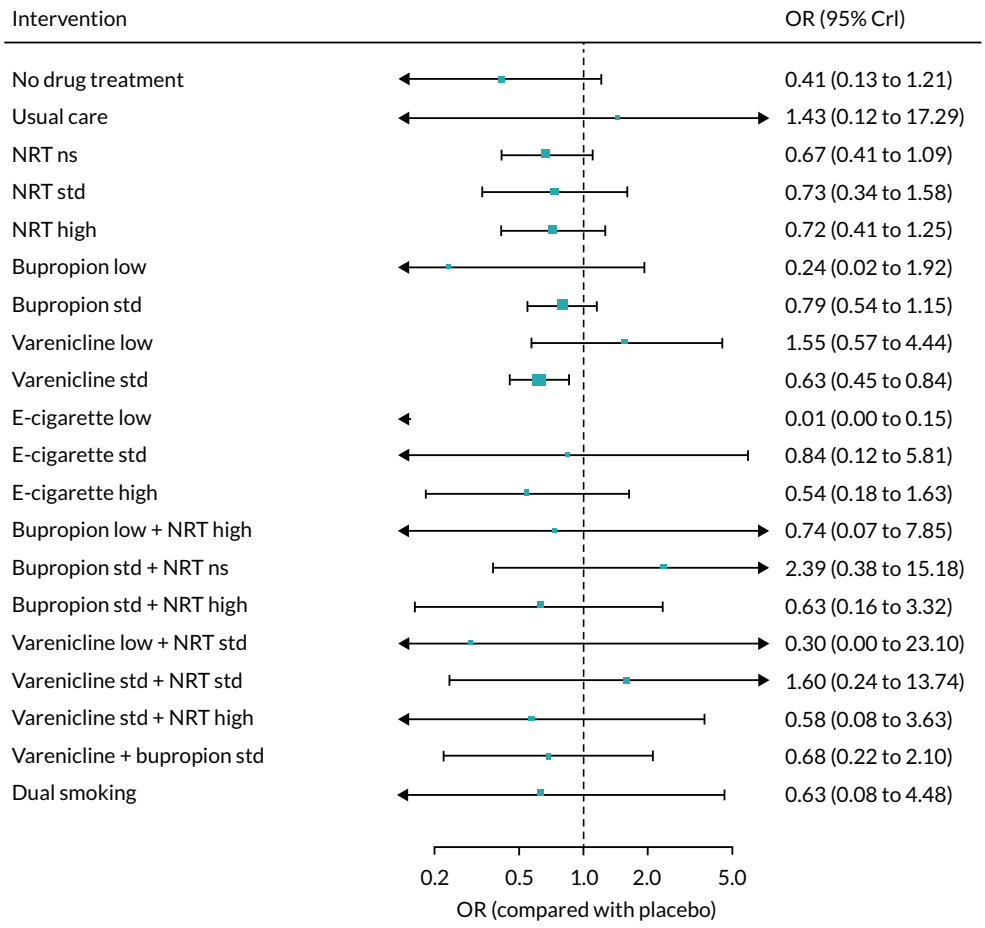

FIGURE 18 Forest plot displaying the NMA results for SAEs, combining randomised and non-randomised evidence. Ns, not specified; std, standard.

standard (OR 0.63, 95% CrI 0.45 to 0.64) and e-cigarette low (OR 0.01, 95% CrI 0.00 to 0.15) might lead to lower odds of SAEs than placebo. The notable influence of the study added might be because of its contribution of 38 events to a network focused on a rare outcome. Furthermore, the non-randomised study, conducted by Manzoli *et al.*,[632] found that no drug treatment might be the safest of the three interventions compared. Given that no drug treatment is one of the main comparators in the network, this finding from a single study is likely to have an impact on the effect estimates for many interventions. In summary, this analysis illustrates the difficulties of drawing solid conclusions about the relative safety of different smoking interventions from the currently available evidence on SAEs.

Major adverse cardiovascular events

Randomised evidence only

A total of 49 studies (38,329 patients) reported MACEs, with 44 studies (36,231 patients) including at least one relevant comparison. The structure of this network is presented at the treatment (see *Figure 81*) and at the class (*Figure 19*) level. We discarded three studies from all analyses owing to small numbers causing convergence problems, namely one study comparing varenicline not specified (1/160 patients with event) with placebo (0/160 patients with event), one study comparing bupropion standard plus NRT inhalator not specified (0/267 patients with event) with usual care (1/271 patients with event) and one study comparing NRT not specified (0/61 patients with event) with usual care (5/61 patients with event). Furthermore, one further study comparing NRT gum standard (25/3923 patients with event) with usual care (12/1964 patients with event) was disconnected from the network and, hence, was excluded from any further analyses.

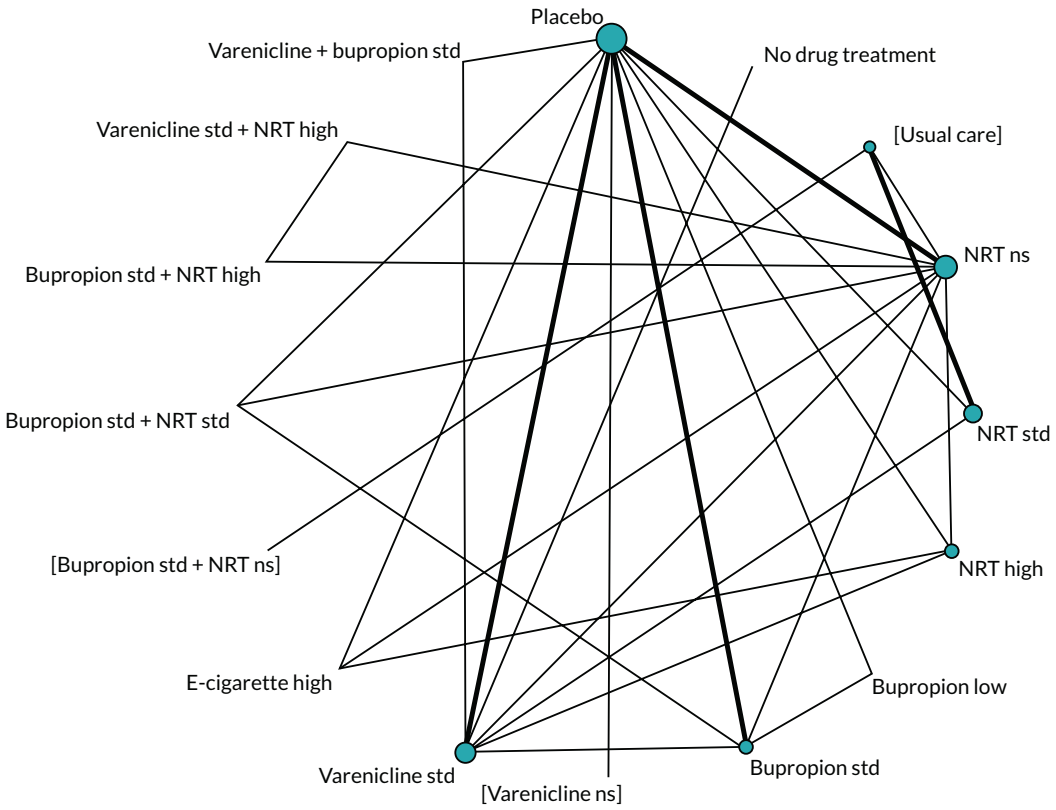

FIGURE 19 Network plot for major adverse cardiovascular events at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

Therefore, the NMA for this outcome was based on 41 studies. The results with placebo as a comparator are presented in *Figure 20*. Owing to the small numbers of events reported across studies, all effect estimates show very wide intervals and, hence, it was not possible to identify differences among any pair of interventions.

Table 7 presents the NMA results with placebo as comparator alongside effect estimates from direct and/or indirect evidence, where available. Although intervals were wide and always included the null, NMA estimates were generally more precise when both direct and indirect evidence were available.

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 7*, *Table 52* and *Figures 83* and *84*). The pairwise comparisons between active interventions presented in *Table 8* were almost entirely obtained through indirect evidence only. All effect estimates had wide intervals including the null, and some effects were very imprecisely estimated. There was inconclusive evidence of effect modification based on comorbidities (see *Figure 85*) and smoking level (see *Figure 86*).

Incorporating non-randomised evidence

A total of 10 non-randomised studies reported at least one major adverse cardiovascular event. The treatments examined in these studies, alongside the arm sizes and events per arm, are listed in *Table 9*. Furthermore, the network plots resulting from combining randomised and non-randomised evidence for this outcome are displayed in *Appendix 7*, *Figure 82* (treatment level) and *Figure 21* (class level). The disparity between sizes of the nodes for different treatments and classes stems from the very large numbers of smokers enrolled in some non-randomised studies (see *Table 9*).

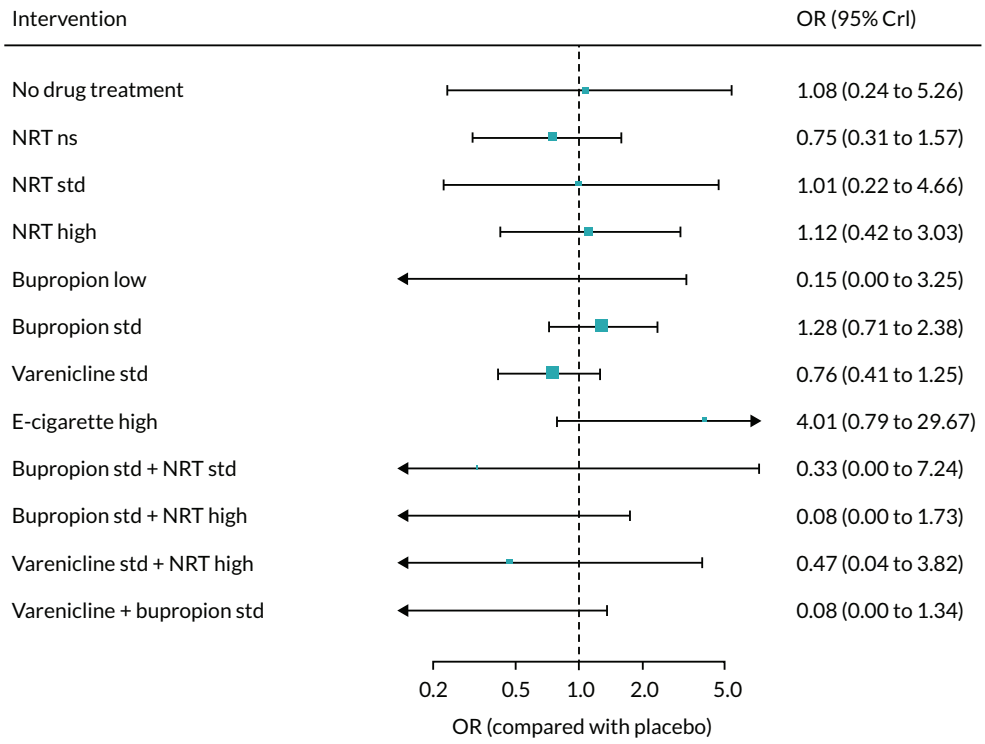

FIGURE 20 Forest plot with results of the fixed-class NMA model for MACEs. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 7 Results for MACEs: comparisons with placebo

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	–	1.08 (0.24 to 5.26)	1.08 (0.24 to 5.26)
NRT not specified	0.82 (0.30 to 2.03)	0.61 (0.15 to 2.52)	0.75 (0.31 to 1.57)
NRT standard	1.28 (0.21 to 8.67)	0.57 (0.03 to 9.47)	1.01 (0.22 to 4.66)
NRT high	0.44 (0.11 to 1.75)	2.98 (0.71 to 12.5)	1.12 (0.42 to 3.03)
Bupropion low	0.15 (0.00 to 3.25)	–	0.15 (0.00 to 3.25)
Bupropion standard	1.31 (0.68 to 2.48)	0.95 (0.08 to 11.0)	1.28 (0.71 to 2.36)
Varenicline standard	0.76 (0.41 to 1.25)	–	0.76 (0.41 to 1.25)
E-cigarette high	2.61 (0.44 to 28.22)	26.8 (0.39 to 1860)	4.01 (0.79 to 29.7)
Bupropion standard plus NRT standard	0.33 (0.00 to 7.24)	–	0.33 (0.00 to 7.24)
Bupropion standard plus NRT high	–	0.08 (0.00 to 1.73)	0.08 (0.00 to 1.73)
Varenicline standard plus NRT high	–	0.47 (0.04 to 3.82)	0.47 (0.04 to 3.82)
Varenicline standard plus bupropion standard	0.08 (0.00 to 1.34)	–	0.08 (0.00 to 1.34)

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TABLE 8 Results for MACEs: pairwise comparisons of interventions

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	–	1.26 (0.26 to 6.15)	1.26 (0.26 to 6.15)
Varenicline standard vs. NRT standard	0.99 (0.03 to 49.3)	0.68 (0.12 to 3.84)	0.73 (0.15 to 3.39)
E-cigarette high vs. NRT standard	–	4.35 (0.42 to 43.1)	4.35 (0.42 to 43.1)
Bupropion standard plus NRT standard vs. NRT standard	–	0.33 (0.00 to 9.83)	0.33 (0.00 to 9.83)
Varenicline standard plus bupropion standard vs. NRT standard	–	0.07 (0.00 to 1.96)	0.07 (0.00 to 1.96)
Varenicline standard vs. bupropion standard	–	0.58 (0.27 to 1.19)	0.58 (0.27 to 1.19)
E-cigarette high vs. bupropion standard	–	3.17 (0.57 to 25.3)	3.17 (0.57 to 25.3)
Bupropion standard plus NRT standard vs. bupropion standard	–	0.26 (0.00 to 5.50)	0.26 (0.00 to 5.50)
Varenicline standard plus bupropion standard vs. bupropion standard	–	0.06 (0.00 to 1.14)	0.06 (0.00 to 1.14)
E-cigarette high vs. varenicline standard	–	5.51 (1.05 to 40.1)	5.51 (1.05 to 40.1)
Bupropion standard plus NRT standard vs. varenicline standard	–	0.44 (0.00 to 10.4)	0.44 (0.00 to 10.4)
Varenicline standard plus bupropion standard vs. varenicline standard	–	0.11 (0.00 to 1.88)	0.11 (0.00 to 1.88)
Bupropion standard plus NRT standard vs. e-cigarette high	–	0.07 (0.00 to 2.97)	0.07 (0.00 to 2.97)
Varenicline standard plus bupropion standard vs. e-cigarette high	–	0.02 (0.00 to 0.55)	0.02 (0.00 to 0.55)
Varenicline standard plus bupropion standard vs. bupropion standard plus NRT standard	–	0.20 (0.00 to 567)	0.20 (0.00 to 567)

TABLE 9 Non-randomised studies reporting major cardiovascular AEs

Study (first author and year)	Treatment	Arm size	Number of events
Manzoli 2015[632]	Dual smoking	319	2
Manzoli 2015[632]	E-cigarette standard	343	4
Manzoli 2015[632]	No drug treatment	693	2
Davies 2015[609]	Varenicline not specified	41,742	531
Davies 2015[609]	NRT choice not specified	84,976	160
Ferketich 2013[615]	NRT combination high	110	1
Ferketich 2013[615]	Varenicline standard	118	0
Kotz 2017[629]	Bupropion not specified	350	155
Kotz 2017[629]	Varenicline not specified	3574	3
Kotz 2017[629]	NRT not specified	10,426	34

continued

TABLE 9 Non-randomised studies reporting major cardiovascular AEs (*continued*)

Study (first author and year)	Treatment	Arm size	Number of events
Kotz 2015[57]	Bupropion not specified	6557	2148
Kotz 2015[57]	Varenicline not specified	51,450	52
Kotz 2015[57]	NRT not specified	106,759	594
Woolf 2012[651]	NRT choice not specified	184	8
Woolf 2012[651]	No drug treatment	479	23
Svanström 2012[648]	Varenicline not specified	17,926	16
Svanström 2012[648]	Bupropion not specified	17,926	21
Graham 2014[618]	Bupropion standard	14,133	216
Graham 2014[618]	Varenicline not specified	74,824	44
Panos 2010[637]	No drug treatment	113	3
Panos 2010[637]	NRT patch (24 hours) not specified	114	6
Deniz 2016[611]	Bupropion not specified	47	1
Deniz 2016[611]	Varenicline not specified	94	0

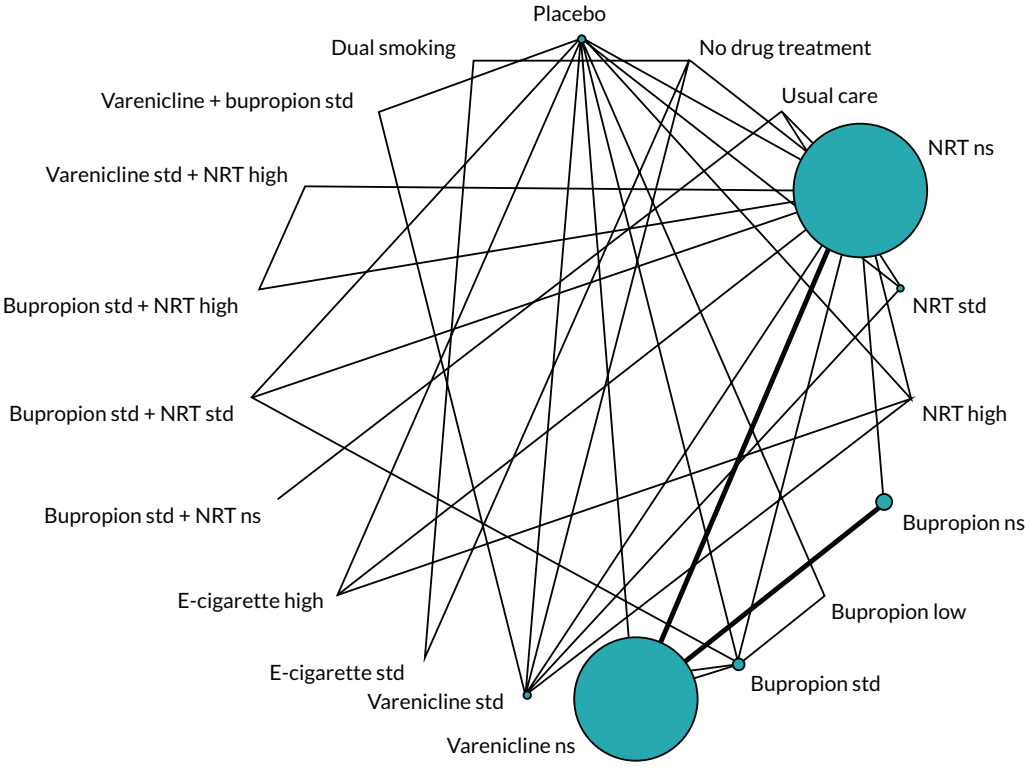

FIGURE 21 Network plot for major adverse cardiovascular events (including randomised and non-randomised studies) at class level. Ns, not specified; std, standard.

The combination of both types of evidence enabled the inclusion of 54 studies in the NMA, as the incorporation of 10 non-randomised studies also made it possible to include some randomised trials that had been excluded from the main analyses owing to small numbers causing convergence problems. The results of this combined analysis, based on a fixed-class random-effects model, are presented in *Figure 22* and suggest that, even with the additional studies, substantial uncertainty remains about the relative safety of the different treatment classes for this outcome.

Major adverse neuropsychiatric events

Randomised evidence only

Major adverse neuropsychiatric events were reported in 75 studies (42,088 patients), with 73 studies (41,483 patients) including at least one relevant comparison. The structure of this network is presented at the treatment (see *Figure 87*) and the class (*Figure 23*) levels, which show that placebo (main comparator), NRT not specified, bupropion standard, and varenicline standard were the best represented interventions. One study comparing bupropion standard plus NRT inhalator not specified (1/267 patients with event) with usual care (1/271 patients with event) was disconnected from the treatment network and, hence, we excluded it from the model comparisons (see *Table 53*), although we were able to include it in the analyses reported in this section. Moreover, we excluded two studies from all analyses owing to small numbers causing convergence problems. One of these excluded studies compared NRT nasal spray standard (1/506 patients with event) with placebo (0/255 patients with event), while the other one compared e-cigarette high (2/440 patients with event) with NRT choice not specified (0/448 patients with event).

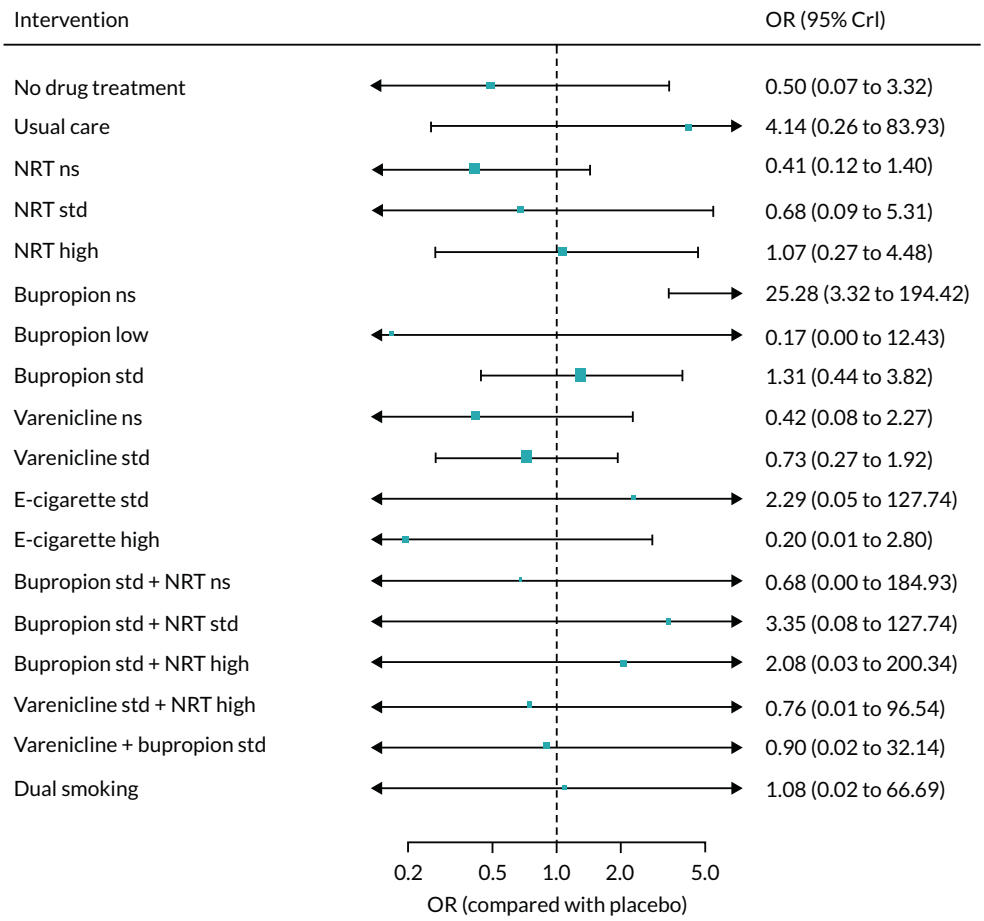

FIGURE 22 Forest plot with results for major adverse cardiovascular events (combining randomised and non-randomised evidence). Ns, not specified; std, standard.

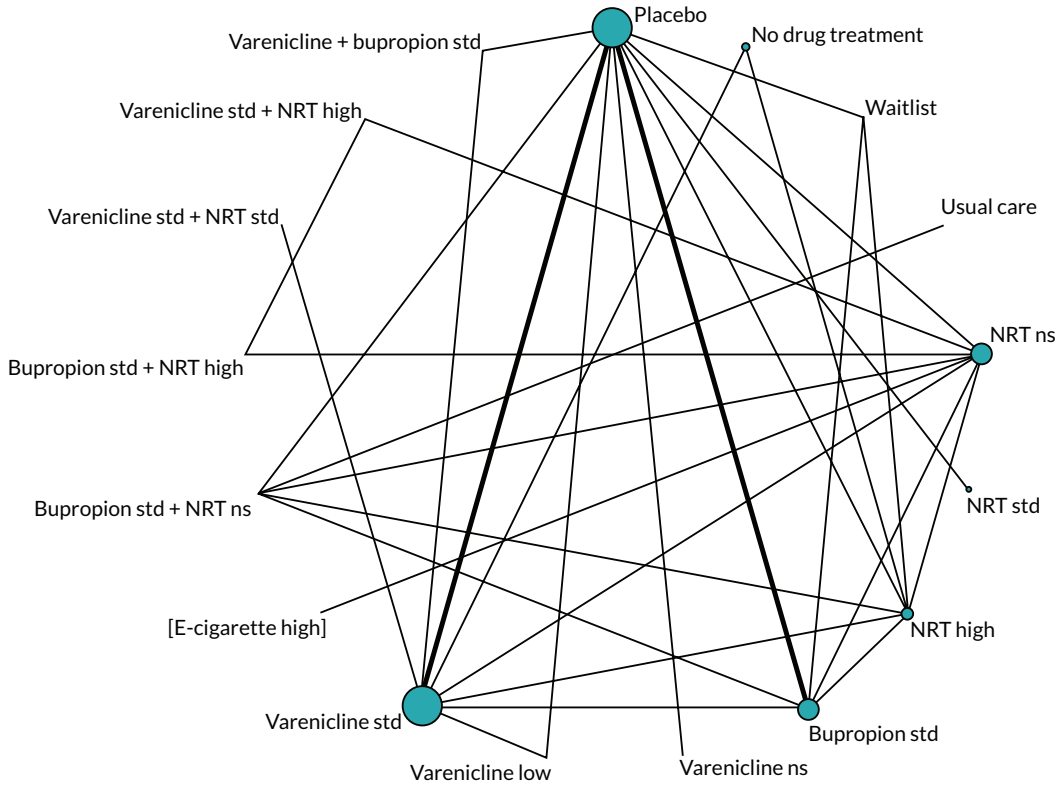

FIGURE 23 Network plot for major adverse neuropsychiatric events at class level. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

The NMA for this outcome was based on 71 studies. The results with placebo as a comparator are presented in *Figure 24* and show wide intervals around the effect estimates owing to small numbers. There was weak evidence that patients randomised to no drug treatment (OR 0.27, 95% CrI 0.05 to 1.05) and strong evidence that those randomised to waitlist (OR 0.03, 95% CrI 0.00 to 0.44) were less likely to report MANEs than those allocated to placebo. Regarding active treatments, there was evidence that patients who received NRT not specified (OR 0.60, 95% CrI 0.36 to 0.89), bupropion standard (OR 0.67, 95% CrI 0.47 to 0.91), bupropion standard plus NRT high (OR 0.21, 95% CrI 0.03 to 0.92) were less likely to report MANEs than those treated with placebo. There was weak evidence for patients randomised to varenicline standard plus bupropion standard (OR 0.15, 95% CrI 0.01 to 1.12) compared with placebo.

Table 10 presents the NMA results with placebo as comparator alongside effect estimates from direct and/or indirect evidence where available. Most comparisons were informed by direct or indirect evidence only, and, where back-calculation of indirect evidence was possible, this led to very imprecise and uninformative estimates.

There was no statistical evidence of inconsistency based on model fit statistics (see *Appendix 7*, *Table 53* and *Figures 89* and *90*). Pairwise comparisons between active interventions are displayed in *Table 11*. Although most effect estimates were imprecisely estimated owing to small numbers, there was evidence of increased odds of MANEs for smokers randomised to varenicline standard compared with those allocated to bupropion standard (OR 1.43, 95% CrI 1.02 to 2.09). There was inconclusive evidence of effect modification based on psychiatric comorbidities (see *Figure 91*).

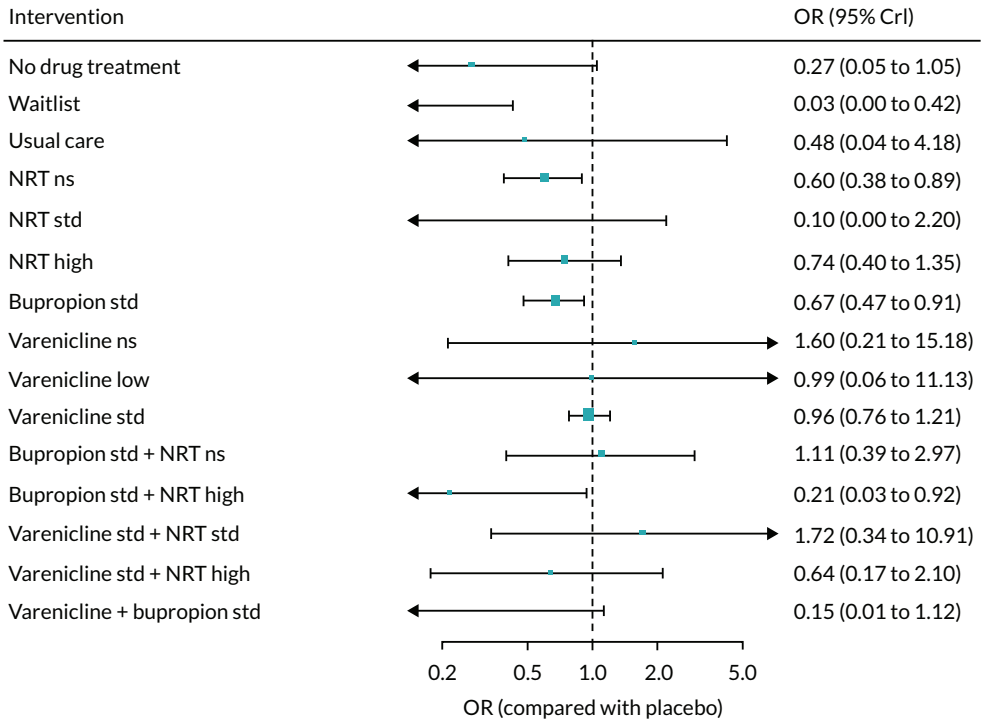

FIGURE 24 Forest plot with results of the fixed-class NMA model for major adverse neuropsychiatric events. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 10 Results for major adverse neuropsychiatric events: comparisons with placebo

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	–	0.27 (0.05 to 1.05)	0.27 (0.05 to 1.05)
Waitlist	0.03 (0.00 to 0.42)	–	0.03 (0.00 to 0.42)
Usual care	–	0.48 (0.04 to 4.18)	0.48 (0.04 to 4.18)
NRT not specified	0.73 (0.49 to 1.09)	5.16 (1.43 to 18.7)	0.60 (0.38 to 0.89)
NRT standard	0.12 (0.00 to 1.93)	0.04 (0.00 to 5506)	0.10 (0.00 to 2.20)
NRT high	0.73 (0.38 to 1.38)	0.80 (0.14 to 4.70)	0.74 (0.40 to 1.35)
Bupropion standard	0.62 (0.44 to 0.82)	0.47 (0.25 to 0.87)	0.67 (0.47 to 0.91)
Varenicline not specified	1.60 (0.21 to 15.2)	–	1.60 (0.21 to 15.2)
Varenicline low	0.99 (0.06 to 11.1)	–	0.99 (0.06 to 11.1)
Varenicline standard	0.96 (0.76 to 1.21)	–	0.96 (0.76 to 1.21)
Bupropion standard plus NRT not specified	2.39 (0.17 to 22.7)	0.94 (0.31 to 2.83)	1.11 (0.39 to 2.97)
Bupropion standard plus NRT high	–	0.21 (0.03 to 0.92)	0.21 (0.03 to 0.92)
Varenicline standard plus NRT standard	–	1.72 (0.34 to 10.9)	1.72 (0.34 to 10.9)
Varenicline standard plus NRT high	–	0.64 (0.17 to 2.10)	0.64 (0.17 to 2.10)
Varenicline standard plus bupropion standard	0.06 (0.00 to 1.05)	0.23 (0.01 to 5.97)	0.15 (0.01 to 1.12)

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TABLE 11 Results for major adverse neuropsychiatric events: pairwise comparisons of interventions

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	–	6.55 (0.29 to 3523)	6.55 (0.29 to 3523)
Varenicline standard vs. NRT standard	–	9.43 (0.43 to 4989)	9.43 (0.43 to 4989)
Varenicline standard plus NRT standard vs. NRT standard	–	18.52 (0.49 to 10,312)	18.52 (0.49 to 10,312)
Varenicline standard plus bupropion standard vs. NRT standard	–	1.45 (0.02 to 950)	1.45 (0.02 to 950)
Varenicline standard vs. bupropion standard	–	1.43 (1.02 to 2.09)	1.43 (1.02 to 2.09)
Varenicline standard plus NRT standard vs. bupropion standard	–	2.58 (0.49 to 16.6)	2.58 (0.49 to 16.6)
Varenicline standard plus bupropion standard vs. bupropion standard	–	0.22 (0.01 to 1.73)	0.22 (0.01 to 1.73)
Varenicline standard plus NRT standard vs. varenicline standard	1.80 (0.35 to 11.2)	–	1.80 (0.35 to 11.2)
Varenicline standard plus bupropion standard vs. varenicline standard	0.22 (0.00 to 5.43)	0.12 (0.00 to 3.20)	0.15 (0.01 to 1.16)
Varenicline standard plus bupropion standard vs. varenicline standard plus NRT standard	–	0.08 (0.00 to 1.19)	0.08 (0.00 to 1.19)

Incorporating non-randomised evidence

A total of 16 non-randomised studies reported one or more major adverse neuropsychiatric events. The treatments compared in those studies, the arm sizes and the event counts are presented in *Table 12*, whereas the network plots combining both types of evidence at the treatment level and class level are displayed in *Appendix 7*, *Figure 88* and *Figure 25*, respectively.

TABLE 12 Non-randomised studies reporting major adverse neuropsychiatric events

Study (first author and year)	Treatment	Arm size	Number of events
Cunningham 2016[608]	Varenicline not specified	11,774	6
Cunningham 2016[608]	NRT patch (24 hours) not specified	23,548	12
Dhelaria 2012[612]	Varenicline not specified	171	2
Dhelaria 2012[612]	NRT not specified	200	0
Ferketich 2013[615]	NRT combination high	110	0
Ferketich 2013[615]	Varenicline standard	118	1
Kotz 2017[629]	NRT not specified	10,426	722
Kotz 2017[629]	Bupropion not specified	350	18
Kotz 2017[629]	Varenicline not specified	3574	176
Jiménez-Ruiz 2017[624]	NRT combination high	215	0
Jiménez-Ruiz 2017[624]	Varenicline standard	134	1
Hodgkin 2013[619]	NRT choice not specified	236	0

TABLE 12 Non-randomised studies reporting major adverse neuropsychiatric events (*continued*)

Study (first author and year)	Treatment	Arm size	Number of events
Hodgkin 2013[619]	Bupropion not specified plus NRT choice not specified	162	3
Hodgkin 2013[619]	Varenicline not specified plus NRT choice not specified	16	2
Jiménez Ruiz 2012[623]	NRT choice not specified	233	5
Jiménez Ruiz 2012[623]	Bupropion standard plus NRT choice not specified	45	1
Jiménez Ruiz 2012[623]	Varenicline standard plus NRT choice not specified	190	6
Kaduri 2015[625]	Varenicline not specified	98	10
Kaduri 2015[625]	NRT choice not specified	98	8
Kotz 2015[57]	NRT not specified	106,759	8814
Kotz 2015[57]	Bupropion not specified	6557	377
Kotz 2015[57]	Varenicline not specified	51,450	2514
Thomas 2013[53]	NRT not specified	81,545	874
Thomas 2013[53]	Bupropion not specified	6741	44
Thomas 2013[53]	Varenicline not specified	31,260	276
Gunnell 2009[54]	NRT choice not specified	63,265	1824
Gunnell 2009[54]	Bupropion not specified	6422	162
Gunnell 2009[54]	Varenicline not specified	10,973	297
Garcia-Portilla 2016[616]	NRT patch (24 hours) not specified	36	0
Garcia-Portilla 2016[616]	Varenicline standard	39	1
Koçak 2015[627]	Varenicline not specified	206	4
Koçak 2015[627]	Bupropion not specified	137	2
Koçak 2015[627]	NRT patch (24 hours) not specified	112	0
Stapleton 2008[646]	NRT choice not specified	204	2
Stapleton 2008[646]	Varenicline not specified	208	10
Pasternak 2013[638]	Varenicline not specified	59,790	4
Pasternak 2013[638]	Bupropion not specified	17,936	1
Shiltz 2012[645]	Bupropion standard plus NRT patch (24 hours) standard	121	18
Shiltz 2012[645]	Varenicline standard plus bupropion standard	204	12
Shiltz 2012[645]	Varenicline standard	164	19

We fitted a fixed-class random-effects NMA model combining randomised and non-randomised evidence for this outcome, which led to the inclusion of 89 studies in total. The results displayed in *Figure 26* suggest that bupropion standard (OR 0.68, 95% CrI 0.50 to 0.91), bupropion standard plus NRT high (OR 0.23, 95% CrI 0.04 to 0.93) and varenicline standard plus bupropion standard (OR 0.36, 95% CrI 0.15 to 0.89) are associated with lower odds of events than placebo. Some of the effect estimates were imprecisely estimated (e.g. e-cigarette high vs. placebo), and there was also one extreme result for varenicline not specified plus NRT not specified, stemming from a single small study in which 2 out of 16 smokers treated with this combination reported an event (see *Table 12*).

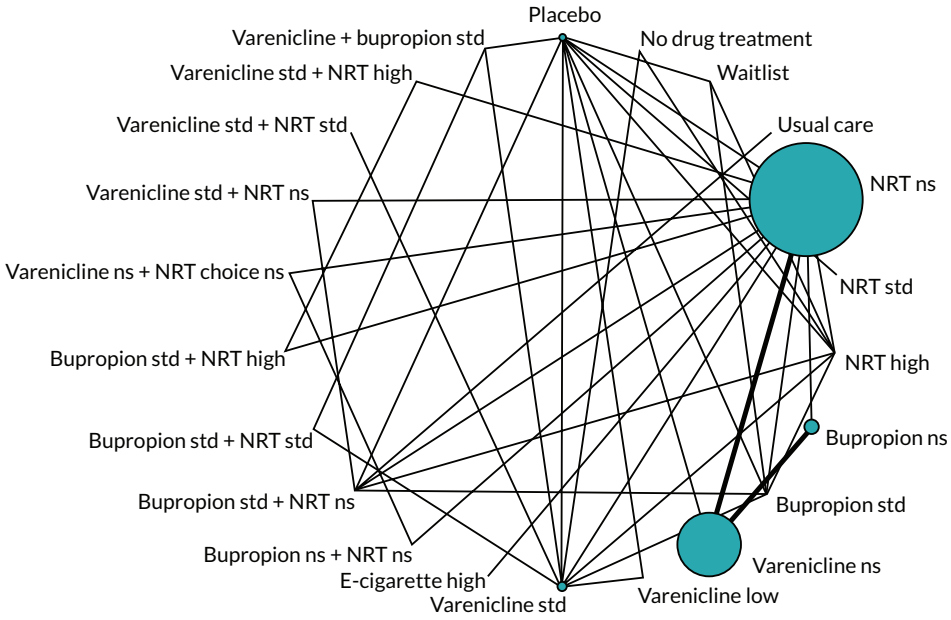

FIGURE 25 Network plot for major adverse neuropsychiatric events (combining randomised and non-randomised evidence) at class level. Ns, not specified; std, standard.

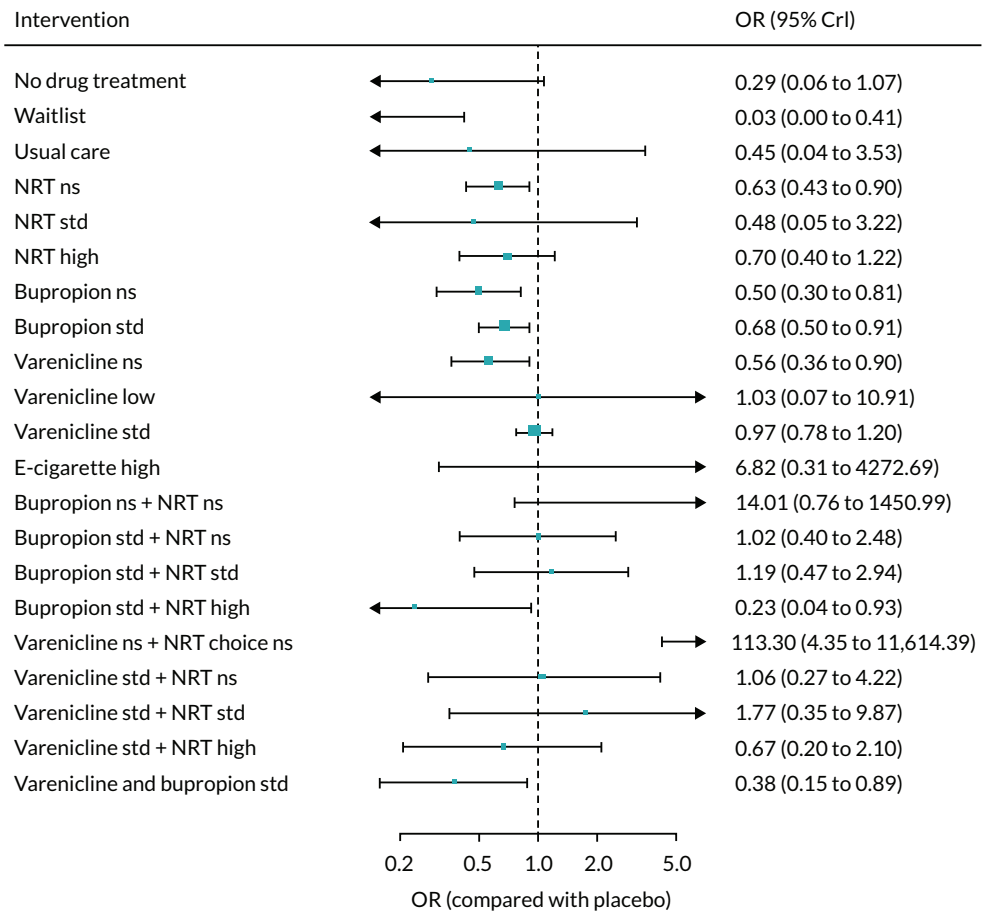

FIGURE 26 Forest plot of NMA results for major adverse neuropsychiatric events (combining randomised and non-randomised evidence). Ns, not specified; std, standard.

Ranking of interventions

Table 13 presents ranks for a selection of classes according to the primary safety outcome, SAEs. Placebo yielded the largest probability of being ranked as the best intervention for reducing the odds of SAEs (0.33) and also showed the lowest mean rank (1.97). Varenicline standard plus NRT standard showed the next largest probability to be ranked best (0.31), but the mean rank for this intervention (4.41) suggests substantial uncertainty about its ranking. On the other hand, the highest mean ranks were obtained by e-cigarette low (6.97), varenicline standard plus bupropion standard (5.94), and e-cigarette high (5.73), suggesting that these interventions were least likely to be ranked highly for reducing the occurrence of SAEs.

Figure 27 is a rank-o-gram displaying the ranking of eight selected intervention classes across the three safety outcomes examined in our NMA models. Placebo was most likely to be ranked best or second best out of eight interventions for SAEs, with lower rankings for MACEs (4/7) and MANEs (5/7). NRT standard was also most likely to be ranked among the best two interventions to reduce the odds of SAEs, with uncertain rankings for the other adverse outcomes. However, these findings may not be robust because of the uncertainty associated with SAE estimates. The rankings for MACEs suggest that bupropion standard plus NRT standard, and varenicline standard plus bupropion standard might be the safest interventions, although we note that these rankings are based on rather imprecise effect estimates (see *Figure 20*). The latter statement also applies to MANEs (see *Figure 24*).

Tertiary and other outcomes

We now present the results for tertiary and other outcomes. The results of NMAs for nausea, headache, dry mouth and skin rash are presented using RCTs identified in the original search. Tables for all other AEs of interest are presented in *Report Supplementary Material 8* for events reported in RCTs and in *Report Supplementary Material 9* for events reported in non-randomised studies.

Nausea

The data set for nausea comprised 168 studies, with a total of 398 arms and 72,875 patients. *Appendix 8*, *Figure 92*, shows the structure of this network at the treatment level. The graph shows a large number of interventions that were mostly connected and had placebo as the main comparator. One study comparing varenicline standard plus NRT gum standard (17/245 patients with event) with varenicline low plus NRT gum standard (13/240 patients with event) was disconnected from the network and, therefore, was excluded from the analyses. Furthermore, to avoid convergence problems, we excluded one study comparing bupropion low (9/169 patients with event) with no

TABLE 13 Mean ranking of interventions for SAEs

Intervention	Pr(best)	Mean rank
Placebo	0.33	1.97
NRT standard	0.17	3.4
Bupropion standard	0	4.5
Varenicline standard	0.06	3.08
E-cigarette low	0.07	6.97
E-cigarette high	0.04	5.73
Varenicline standard plus NRT standard	0.31	4.41
Varenicline standard plus bupropion standard	0.03	5.94

Pr, probability.

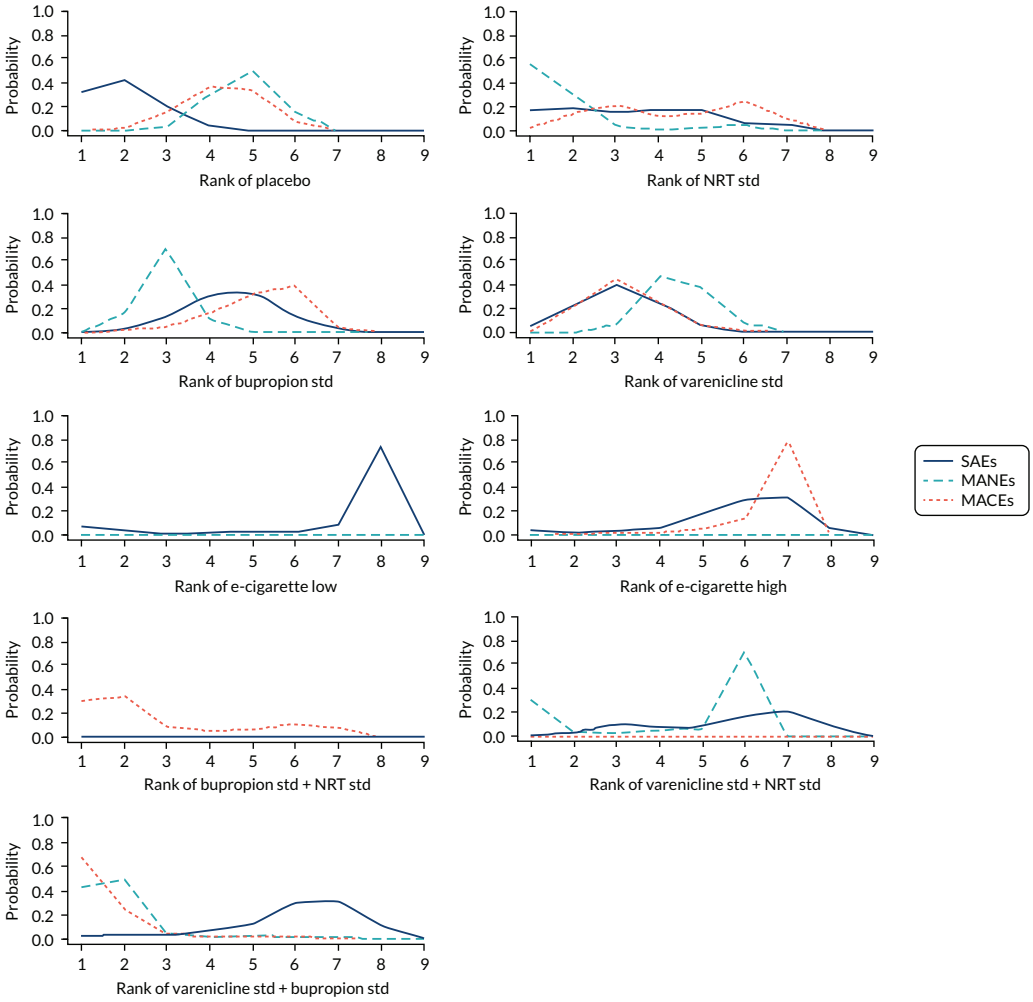

FIGURE 27 Rank-o-gram of interventions across safety outcomes. Std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

treatment (0/36 patients with event) and another study comparing e-cigarette high plus NRT patch (24 hours) not specified (2/20 patients with event) with NRT not specified (0/20 patients with event). Last, to avoid computational problems, we excluded the varenicline standard arm (24 events in 16 patients) from a three-arm trial that also examined no treatment (0 events in 16 patients) and NRT combined not specified (11 events in 16 patients).

The NMA results are presented in *Appendix 8*, *Figure 93* (standard NMA results are presented in *Appendix 8*, *Figure 94*). There was evidence that patients randomised to no treatment were less likely to report nausea than those receiving placebo (OR 0.18, 95% CrI 0.08 to 0.39). Conversely, those allocated to bupropion standard (OR 1.62, 95% CrI 1.30 to 2.05), varenicline standard (OR 3.86, 95% CrI 3.25 to 4.62), varenicline high (OR 19.11, 95% CrI 5.75 to 64.07), varenicline standard plus NRT standard (OR 5.21, 95% CrI 2.32 to 11.7), varenicline plus bupropion standard (OR 2.92, 95% CrI 1.49 to 5.64), and NRT high (OR 1.82, 95% CrI 1.01 to 3.46) were more likely to report nausea than those in the placebo group. There was weak evidence for those allocated to varenicline low (OR 1.43, 95% CrI 0.95 to 2.18), bupropion standard plus NRT high (OR 1.95, 95% CrI 0.95 to 4.01), varenicline standard plus NRT high (OR 2.01, 95% CrI 0.91 to 4.44), NRT standard (OR 1.45, 95% CrI 0.92 to 2.29) and e-cigarette (OR 2.48 95% CrI 0.61 to 12.18).

Headache

The data set for headache comprised 152 studies, with a total of 356 arms and 67,956 patients. *Appendix 8*, *Figure 95* presents the structure of the network for headache. Two studies were disconnected from the network and, therefore, were excluded from the analyses: one study comparing varenicline standard plus NRT gum standard (5/245 patients with event) with varenicline low plus NRT gum standard (2/240 patients with event), and another study comparing bupropion standard plus NRT Inhalator not specified (34/267 patients with event) with usual care (13/271 patients with event). Furthermore, we excluded three studies owing to small numbers causing convergence problems: one study comparing e-cigarette high plus NRT patch (24 hours) not specified (1/20 patients with event) with NRT not specified (0/20 patients with event), one study comparing NRT inhalator standard (1/145 patients with event) with placebo (0/141 patients with event), and another study comparing NRT patch (24 hours) standard (1/40 patients with event) with placebo (0/40 patients with event).

The NMA results for this outcome are presented in *Appendix 8*, *Figure 96* (standard NMA results are presented in *Appendix 8*, *Figure 97*). There was evidence that patients randomised to no treatment reported headache less frequently than those receiving placebo (OR 0.26, 95% CrI 0.13 to 0.48), Furthermore, there was inconclusive evidence of any differences between patients randomised to any of the experimental drugs and those in the placebo group.

Dry mouth

The data set for dry mouth comprised 88 studies, with a total of 216 arms and 40,721 patients. *Appendix 8*, *Figure 98* shows the structure of this network, which is smaller than the ones presented before for other tertiary outcomes. One study comparing bupropion standard plus NRT inhalator not specified (14/267 patients with event) with usual care (0/272 patients with event) was disconnected from the main network and, therefore, was excluded from the analyses. Moreover, to avoid convergence problems, we also excluded one study comparing e-cigarette low (8/306 patients with event) with no treatment (0/102 patients with event). Last, to avoid computational problems we excluded the varenicline standard arm (36 events in 16 patients) from a three-arm trial that also examined no treatment (0 events in 16 patients) and NRT combined not specified (5 events in 16 patients).

The NMA results for dry mouth are displayed in *Appendix 8*, *Figure 99* (standard NMA results are presented in *Appendix 8*, *Figure 100*). We found strong evidence that smokers allocated to the no treatment group (OR 0.05, 95% CrI 0.00 to 0.36) and weak evidence that those allocated to waitlist (OR 0.23, 95% CrI 0.03 to 1.12) were less likely to report dry mouth problems than those receiving placebo. Conversely, there was evidence that smokers randomised to bupropion standard (OR 1.92, 95% CrI 1.58 to 2.34), bupropion standard plus NRT high (OR 1.99, 95% CrI 1.20 to 3.42), and varenicline plus bupropion standard (OR 2.44, 95% CrI 1.28 to 4.66) were more prone to dry mouth than those receiving placebo. There was weak evidence that smokers randomised to bupropion low were more likely to experience dry mouth than those randomised to placebo (OR 1.65, 95% CrI 0.90 to 3.03).

Skin rash

The data set for skin rash comprised 43 studies, with a total of 103 arms and 16,147 patients. *Appendix 8*, *Figure 101* shows that this outcome was reported less often than the previous outcomes. To avoid convergence problems, we excluded one study comparing NRT gum high (2/54 patients with event) with NRT gum standard (0/162 patients with event) and another study comparing e-cigarette low (6/306 patients with event) with no treatment (0/102 patients with event).

The NMA results for this outcome are presented in *Appendix 8*, *Figure 102* (standard NMA results are presented in *Appendix 8*, *Figure 103*). We found evidence that patients receiving no drug treatment were less likely to suffer from skin rash than those allocated to placebo (OR 0.03, 95% CrI 0.00 to 0.65). Conversely, patients randomised to bupropion standard were more likely to report skin rash problems than those in the placebo group (OR 2.23, 95% CrI 1.06 to 4.76).

Chapter 7 Results: cost-effectiveness

Table 14 shows the primary results of the probabilistic analysis. The expected (average) total discounted costs and QALYs for all interventions are reported, which represent the estimated average costs and benefits (allowing for length and quality of life) per smoker, having accounted for uncertainty in the inputs to the economic model. This analysis includes disutilities and costs related to depression and self-harm. Interventions are ordered by increasing expected total cost, with NRT low having the lowest expected total cost and varenicline standard plus NRT standard having the highest expected total cost. E-cigarette low has the highest expected QALYs, followed by varenicline standard plus bupropion standard, and varenicline standard plus NRT standard. NRT low has the lowest expected QALYs.

We prefer interventions with lower costs and higher QALYs. Any intervention that has a higher expected cost and lower expected QALYs than another intervention is said to be dominated. As can be seen in *Table 14*, all treatments apart from NRT low are dominated by e-cigarette low, which is more effective, in terms of increased utility, and less expensive than the other interventions. If the funder is not willing to pay £56 per QALY, then NRT low is estimated to be most cost-effective. If the funder is willing to pay ≥ £56 per QALY, then e-cigarette low is estimated to be most cost-effective.

If the payer is willing to pay up to £20,000 per QALY, e-cigarette low has the highest expected net benefit (£7085), followed by varenicline standard plus bupropion standard (£6756), and varenicline standard plus NRT standard (£6591).

We present the uncertainty surrounding the cost-effectiveness of the various interventions using a CEAC (*Figure 28*), which plots the probability that each intervention is the most cost-effective at a given willingness-to-pay threshold. Only interventions with a probability of being the optimal treatment of > 10% at any willingness-to-pay value are plotted.

TABLE 14 Expected total costs, expected total utilities, ICERs and expected net benefit at a £20,000 willingness-to-pay threshold

Treatment	Total costs (£)	Total QALYs	ICER (£)	ENB (£)
NRT low	10,259	10.934		0
E-cigarette low	10,279	11.290	56	7085
Bupropion low	10,283	11.038	Dominated	2056
NRT standard	10,292	11.119	Dominated	3663
Bupropion standard	10,304	11.033	Dominated	1937
NRT high	10,309	11.092	Dominated	3092
E-cigarette high	10,319	11.189	Dominated	5036
Bupropion standard plus NRT high	10,346	11.128	Dominated	3786
Varenicline standard	10,413	11.127	Dominated	3697
Varenicline standard plus bupropion standard	10,437	11.281	Dominated	6756
Varenicline low	10,440	10.959	Dominated	308
Varenicline standard plus NRT high	10,467	11.117	Dominated	3440
Varenicline low plus NRT standard	10,587	11.273	Dominated	6454
Varenicline standard plus NRT standard	10,587	11.280	Dominated	6591

ENB, expected net benefit.

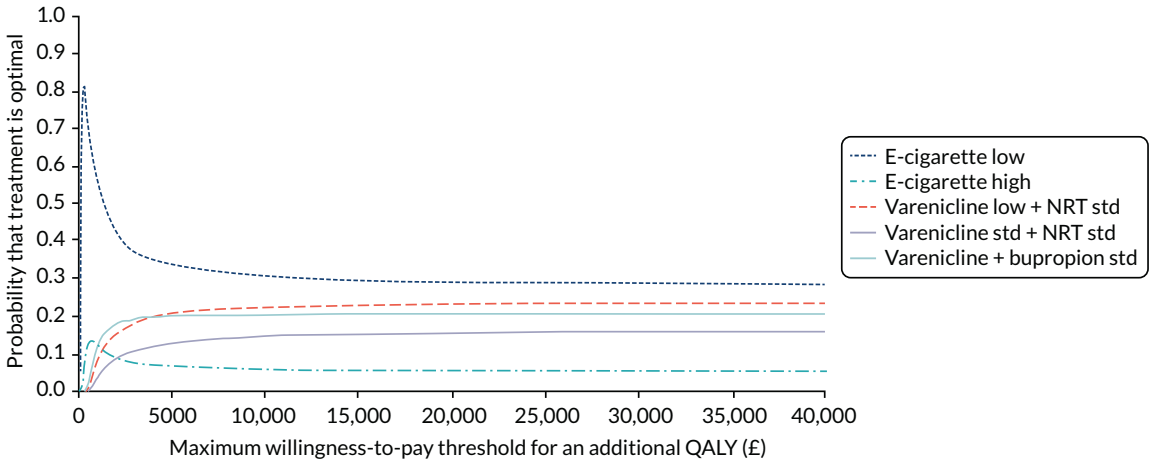

FIGURE 28 Cost-effectiveness acceptability curve. Probability that treatment is optimal plotted against different willingness-to-pay per unit increase in utility (ceiling ratio). Based on 5000 Monte Carlo simulations. Std, standard.

Figure 28 shows that, at any willingness-to-pay value, e-cigarette low has the highest probability of being cost-effective, followed by varenicline low plus NRT standard. At any threshold above £20,000, the probability of e-cigarette low being the most cost-effective intervention is never > 30%, indicating a high degree of uncertainty about the optimal intervention.

The rank-o-grams presented in *Figure 29* further demonstrate the uncertainty in the results. The lines are relatively flat for most interventions, showing that there is no strong probability that they will be the most or least cost-effective at a willingness-to-pay threshold of £20,000 per QALY. The exception is NRT low, which shows a clear probability that it is among the least cost-effective interventions if the payer is willing to pay £20,000 per QALY. There is a similar trend for bupropion low, bupropion standard and varenicline low, which have higher probabilities of being among the worst interventions than being among the best. The reverse trend is seen for e-cigarette low, e-cigarette high, varenicline low plus NRT standard, varenicline standard plus NRT standard and varenicline plus bupropion standard.

Value-of-information analysis

Table 15 shows the results of the value-of-information analyses for the base-case model at a willingness to-pay per QALY threshold of £20,000. EVPI estimates the most the funder would be prepared to pay to eliminate uncertainty in the model input parameters. EVPI is helpful for understanding whether or not future research may potentially be of value. The per-quitter EVPI is £3645 and the population EVPI, representing all of the smokers attempting to quit in England, is £999M over a 1-year time horizon and £4994M over a 5-year time horizon. These values are substantial and suggest that future research studies to reduce parameter uncertainty in the model would be valuable, as the decision is clearly sensitive to uncertainty in the model inputs.

Expected value of partial perfect information (EVPPI) estimates the most that the funder would be prepared to pay to eliminate uncertainty in a specific subset of model input parameters. Comparing EVPPI for different parameters allows us to identify the subsets of model inputs to which the decision is most sensitive. This can indicate where future research efforts may be invested most effectively. There is a high value per smoker in reducing uncertainty in all of the abstinence probabilities (£3053) but less of a value in reducing uncertainty in all of the AEs probabilities (£1654). EVPPI is marginally higher for cost parameters (£1216) than for utility parameters (£947).

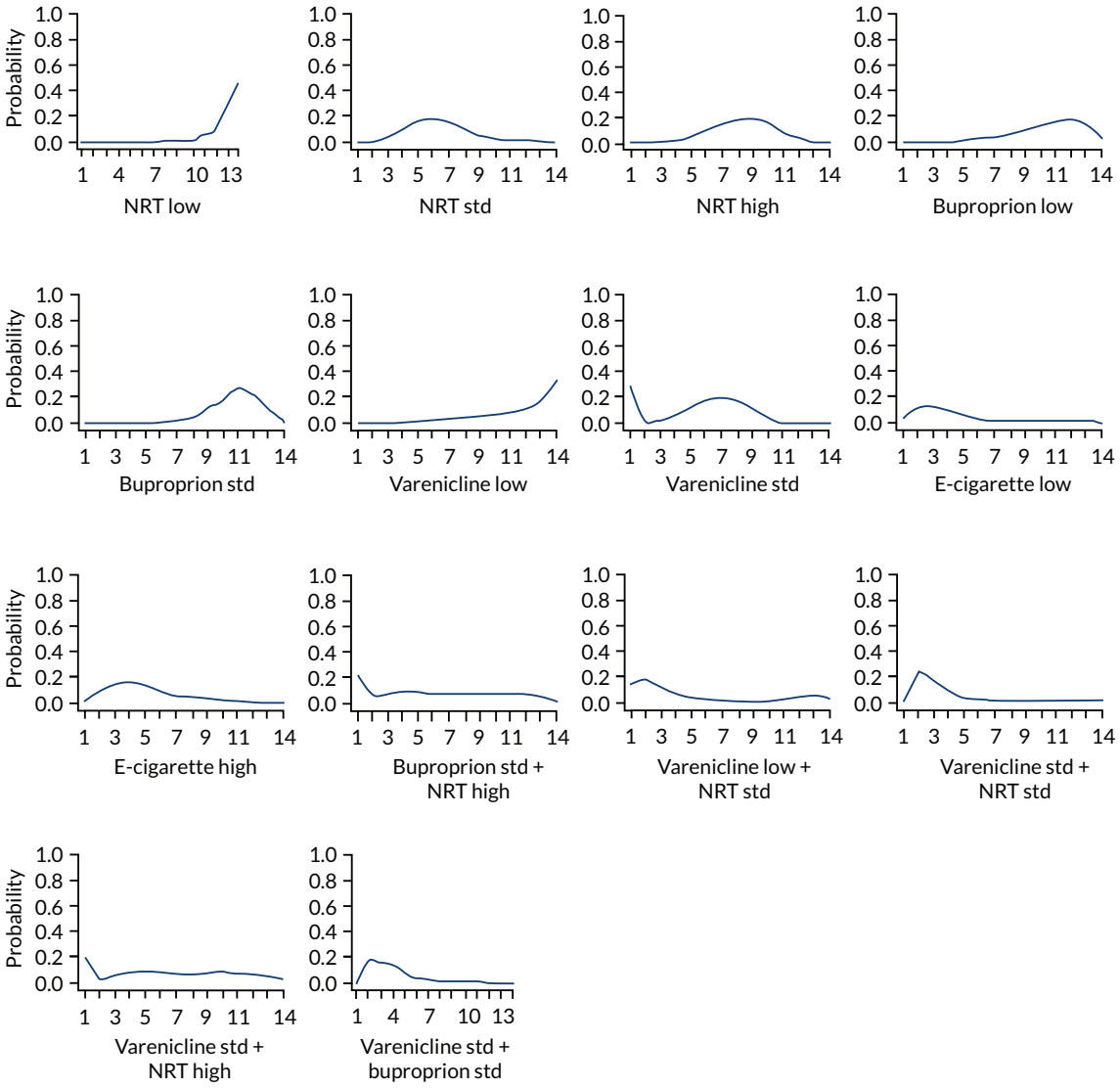

FIGURE 29 Rank-o-grams showing the probability that each intervention is ranked first, second, etc. based on net benefit at a willingness-to-pay threshold of £20,000 per QALY. Std, standard.

We explored the potential value of a new trial comparing the two interventions with the highest expected net benefit, e-cigarette low and varenicline standard plus bupropion standard, which would provide information on the effectiveness of the interventions, costs and utilities. This gives a per-quitter EVPPI of £2342 and a population EVPPI of £642M over a 1-year time horizon and £3869M over a 5-year time horizon. Restricting to the collection of intervention effects only would reduce this value marginally to £1676, suggesting that a large trial, conducted well and adequately powered, may be a cost-effective area of future research, but that it may be most important to collect information on probabilities of abstinence and AEs. In particular, a trial comparing e-cigarettes with an active comparator such as varenicline standard plus NRT standard or NRT standard is likely to be a cost-effective investment.

TABLE 15 Expected value of perfect information and EVPPI for various subsets of model parameters, at a £20,000 willingness-to-pay value per QALY

Model parameter subsets	EVPPI per smoker attempting to quit (£)	1-year population EVPPI (£M to 1 decimal place)	5-year population EVPPI (£M to 1 decimal place)
All (EVPI)	3645	998.8	4994.0
All costs	1216	333.3	1666.7
All utilities	947	259.4	1297.1
All costs and utilities	1415	387.9	1939.2
All abstinence probabilities	3053	836.7	4182.4
All depression and self-harm probabilities	1654	453.1	2265.7
E-cigarette low vs. varenicline standard plus NRT standard (probabilities, costs and utilities)	2342	641.8	3209.0
E-cigarette low vs. varenicline standard plus NRT standard (probabilities only)	1676	459.3	2296.7

Sensitivity analysis with results based on abstinence alone

Table 16 shows the primary results of the sensitivity analysis when the impact of depression and self-harm is removed from the model. In this case, bupropion low has the lowest expected total cost. Varenicline standard plus NRT standard, again, has the highest expected total cost. Varenicline standard plus NRT standard has the highest expected QALYs, followed by varenicline low plus NRT standard. NRT low has the lowest expected QALYs.

TABLE 16 Expected total costs, expected total utilities, ICERs and expected net benefit at a £20,000 willingness-to-pay threshold, based on abstinence alone

Treatment	Total costs (£)	Total QALYs	ICER (£)	ENB (£)
Bupropion low	10,219	11.135		3159
NRT low	10,231	10.977	Dominated	0
NRT high	10,238	11.198	Extendedly dominated	4400
Bupropion standard	10,240	11.130	Dominated	3041
E-cigarette high	10,248	11.295	Extendedly dominated	6335
E-cigarette low	10,250	11.332	159	7072
NRT standard	10,264	11.162	Dominated	3657
Bupropion standard plus NRT high	10,319	11.168	Dominated	3721
Varenicline low	10,320	11.138	Dominated	3120
Varenicline standard	10,327	11.254	Dominated	5434
Varenicline standard plus NRT high	10,402	11.214	Dominated	4556
Varenicline plus bupropion standard	10,415	11.314	Dominated	6558
Varenicline low plus NRT standard	10,446	11.476	Extendedly dominated	9759
Varenicline standard plus NRT standard	10,447	11.483	1302	9895

ENB, expected net benefit.

An intervention is said to be 'extendedly dominated' if a mix of two interventions can provide the same QALYs at a lower cost. As can be seen in *Table 16*, all treatments apart from NRT high, e-cigarette high, e-cigarette low, varenicline low plus NRT standard and varenicline standard plus NRT standard are dominated by bupropion low, which is more effective, in terms of increased utility, and less expensive than the other interventions.

The interventions on the efficiency frontier (i.e. those that are not dominated or extendedly dominated) are NRT low, e-cigarette low and varenicline standard plus NRT standard. If the payer is not willing to pay £159 per QALY, then bupropion low is estimated to be most cost-effective. If the payer is willing to pay between £159 and £1302 per QALY, then e-cigarette low is estimated to be most cost-effective, and if the willingness to pay per QALY is above £1302, then varenicline standard plus NRT standard is estimated to be most cost-effective.

At a willingness-to-pay threshold of £20,000, varenicline standard plus NRT standard has the highest expected net benefit (£9895), followed by varenicline low plus NRT standard (£9759).

We present the uncertainty surrounding the cost-effectiveness of the various interventions, using a CEAC (*Figure 30*). Only those interventions with a probability of being the optimal treatment of more than 10% at any willingness-to-pay value are plotted. *Figure 30* shows that, at any willingness-to-pay value, varenicline low plus NRT standard has the highest probability of being cost-effective, followed by varenicline standard plus NRT standard. At any threshold above £20,000, the probability of any intervention being the most cost-effective intervention is never > 40%, again, indicating a degree of uncertainty in the optimal intervention.

The rank-o-grams are presented in *Figure 31*.

Sensitivity analysis with only UK-licensed interventions included

Table 17 shows the primary results of the sensitivity analysis including only interventions that are licensed in the UK (NRT low, standard and high, bupropion low and standard, and varenicline low and standard). In this case, NRT low has the lowest expected total cost and varenicline low has the highest expected total cost. Varenicline standard has the highest expected QALYs, followed by NRT standard. NRT low has the lowest expected QALYs.

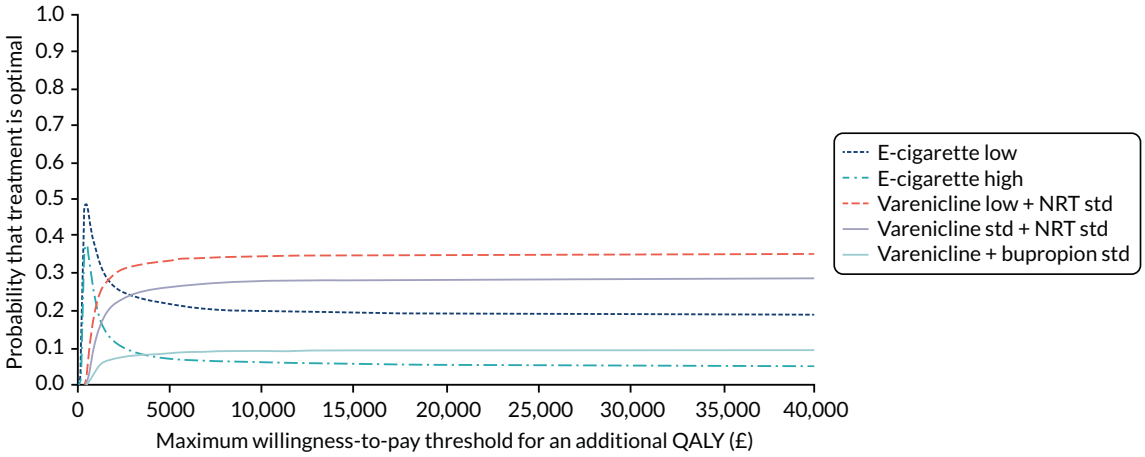

FIGURE 30 Cost-effectiveness acceptability curve. Probability that treatment is optimal plotted against different willingness-to-pay per unit increase in utility (ceiling ratio). Based on 5000 Monte Carlo simulations. Sensitivity analysis based on abstinence alone. Std, standard.

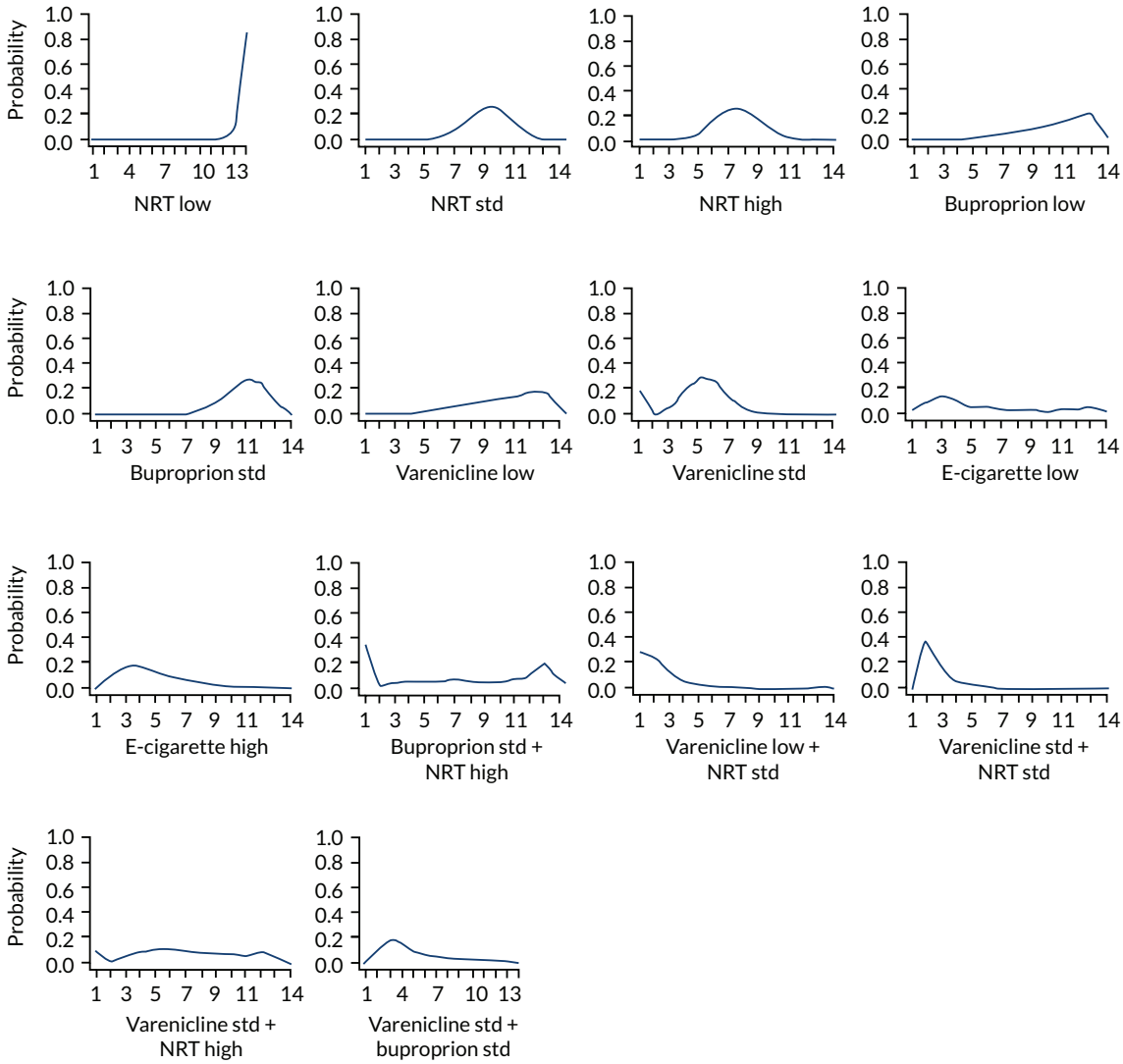

FIGURE 31 Rank-o-grams showing the probability that each intervention is ranked first, second, etc. based on net benefit at a willingness-to-pay threshold of £20,000 per QALY. Sensitivity analysis based on abstinence alone. Std, standard.

TABLE 17 Expected total costs, expected total utilities, ICERs and expected net benefit at a £20,000 willingness-to-pay threshold, based on licensed interventions only

Treatment	Total costs (£)	Total QALYs	ICER (£)	ENB (£)
NRT low	10,259	10.934		0
Bupropion low	10,283	11.038	Extendedly dominated	2056
NRT standard	10,292	11.119	32	3663
Bupropion standard	10,304	11.033	Dominated	1937
NRT high	10,309	11.092	Dominated	3092
Varenicline standard	10,413	11.127	15,665	3697
Varenicline low	10,440	10.959	Dominated	308

ENB, expected net benefit.

As can be seen in *Table 17*, all treatments apart from NRT low, bupropion low and NRT standard are dominated by varenicline standard, which is more effective, in terms of increased utility, and less expensive than the other interventions. Bupropion low is extendedly dominated by NRT standard.

The interventions on the efficiency frontier are NRT low, NRT standard and varenicline standard. If the payer is not willing to pay £32 per QALY, then NRT low is estimated to be most cost-effective. At a willingness to pay per QALY above £32, but below £15,665, NRT standard is estimated to be most cost-effective. At a willingness to pay per QALY above £15,665, varenicline standard is estimated to be most cost-effective.

At a willingness-to-pay threshold of £20,000, varenicline standard has the highest expected net benefit (£3697), followed by NRT standard (£3663).

We present the uncertainty surrounding the cost-effectiveness of the various interventions using a CEAC (*Figure 32*). Only those interventions with a probability of being the optimal treatment of more than 10% at any willingness-to-pay value are plotted. *Figure 32* shows that, at any willingness-to-pay value above £5000, NRT standard has the highest probability of being cost-effective, followed by varenicline standard.

The rank-o-grams are presented in *Figure 33*. These show that, at a willingness-to-pay value of £20,000, NRT standard and varenicline standard have the highest probabilities of being the most cost-effective treatment. NRT low and varenicline low have very low probabilities of being the most cost-effective.

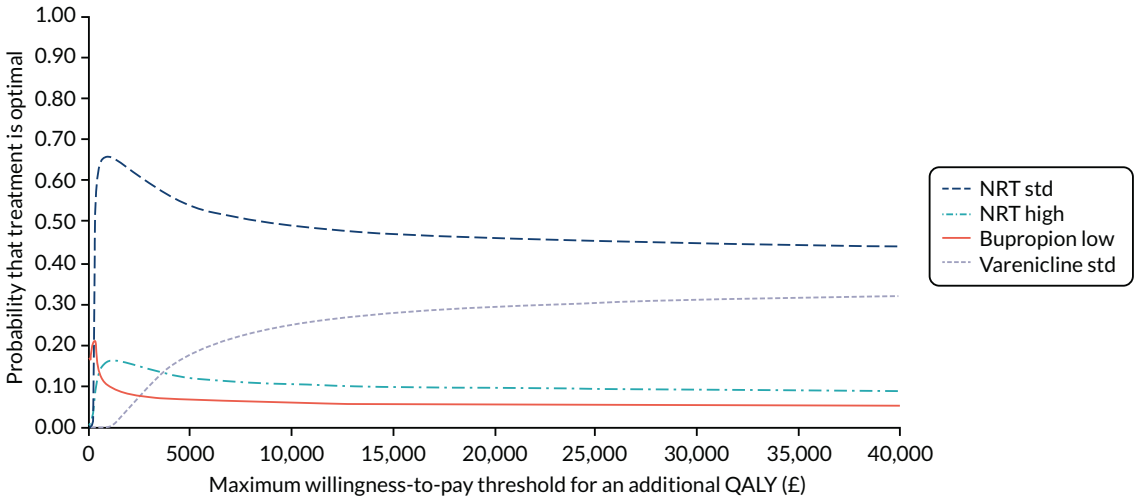

FIGURE 32 Probability treatment is optimal plotted against different willingness-to-pay per unit increase in utility (ceiling ratio). Based on 5000 Monte Carlo simulations. Sensitivity analysis based on licensed interventions. Std, standard.

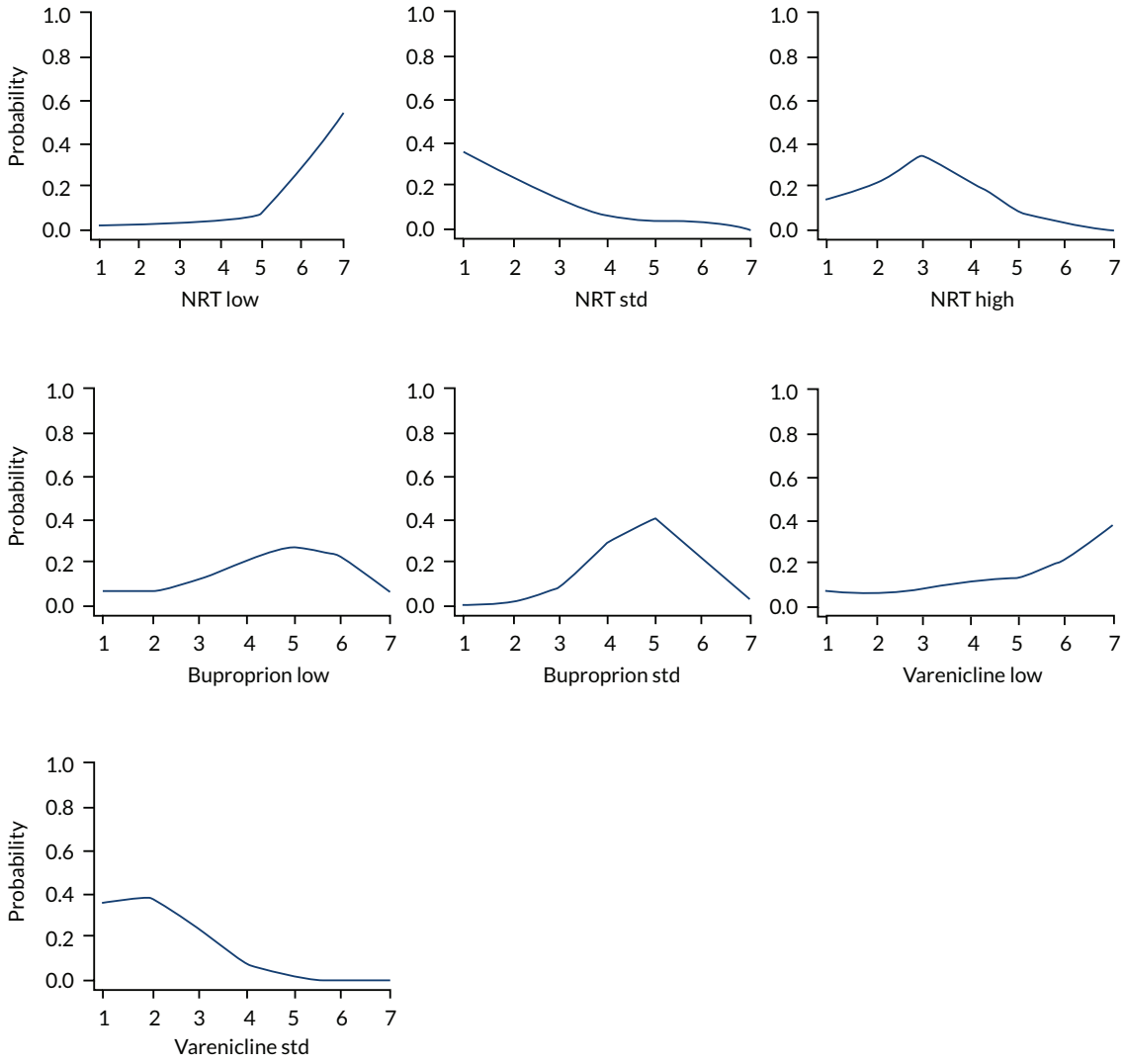

FIGURE 33 Rank-o-grams showing the probability that each intervention is ranked first, second, etc. based on net benefit at a willingness-to-pay threshold of £20,000 per QALY. Sensitivity analysis based on licensed interventions only. Std, standard.

Chapter 8 Discussion and conclusions

Key findings

The main findings for the clinical effectiveness, safety and cost-effectiveness analyses are summarised in the following sections.

Key findings of the effectiveness network meta-analysis

We performed a systematic review and NMA to investigate the effectiveness of UK-licensed smoking cessation medicines and e-cigarettes for smoking cessation. We included 363 trials that reported on one or more effectiveness outcomes, involving 201,045 participants, that took place internationally across a range of settings. We found that only 13% of trials were rated as being at low risk of bias, with 40% rated as being at high risk of bias.

We found evidence that most monotherapies and combination treatments were more effective than placebo at helping participants achieve sustained abstinence. The three most effective treatments compared with placebo were varenicline standard plus NRT standard (OR 5.75, 95% CrI 2.27 to 14.88), varenicline low plus NRT standard (OR 5.70, 95% CrI 1.57 to 21.12) and e-cigarette low (OR 3.22, 95% CrI 0.97 to 12.55). Smokers randomised to varenicline standard plus NRT standard were more likely to achieve sustained abstinence than participants receiving NRT standard or bupropion standard. We also found that varenicline standard resulted in higher odds of sustained abstinence than NRT standard or bupropion standard, and weak evidence that e-cigarette high may increase the odds compared with bupropion standard. As combination therapies are currently not licensed in the UK, when limiting our findings to interventions that are licensed in the UK (NRT low, standard and high, bupropion low and standard, and varenicline low and standard), varenicline standard (OR 2.83, 95% CrI 2.34 to 3.39), NRT high (OR 2.32, 95% CrI 1.88 to 2.86), and NRT standard (OR 2.01, 95% CrI 1.68 to 2.41) were the three most effective treatments compared with placebo at helping participants achieve sustained abstinence.

The results of our threshold analyses confirmed that varenicline standard plus NRT standard's first-place ranking (offering the highest estimated odds of sustained abstinence) was relatively robust. However, uncertainty or potential biases in a small number of studies could lead to one of varenicline standard plus bupropion standard, e-cigarette low, or e-cigarette high being ranked first. Finally, we found evidence of effect modification, whereby interventions delivered with counselling were associated with a higher proportion of smokers achieving sustained abstinence than those same interventions delivered without counselling, and we also found a higher OR of sustained abstinence among participants who had higher average dependence scores.

The results for the secondary effectiveness outcomes were largely similar to those for sustained abstinence. Although reported in fewer studies and for fewer interventions, we found evidence that smokers treated with NRT high, bupropion standard, varenicline standard and varenicline standard plus bupropion standard were more likely to achieve prolonged abstinence than those using placebo. Bioverified prolonged abstinence data at $\geq$ 6 months for e-cigarette or varenicline standard plus NRT standard were not available. When considering pairwise comparisons between interventions, there was inconclusive evidence that bupropion standard, varenicline standard and varenicline standard plus bupropion standard differed from each other in the odds of resulting in prolonged abstinence.

For our 'any abstinence' outcome, as for sustained abstinence, we found that most interventions were more effective than placebo at helping participants abstain from smoking, including e-cigarette at low and high doses. The three most effective treatments compared with placebo were bupropion low plus

NRT high, varenicline standard plus NRT standard and varenicline not specified. For 'any abstinence', our NMA indicated that smokers randomised to varenicline standard were more likely to achieve abstinence than those allocated to NRT standard or bupropion standard. We also found that varenicline standard plus NRT standard led to higher odds of abstinence than NRT standard, bupropion standard, and bupropion standard plus NRT standard, while varenicline standard plus bupropion standard led to higher odds of abstinence than bupropion standard alone.

Finally, there was evidence that a number of interventions were more effective than placebo at attaining 7-day PPA, including e-cigarette high. The three most effective treatments compared with placebo, were bupropion low plus NRT high, varenicline standard plus NRT standard and varenicline not specified. In terms of 7-day PPA, our NMA indicated that smokers allocated to varenicline standard achieved abstinence more often than those using NRT standard or bupropion standard. We also found that varenicline standard plus NRT standard led to higher odds of abstinence than NRT standard, bupropion standard or varenicline standard.

Ranking the interventions based on smokers attaining sustained abstinence, varenicline standard plus NRT standard had the highest probability of being ranked first, followed by e-cigarette low, varenicline standard plus bupropion standard, and e-cigarette high, with placebo in last place. Based on our rank-o-grams, ranking the interventions across primary and secondary effectiveness outcomes, varenicline standard plus NRT standard showed a high probability of being ranked as the best or second-best intervention for all outcomes, with the exception of prolonged abstinence, for which there were no data. Varenicline standard plus bupropion standard had the highest probability of being ranked as best for prolonged abstinence, but its rankings for other outcomes were less certain. Finally, varenicline standard showed high probabilities of being ranked second- to fourth-best across outcomes, while e-cigarette rankings were uncertain, and placebo was consistently ranked last.

Comparison with other studies

Our findings are largely comparable to those of previous NMAs.[25,123] We found evidence that nearly all identified doses of smoking cessation medicines increased the probability of sustained abstinence compared with placebo. An exception to this is bupropion plus NRT; a health technology assessment (HTA) report of smoking cessation interventions by the HIQA[123] found evidence that this treatment improved the likelihood of cessation (from the quit date or PPA) compared with placebo (control), whereas we saw this result for the 'any abstinence' and 7-day PPA outcomes only. Similar to our findings, previous NMAs also found evidence that varenicline increased the chance of cessation compared with bupropion and with NRT, while not finding evidence of a difference in likelihood of quitting between bupropion and NRT.[25,123] Findings were also consistent for varenicline plus NRT, which showed improved probability of quitting compared with bupropion and with NRT. However, although the HIQA HTA found evidence that varenicline plus bupropion was more effective than bupropion or NRT delivered as monotherapies, we did not.[123] Nonetheless, the results of the ranking of treatments for smoking cessation were similar across NMAs.[25,123]

Key findings of the safety network meta-analysis

A systematic review and NMA were performed to investigate the safety of UK-licensed smoking cessation medicines and electronic cigarettes. We included 355 trials that reported on one or more safety outcomes involving 159,101 participants, and 53 observational studies involving 8,783,403 participants that took place internationally across a range of settings. We found that only 16% of trials were rated as being at low risk of bias, while one-third (33%) were rated as being at high risk of bias. All observational studies were rated as being at high risk of bias owing to their non-randomised nature.

There was evidence that, compared with placebo, bupropion standard increased the odds of experiencing SAEs (OR 1.27, 95% CrI 1.04 to 1.58). The results of our threshold analyses indicated that the first- and last-place rankings were very sensitive to the level of uncertainty and risk of bias in the evidence. Unlike our effectiveness analyses, we found inconclusive evidence of effect modification on the likelihood of

experiencing a SAE. Placebo yielded the largest probability of being ranked the best intervention for reducing the odds of experiencing a SAE; however, the first-place ranking could change to NRT standard, varenicline standard plus NRT standard, e-cigarette high, e-cigarette low, or varenicline plus bupropion standard simply owing to sampling error. NRT standard was also the most likely to be ranked among the best two interventions for reducing the odds of SAEs. The last-place ranking is held by e-cigarette low, but this is very sensitive to the high level of uncertainty in the single study by Cravo *et al.*[525] Changes to the estimate could result in e-cigarette low being replaced by varenicline standard plus bupropion standard in last place or see e-cigarette low replace placebo in first place, both of which are plausible owing to sampling error. Therefore, the first- and last-place rankings for SAEs are not very robust, as they are sensitive to levels of uncertainty in the data and plausible biases in at-risk studies that could alter the rankings. Although only one observational study[632] reported one or more SAE, incorporating this study into our analyses resulted in the effect estimates changing substantially, suggesting that varencline standard and e-cigarette low might lead to lower odds of experiencing a SAE than placebo. This may be a result of the observational study adding a substantial number of events to a network of what was otherwise a rare outcome.

Regarding secondary outcomes, we could not find any differences between interventions for MACEs owing to the rarity of events reported across studies, resulting in effect estimates with very wide CIs. This did not change with the addition of 10 observational studies to our analyses; there is substantial uncertainty regarding the relative cardiovascular safety of the treatments. For MANEs, there was evidence that smokers receiving NRT not specified, bupropion standard, bupropion standard plus NRT high or varenicline standard plus bupropion standard were less likely to report MANEs than smokers treated with placebo. In pairwise comparisons between interventions, there was evidence of increased odds of MANEs among smokers randomised to varenicline standard compared with those using bupropion standard. Although 16 observational studies reported one or more MANEs, our analyses incorporating these studies produced similar results to that of the randomised evidence. We found that bupropion standard, bupropion standard plus NRT high and varenicline standard plus bupropion standard were associated with lower odds of experiencing a MANE than placebo. Whereas placebo and varenicline standard plus NRT standard yielded the largest probabilities of being ranked the best interventions to reduce the odds of SAEs, e-cigarette low, varenicline standard plus bupropion standard and e-cigarette high were the least likely to be ranked highly. Based on our rank-o-grams, ranking the interventions across primary and secondary safety outcomes, placebo and NRT standard were most likely to be ranked among the best interventions for reducing the odds of experiencing SAEs, but were ranked lower for MACEs and MANEs. Bupropion standard plus NRT standard, and varenicline standard plus bupropion standard may be the safest interventions in terms of MACEs and MANEs, but these rankings were based on imprecise effect estimates.

We conducted random-effects NMAs at the class level for a number of our tertiary and other safety outcomes based on data from studies identified from our initial searches ending in March 2017. Compared with smokers randomised to placebo, we found evidence of increased odds of experiencing nausea among smokers allocated to bupropion standard, varenicline standard, varenicline high, varenicline standard plus NRT standard, varencline standard plus bupropion standard, NRT not specified, NRT high and bupropion standard plus NRT not specified. However, we did not find any evidence of a difference between interventions in the odds of experiencing headache. We found evidence of increased odds of experiencing dry mouth among smokers using bupropion standard, bupropion standard plus NRT high, varenicline standard plus bupropion standard and bupropion standard plus NRT not specified compared with those allocated to placebo. Finally, we found that smokers randomised to bupropion standard had higher odds of experiencing skin rash than smokers allocated to placebo.

Comparison with other studies

The finding of our NMA of MACEs mirrors that of Mills *et al.*,[39] as we also did not find evidence that any smoking cessation increased the likelihood of experiencing a MACE compared with placebo or with

each other. As pairwise comparisons between active interventions were almost entirely based on indirect evidence only, and because MACEs were uncommon, it was very difficult to effectively compare treatments with each other. Other NMAs[25,123] only summarised safety data from previous reviews and did not analyse them; this study is the first, to our knowledge, to conduct a NMA of SAE, MANE and other AE data. Although the HIQA HTA[123] reported that its two included trials of e-cigarettes did not report SAEs linked to their use, we included the SAEs reported by Bullen *et al.*,[192] as we included all events whether or not study authors attributed them to the use of the medication. The authors of Cochrane's review of electronic cigarettes similarly chose to consider SAEs that were deemed related to e-cigarette use only, however, the occurrence of other AEs that we have presented in our NMA in outcome tables were reported in *Report Supplementary Materials 8* and *9*.[72]

Key findings of the cost-effectiveness analysis

This analysis has shown that, in the base case, e-cigarette low appears to be the most cost-effective intervention at any willingness to pay per QALY value above £56. However, these findings are uncertain, with no intervention having more than a 40% chance of being the most cost-effective intervention at a willingness to pay per QALY above £5000. When the impact of the safety outcomes of depression and self-harm are excluded, varenicline standard plus NRT standard and varenicline low plus NRT standard are the most cost-effective interventions. There is, again, considerable uncertainty about the optimal intervention. When the analysis is limited to interventions that are licensed in the UK, varenicline standard is the most cost-effective intervention at any willingness-to-pay value above £15,665, followed by NRT standard. Value-of-information analyses indicated that a trial comparing e-cigarettes with an active comparator such as varenicline standard and bupropion standard or NRT standard is likely to be a cost-effective investment.

Comparison with other studies

No previous cost-effectiveness analysis could be identified that compared a similar range of interventions, compared the standard licensed interventions with combination therapies and e-cigarettes, or incorporated safety outcomes. A recent systematic review of cost-effectiveness analyses[123] identified four studies[98,104,654,655] published in the last 10 years that compared varenicline, bupropion or NRT with each other or with standard of care. All but one of these studies[655] also used the BENESCO model, but did not adjust to account for safety outcomes. The studies consistently found varenicline to be the most cost-effective intervention. A report by Leaviss *et al.*[58] compared the cost-effectiveness of varenicline and cytisine in a UK setting, also using the BENESCO model. This study found cytisine to be the most cost-effective intervention; however, cytisine was beyond the scope of this review. Our results show that, although the varenicline combination treatments dominate the other interventions, among the treatments licenced in the UK, NRT standard is the most cost-effective.

One previous study[61] was identified that compared the cost-effectiveness of e-cigarettes with that of NRT in stop smoking services in England. Similar to our study, in which an ICER of £56 was calculated for e-cigarette low compared with NRT low, this previous study found an ICER of £65 per QALY gained by using e-cigarettes as a smoking cessation aid, in comparison with NRT. This suggests strong evidence of the cost-effectiveness of e-cigarettes compared with NRT; however, to our knowledge, our study is the first to assess the cost-effectiveness of e-cigarettes compared with all other interventions in the UK.

Strengths and limitations

Strengths and limitations of the effectiveness and safety network meta-analyses

Strengths

This is the first NMA of SAEs, MANEs and other AEs associated with smoking cessation medicines, and the second to analyse MACEs. Whereas a previous NMA suffered from insufficient data for AE

outcomes,[25] our decision to include RCTs of any duration and the inclusion of observational studies allowed us to utilise as many data as possible to create our networks (although this also brings some limitations; see *Limitations*). Most NMAs[25,123] failed to include RCTs of less than 6 months' duration for AEs, based on their inclusion criteria for analysing effectiveness outcomes. Given that AEs can occur within a short time after treatment has started, previous reviews would have excluded several of the studies that we included in our safety analyses. We also benefited from the publication of some large studies since the start of our study that made important contributions to our analyses, such as the EAGLES trial,[33] and several electronic cigarette studies, including a large trial by Hajek *et al.*[19] Therefore, these decisions allowed us to include and analyse data from more participants in more studies reporting AEs than any previous NMA of these licensed medicines.[25,39,123] A significant strength of this study is the inclusion of combined therapies of smoking cessation medicines, as most reviews have only included monotherapies and combination NRT. This proved to be a crucial decision, as our study has found combined therapies, notably varenicline standard plus NRT standard, to be among both the most effective and cost-effective treatments for smoking cessation. Although we only found evidence of effect modification for the inclusion of counselling with smoking cessation treatment, the size of our study allowed us to investigate the influence of several important covariates as potential effect modifiers for our primary outcomes. Additionally, this is the first NMA to compare medicines stratified by dosage. This allowed us to more specifically identify how dose affected a medicine's effectiveness and safety across outcomes, revealing differential effects by dose that would otherwise have been lost. This includes the investigation of data for each licensed form of NRT by dose in our full interaction models. We also reported effectiveness across multiple specific cessation outcomes rather than using the approach in past NMAs of authors using the most rigorous definition of abstinence available. Finally, this study was the first NMA of smoking cessation medicines to use threshold analysis.[91,92] This technique allowed us to visualise thresholds of how much the evidence could change before our recommendation based on the ranking of our treatments would change, and helps readers to understand the robustness of our treatment recommendations.

Limitations

Despite the large number of studies we were able to include in our review, there were still limitations in the data available. Primary and secondary safety outcomes included rare events, which limited the ability of analyses to draw firm conclusions. Pairwise comparisons between active interventions were almost exclusively informed by indirect evidence and were affected by the small number of events, resulting in imprecisely estimated effects and wide intervals, often including the null. Additionally, there were instances of extreme results based on the findings of a single or very few studies, which may be particularly problematic when attempting to draw conclusions about the safety of e-cigarettes (e.g. Cravo *et al.*[525]). For the SAE, MACE, and MANE outcomes, we conducted a NMA that incorporated both RCT and non-randomised evidence, as well as a NMA restricted to RCTs. Although including non-randomised evidence increases the precision of the estimates, this comes with a risk of introducing bias in the resulting estimates. Non-randomised evidence is vulnerable to bias by confounding, and there was no attempt to adjust for this (which would have required the availability of individual participant data). Identifying methods to combine RCT and non-randomised evidence while adjusting for bias using individual patient data is an area for further research.

Network meta-analysis (like any pairwise meta-analysis) makes the assumption that the included studies do not differ in the distribution of factors that might moderate the relative treatment effects (effect modifiers). This assumption can be assessed statistically by checking for evidence of heterogeneity (different effects across studies making the same comparison) and by checking for evidence of inconsistency (different effects from studies providing direct and indirect estimates). There was a moderate level of heterogeneity in all of our NMAs (as has also been found in previous meta-analyses and NMAs in this field). We explored a range of covariates to explain the heterogeneity in meta-regression analyses, and did not find any evidence of effect modification other than using counselling alongside pharmacological treatments. We made an assumption that the effect of counselling is additive when given together with a pharmacotherapy, which is a potential limitation of our findings.

It may be that there is a synergistic (or even antagonistic) effect of counselling when it is used together with pharmacotherapies. We explored this in a sensitivity analysis and found some evidence to support a synergistic effect. Future research to explore this potential synergistic effect of smoking cessation medicines being used together with counselling would be of value. There may be other important effect modifiers that we have not included, for example changes in practice over time. However, although absolute cessation rates are expected to change with time, this will be the case for all study arms, and we found no evidence that year of publication was an effect modifier. We did not find any statistical evidence of inconsistency for any of the outcomes. An inspection of direct and indirect estimates, where both can be calculated, shows that in general there is good overlap of the credible intervals for the direct and indirect estimates, although there are some differences in the point estimates. We conclude that, for each outcomes, there is evidence of effect modification that manifests as heterogeneity between estimates from studies on the same comparison, but no systematic differences between direct and indirect estimates (over and above the heterogeneity seen across the entire network of evidence).

Unlike previous NMAs, we opted to use only bioverified cessation data, as most studies in our review reported one or more bioverified outcomes. However, it is possible that more data would have been included in our networks had we adopted the approaches used in previous projects and included self-reported cessation data. Finally, despite extensive efforts, we were unable to obtain safety data for industry-funded trials from pharmaceutical companies. Although we hoped to include as many safety data as possible from these trials, our findings are limited to those events reported in publications. Finally, we were unable to include and analyse craving and withdrawal data, as these were rarely reported across included studies and the outcomes were assessed using a variety of measures and scales that made summarising or analysing these data impossible.

Strengths and limitations of the cost-effectiveness analysis

This analysis has improved on previous analyses of smoking cessation interventions, as it has taken into account not only effectiveness in terms of abstinence from smoking but also potential AEs of treatment (depression and self-harm). The effects of the interventions on each of these outcomes have been informed by NMAs that have shown that, although the combination of varenicline (low or standard) plus NRT standard gives the highest probability of continuous abstinence at 1 year, this is slightly offset by the association of this combination with a higher probability of depression and self-harm than the other interventions. This has led to e-cigarette low being slightly more cost-effective (the intervention with the highest expected net benefit) than varenicline (low or standard) plus NRT standard, although these results are very uncertain.

In terms of limitations, no comparative evidence on subsequent quit attempts in these treatments could be identified in the literature. The model, therefore, assumes that no further attempts to quit are made and that those who fail to quit remain smokers until death. In reality, people often make several quit attempts before they are successful and despite a failed attempt a person may have moved forward towards their future successful attempt. We would expect our qualitative findings to be robust to this as long as the likelihood of a successful subsequent quit attempt does not depend on the treatment used for the index quit attempt.

Another data limitation is the assumption that the risk ratios of developing or dying from smoking-related diseases in current smokers and former smokers compared with non-smokers (incidence and mortality) are equal to the risk ratios of having smoking-related diseases (prevalence). We considered this to be a reasonable assumption given that no alternative sources of information on the relative incidence or mortality from these diseases within the relevant age and sex categories could be identified. Longitudinal studies measuring these outcomes for the different smoking categories would be useful to test this assumption.

This 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. One issue is that this is not necessarily the same as the

distribution of smokers making a quit attempt. Another issue is that data availability meant that this cohort needed to be grouped into quite broad age categories (18–34, 35–64 and ≥ 65 years) that were assigned the same prevalence, incidence and probability of mortality from diseases. It is likely, therefore, that greater variation exists in these categories than is being accounted for. A study measuring patient characteristics of those seeking treatment to make a quit attempt would be useful to update the model to better reflect the population of interest.

As e-cigarettes are not medically licensed in the UK, it is difficult to estimate a prescribing cost if they were to be prescribed on the NHS. The best evidence we could find on this was from the HIQA HTA,[123] which costed a 12-week supply of e-cigarettes at €93.80. Current high-street/internet prices may be considerably lower than this. However, it is unclear whether the NHS would be able to access these lower prices if e-cigarettes were made available on the NHS. If a lower price could be accessed, this could only have the impact of increasing the cost-effectiveness of e-cigarettes compared with the other interventions.

In addition, as no data were available, assumptions had to made about the relative effectiveness of several interventions for the outcomes of depression and self-harm. It was assumed that (1) NRT low and e-cigarette low have the same effect as NRT standard, (2) e-cigarette high has the same effect as NRT high, (3) bupropion low has the same effect as bupropion standard, and (4) varenicline low plus NRT standard has the same effect as varenicline standard plus NRT standard. The assumption that NRT and e-cigarettes have the same impact on psychological outcomes is reasonable as the active ingredient is the same in both (nicotine). Although a higher dose of bupropion or varenicline may increase the probability of depression or self-harm, no evidence was available to inform this. A study comparing the impact of different doses of these interventions on psychological outcomes would be useful to inform the model.

We did not explicitly model treatment discontinuation, although it should be noted that the RCTs included in the NMA will have included outcomes for patients who did not adhere to treatment, and the treatment costs are likely to be incurred regardless of discontinuation. A final limitation was a lack of available data to explore the cost-effectiveness of these interventions in subgroups such as those with psychiatric illness, heavy smokers or smokers not willing to quit.

Conclusions

Implications for practice

Our findings suggest that combined therapies of smoking cessation medicines are among the most effective, safe and cost-effective treatment options for smokers. Although combination NRT is commonly prescribed, combined therapy of NRT delivered alongside varenicline at standard doses (currently unlicensed) was shown to be the most effective treatment for most cessation outcomes. Using combined therapies instead of monotherapy treatments may offer smokers a better chance of successfully quitting smoking over both short and long periods of time. We also found that interventions that included counselling were more effective at helping smokers to quit and should be considered when planning a cessation attempt. Although the use of bupropion standard may increase the odds of SAEs compared with placebo, we did not find strong evidence of any other negative associations between medicines and SAEs, MACEs or MANEs relative to placebo. Although electronic cigarettes showed promise as cessation tools, their safety profile remains uncertain and no existing model of the devices has been licensed as a medicine. This study has used the most up-to-date information to give an estimate of the most cost-effective intervention for smoking cessation in the UK today. This analysis has shown that, in the base case, e-cigarette low, varenicline standard plus NRT standard, and varenicline standard plus bupropion standard appear to be the most cost-effective interventions. When the impact of the safety outcomes of depression and self-harm is excluded, varenicline standard plus NRT standard and varenicline low plus NRT standard are the most cost-effective interventions. These results should be

taken with the caveat of substantial uncertainty, however, with no intervention having a probability of being the most cost-effective of > 30% at any willingness-to-pay per QALY threshold above £20,000.

Recommendations for research

Based on the findings of this study, we propose several recommendations.

First, given the relatively small number of studies rated as being at low risk of bias overall (including recent publications), we recommend that study authors ensure complete and accurate reporting of their study methodology. Most domains were predominantly rated as unclear risk of bias owing to a lack of detailed description of study procedures. Although some of these ambiguities were resolved following contact with corresponding authors, details pertinent to assessments of bias should be reported in the main body or supplemental material of publications. We also urge those designing future studies to think carefully about potential biases when designing their studies.

Second, there were also large discrepancies in the completeness of safety reporting. A significant number of trials did not report any safety data at all, while those that did varied substantially in their reporting. This included not providing definitions of what they considered to be a SAE, not providing details about SAEs, not reporting AEs by study arm, and a wide array of reported events with seemingly no consistency across studies (e.g. a study recording events of nausea or headache vs. another study recording events of dry mouth, headache and abnormal dreams). There may be scope for the creation of a core outcome set for safety outcomes for studies of smoking cessation medicines to ensure systematic recording and reporting of AEs, as this information is of importance to patients, practitioners and policy-makers.

Third, although we included non-randomised evidence in our safety analyses to increase the precision of our estimates, the use of non-randomised data may introduce bias. Further research should explore methods for combining randomised and non-randomised data to most effectively incorporate all of the available safety evidence.

Fourth, there have been few published trials or observational studies of electronic cigarettes with control groups. Although our findings suggest that e-cigarettes show promise for smoking cessation, the limited amount of evidence available results in uncertainty about their safety profile and how they compare with licensed medicines. Although e-cigarettes are regulated by *The Tobacco and Related Products Regulations 2016*,[656] no available e-cigarette devices are licensed as a smoking cessation medicine at present. Medicinal e-cigarettes would need to meet the standards for consumer e-cigarettes as well as any additional requirements needed to meet efficacy, safety and quality criteria under medicines regulation.[657] We recommend that researchers continue to investigate the use of e-cigarettes for smoking cessation, particularly with respect to long-term effectiveness and safety outcomes, preferably in studies with active interventions as comparators. Our value-of-information analysis suggested that a large adequately powered and well-conducted trial comparing e-cigarettes with an active comparator such as varenicline standard plus NRT standard or NRT standard is likely to be a cost-effective use of resources.

Finally, although it was not the focus of this report, we found in our NMA that combining counselling and pharmacological treatments increased cessation rates compared with pharmacological treatment alone. Further research to explore the clinical effectiveness and cost-effectiveness of combination pharmacological and psychological interventions that account for AEs are likely to be of value.

Chapter 9 Patient and public involvement

A lay summary of this project was reviewed by participants of the UK Centre for Tobacco and Alcohol Studies (UKCTAS) smokers' panel and was presented to members of the Elizabeth Blackwell Institute's Public Advisory Group. Originally set up in 2008, the UKCTAS smokers' panel consists of active smokers and recent quitters who meet two or three times per year in Nottingham. The panel meets regularly to discuss tobacco, tobacco policy, approaches to smoking cessation and new developments in tobacco harm reduction. Panel members also serve as lay advisers on research applications submitted from UKCTAS universities, which involves commenting on study information sheets, consent forms and data collection instruments (literature review protocols, data management plans and other key documents); commenting on press releases and communication plans; participating in bespoke meetings to develop or advise on new studies; and other forms of engagement as appropriate. The Elizabeth Blackwell Institute's Public Advisory Group comprises key stakeholders in public engagement and health and social care as well as representatives of patient and public involvement groups linked to research projects at the University of Bristol. The Public Advisory Group works with the Elizabeth Blackwell Institute to ensure excellent engagement across the research life cycle. The group meets a few times per year, and researchers across the University of Bristol are invited to share their research with the group and receive feedback. During the course of the project, we interviewed vapers from the UKCTAS smokers' panel for input on our outcomes and planned analyses. We also presented preliminary findings based on data from studies identified in our original searches to the Elizabeth Blackwell Institute's Patient Advisory Panel for feedback and suggestions for further analyses.

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Contributions of authors

Kyla H Thomas (https://orcid.org/0000-0001-5418-4034) (Consultant Senior Lecturer in Public Health Medicine) co-conceived the project, led the grant application, planned the data extraction and statistical analyses, led the project, contributed to analyses (screening and checking data extraction, assessment of risk of bias) and planning of statistical analyses, drafted sections of the report and finalised the report.

Michael N Dalili (https://orcid.org/0000-0002-6687-5374) (Senior Research Associate in Public Health) screened, extracted and checked data, assessed risk of bias, contributed to drafting the report, including preparation of tables and figures, and reviewed the final report.

José A López-López (https://orcid.org/0000-0002-9655-3616) (Research Fellow in Medical Statistics) undertook the statistical analyses of clinical effectiveness and safety and drafted relevant parts of the report.

Edna Keeney (https://orcid.org/0000-0002-4763-8891) (Senior Research Associate in Statistical and Health Economic Modelling) contributed to the cost-effectiveness analysis and drafting relevant chapters, and reviewed the final report.

David Phillippo (https://orcid.org/0000-0003-2672-7841) (Research Associate in Evidence Synthesis) carried out the threshold analyses and reviewed the final report.

Marcus R Munafò (https://orcid.org/0000-0002-4049-993X) (Professor of Biological Psychology) provided critical insight and reviewed the final report.

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Data-sharing statement

All study data will be available from the corresponding author on request, once papers reporting the study findings have been published. Corresponding author's contact details: Population Health Sciences, Bristol Medical School, University of Bristol.

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Appendix 1 MEDLINE search strategies

MEDLINE search strategy for randomised controlled trials

1. Smoking/ (134,671)
2. Tobacco Smoking/ (397)
3. Tobacco/ (29,151)
4. Nicotine/ (24,376)
5. Tobacco Products/ (3005)
6. Smoking Cessation/ (26,370)
7. "Tobacco Use Cessation"/ (1045)
8. "Tobacco Use Disorder"/ (10,555)
9. (smoking or smoker*).ti,ab,kf. (231,897)
10. (tobacco* or cigar* or cigarette* or nicotine).ti,ab,kf. (164,203)
11. or/1-10 (353,307)
12. Bupropion/ (2887)
13. Varenicline/ (1147)
14. Nicotinic Agonists/ (6990)
15. (NRT or nicotine replacement).ti,ab,kf. (3901)
16. bupropion.ti,ab,kf. (4038)
17. (amfebutamone or quomen or wellbutrin or zyban or zyntabac).ti,ab,kf. (201)
18. varenicline.ti,ab,kf. (1578)
19. (champix or tabex or chantix).ti,ab,kf. (125)
20. (nicotine adj2 (patch* or gum* or nasal spray* or lozenge* or tablet* or sublingual* or inhal* or replacement or chewing or polac* or transdermal* or product*)).ti,ab,kf. (5818)
21. (nicorette or niquitin or nicotinell).ti,ab,kf. (110)
22. (nicotinic adj3 agonist*).ti,ab,kf. (2237)
23. (benzazepine* adj2 derivative*).ti,ab,kf. (84)
24. nicotinic receptor partial agonist*.ti,ab,kf. (58)
25. or/12-24 (17,839)
26. Electronic Nicotine Delivery Systems/ (2174)
27. Vaping/ (237)
28. (electr* adj2 (cig* or nicotine or device*)).ti,ab,kf. (17,861)
29. (ecig* or e-cig*).ti,ab,kf. (2982)
30. (nicotine adj4 (electr* or ENDS or aerosol*)).ti,ab,kf. (1023)
31. (vape or vaper or vapers or vaping or vapor or vapour).ti,ab,kf. (42,208)
32. or/26-31 (60,589)
33. ((smoking or tobacco) adj5 (cessation or ceas* or quit* or stop* or giv* or prevent* or abstain* or abstin* or control*)).ti,kf. (18,876)
34. randomized controlled trial.pt. (475,058)
35. controlled clinical trial.pt. (92,883)
36. pragmatic clinical trial.pt. (951)
37. clinical trial.pt. (514,264)
38. clinical trial/ or clinical trial, phase i/ or clinical trial, phase ii/ or clinical trial, phase iii/ or clinical trial, phase iv/ or controlled clinical trial/ (575,942)
39. Random Allocation/ (97,344)
40. randomized controlled trial/ (475,058)
41. pragmatic clinical trial/ (951)
42. Double-Blind Method/ (149,187)
43. Single-Blind Method/ (26,163)
44. Placebos/ (34,201)

45. ((clin* or randomi?ed) adj5 trial*).ti,ab,kf. (586,919)
46. ((singl* or doubl* or trebl* or tripl*) adj5 (blind* or mask*)).ti,ab,kf. (163,772)
47. placebo*.ti,ab,kf. (202,178)
48. control groups/ (1604)
49. randomi?ation.ti,ab,kf. (32,653)
50. randomly.ab. (304,261)
51. (random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion or number* or place* or recruit* or subsitut* or treat*)).ab. (429,094)
52. drug therapy.fs. (2,077,773)
53. trial.ti,ab,kf. (534,702)
54. groups.ab. (1,874,309)
55. (control* adj3 (trial* or study or studies)).ab,ti. (470,250)
56. ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dummy*)).mp. (222,854)
57. (quasi adj (experimental or random$)).ti,ab. (15,129)
58. ((waitlist* or wait* list* or treatment as usual or TAU) adj3 (control or group)).ab. (5264)
59. or/34-58 (4,771,652)
60. 11 and (25 or 32) and 59 (6074)
61. (animals not (humans and animals)).sh. (4,506,319)
62. 60 not 61 (5269)
63. (2017* or 2018*).yr,dp,dt,ep,ez. (2,712,640)
64. 62 and 63 (740)
65. (2018* or 2019*).yr,dp,dt,ep,ez. (1,556,937)
66. 62 and 65 (438).

MEDLINE search strategy for non-randomised studies

1. Smoking/ (134,503)
2. Tobacco Smoking/ (424)
3. Tobacco/ (29,125)
4. Nicotine/ (24,327)
5. Tobacco Products/ (3020)
6. Smoking Cessation/ (26,263)
7. “Tobacco Use Cessation”/ (1039)
8. “Tobacco Use Disorder”/ (10,482)
9. (smoking or smoker*).ti,ab,kf. (231,830)
10. (tobacco* or cigar* or cigarette* or nicotine).ti,ab,kf. (164,354)
11. or/1-10 (353,421)
12. Bupropion/ (2875)
13. Varenicline/ (1143)
14. Nicotinic Agonists/ (6977)
15. (NRT or nicotine replacement).ti,ab,kf. (3893)
16. bupropion.ti,ab,kf. (4026)
17. (amfebutamone or quomen or wellbutrin or zyban or zyntabac).ti,ab,kf. (200)
18. varenicline.ti,ab,kf. (1574)
19. (champix or tabex or chantix).ti,ab,kf. (125)
20. (nicotine adj2 (patch* or gum* or nasal spray* or lozenge* or tablet* or sublingual* or inhal* or replacement or chewing or polac* or transdermal* or product*)).ti,ab,kf. (5809)
21. (nicorette or niquitin or nicotinell).ti,ab,kf. (110)
22. (nicotinic adj3 agonist*).ti,ab,kf. (2235)
23. (benzazepine* adj2 derivative*).ti,ab,kf. (84)
24. nicotinic receptor partial agonist*.ti,ab,kf. (58)
25. or/12-24 (17,812)

26. Electronic Nicotine Delivery Systems/ (2189)
27. Vaping/ (243)
28. (electr* adj2 (cig* or nicotine or device*)).ti,ab,kf. (17,929)
29. (ecig* or e-cig*).ti,ab,kf. (3005)
30. (nicotine adj4 (electr* or ENDS or aerosol*)).ti,ab,kf. (1026)
31. (vape or vaper or vapers or vaping or vapor or vapour).ti,ab,kf. (42,034)
32. or/26-31 (60,491)
33. ((smoking or tobacco) adj5 (cessation or ceas* or quit* or stop* or giv* or prevent* or abstain* or abstin* or control*)).ti,kf. (18,825)
34. epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/ (2,244,426)
35. ((epidemiologic or prospective or retrospective or cross-sectional or case control* or cohort or longitudinal or followup or follow-up) adj3 (study or studies)).ti,ab,kf. (1,011,257)
36. (cross-sectional or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti. (563,430)
37. cohort?.ti,ab,kf. (497,828)
38. (case control* or case series).ti,ab,kf. (179,847)
39. or/34-38 (2,928,405)
40. (dream* or nightmare? or aggression or aggressive* or anxiety or anxious or (angina or arrhythmia* or cardiac or cardiovascular or coronary or myocardi* or heart failure? or heart attack? or isch? emi*) or COPD or chronic obstructive pulmonary disease or death? or mortalit* or (depression or depressive) or dry mouth or fatigue or headache? or migraine? or hospitali* or (insomnia* or sleep disorder* or somnolence) or irritability or irritable or (nausea or vomiting) or palpitations or pruritus or seizure* or rash or (stroke or strokes or thrombo* or thrombus or emboli* or VTE or DVT or TIA or bleed* or h?emorrhag*) or suicid* or parasuicid* or selfharm* or self-harm* or selfinjur* or self-injur*).mp. (5,115,897)
41. exp Hypersensitivity/ (327,542)
42. Drug Interactions/ or exp "drug-related side effects and adverse reactions"/ (187,530)
43. exp Product Surveillance, Postmarketing/ (14,019)
44. adverse effects.fs. (1,622,477)
45. drug effects.fs. (2,835,326)
46. complications.fs. (1,875,364)
47. poisoning.fs. (64,263)
48. toxicity.fs. (399,562)
49. chemically induced.fs. (559,975)
50. (safe* or adverse or tolerability or toxicity or toxic or adrs or adr or tolerance or tolerat* or harm or harms or harmful or complication* or drug? interaction? or hypersensitiv* or hyper-sensitiv*).ti,kf. (650,849)
51. ((adverse adj2 (event? or react*)) or side effect* or treatment emergent or undesirable effect*).ti,ab,kf. (417,393)
52. ((discontinu* or withdr*) adj3 (study or treatment) adj3 due to).ti,ab,kf. (2430)
53. or/40-52 (9,947,953)
54. (11 and (25 or 32)) or 33 (31,504)
55. (2017* or 2018* or 2019*).yr,dp,dt,ep,ez. (2,836,508)
56. 39 and 53 and 54 and 55 (405).

Appendix 2 Inputs into the economic model

TABLE 18 Data informing demographic distribution of cohort

Model parameter	Source	Age and sex category					
		Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
General population (*n*)	ONS 2016[107]	7,459,224	12,446,202	5,359,995	7,288,586	12,759,446	6,454,090
Smoking prevalence (% of population)	ONS 2016[107]	22.48	18.75	8.80	17.85	15.06	7.80
Risk of all-cause mortality in the general population (annual probability of all-cause mortality) (%)	ONS 2016[107]	0.07	0.40	4.40	0.03	0.26	4.13

TABLE 19 Prevalence of disease in general UK population

Disease	Data source	*n*	Age and sex category (%)					
			Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	British Lung Foundation 2012[109]	12.6 million	0.0	1.0	7.0	0.0	1.0	7.0
Lung cancer	Maddams *et al.* 2009[111]	7.7 million	0.0	0.1	0.7	0.0	0.1	0.3
History of CHD	Health Survey for England 2016[113]	8011	0.2	4.5	20.9	0.4	1.9	12.0
History of stroke	Bhatnagar *et al.* 2015[114]	35 million	0.1	1.8	10.6	0.1	1.4	8.4
Asthma exacerbation	British Lung Foundation 2012[109]	12.6 million	19.0	12.0	11.0	19.0	12.0	11.0

TABLE 20 Prevalence of disease in simulated cohort of UK smokers at beginning of model[a]

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.0	2.1	12.1	0.0	2.3	15.2
Lung cancer	0.0	0.3	2.5	0.0	0.2	1.3
History of CHD	0.2	9.1	29.0	0.4	4.6	18.6
History of stroke	0.1	4.4	17.8	0.1	4.0	14.6
Asthma exacerbation	24.8	12.1	12.1	25.2	12.2	12.1

a Calculated from the prevalence of smokers (see *Table 18*), prevalence of disease (see *Table 19*) and RRs for smokers relative to never-smokers for each disease (source: Statistics on Smoking England 2017,[115] Cassino *et al.* 1999[116]).

TABLE 21 Annual incidence of lung cancer

Original source	Age and sex category					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
ONS (2005b) Registrations of Cancer Diagnosed in 2003[658]	0	0.05	0.4	0	0.03	0.2
Cancer Registration Statistics, England, 2016 (First Release) ONS[118]	0	0.04	0.4	0	0.04	0.3

TABLE 22 Annual incidence of diseases in general population by age and sex category

Disease	Data source	*n*	Age and sex category (%)					
			Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	Pfizer 2007[117]	UK population	0.00	0.01	0.30	0.00	0.01	0.20
Lung cancer	ONS 2005[658]	Population of England	0.00	0.04	0.40	0.00	0.04	0.33
CHD (first non-fatal event)	British Heart Foundation 2006[659]	151,000	0.00	0.08	0.80	0.00	0.02	0.60
CHD (any non-fatal event)	Volmink *et al.* 1998[660]	568,800	0.00	0.12	1.40	0.00	0.03	0.90
Stroke (first non-fatal event)	ONS 2001[661]	UK population	0.00	0.15	0.65	0.00	0.10	0.60
Stroke (any non-fatal event)	ONS 2001[661]	UK population	0.00	0.20	1.00	0.00	0.14	1.00
Asthma	Asthma UK[662]		0.06	0.05	0.06	0.06	0.05	0.05

TABLE 23 Annual incidence of diseases in smokers by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.00	0.02	0.52	0.00	0.02	0.44
Lung cancer	0.00	0.13	1.35	0.00	0.14	1.34
CHD (first non-fatal event)	0.00	0.16	1.11	0.00	0.05	0.93
Stroke (first non-fatal event)	0.00	0.36	1.09	0.00	0.28	1.04
CHD (any non-fatal event)	0.00	0.24	1.94	0.00	0.07	1.40
Asthma	0.08	0.05	0.07	0.08	0.05	0.06
Stroke (any non-fatal event)	0.00	0.49	1.68	0.00	0.40	1.73

TABLE 24 Annual incidence of diseases in recent quitters by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.00	0.02	0.47	0.00	0.02	0.43
Lung cancer	0.00	0.05	0.50	0.00	0.05	0.48
CHD (first non-fatal event)	0.00	0.09	0.83	0.00	0.02	0.64
Stroke (first non-fatal event)	0.00	0.11	0.63	0.00	0.08	0.61
CHD (any non-fatal event)	0.00	0.13	1.46	0.00	0.03	0.96
Asthma	0.06	0.05	0.06	0.06	0.05	0.05
Stroke (any non-fatal event)	0.00	0.14	0.97	0.00	0.11	1.02

TABLE 25 Annual incidence of diseases in long-run quitters by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.000	0.001	0.030	0.000	0.002	0.036
Lung cancer	0.00	0.05	0.50	0.00	0.05	0.48
CHD (first non-fatal event)	0.000	0.048	0.693	0.000	0.012	0.533
Stroke (first non-fatal event)	0.000	0.097	0.575	0.000	0.062	0.533
CHD (any non-fatal event)	0.000	0.072	1.213	0.000	0.018	0.799
Asthma	0.055	0.050	0.059	0.056	0.050	0.050
Stroke (any non-fatal event)	0.000	0.130	0.885	0.000	0.087	0.889

TABLE 26 Annual mortality for the general population by age and sex category

Disease	Data source	*n*	Age and sex category (%)					
			Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	BHF 2018[120]	UK population	0.00	1.45	4.22	0.00	1.26	3.63
Lung cancer	BHF 2018[120]	UK population	0.00	29.30	48.80	0.00	23.80	34.30
Stroke (first non-fatal event)	Assumption. The same split between first event and all events is assumed for first/subsequent for mortality as for incidence	UK population	0.41	0.51	1.78	0.14	0.58	2.74
Stroke (any non-fatal event)	BHF 2018[120]	UK population	0.60	0.68	2.74	0.20	0.81	4.57
CHD (first non-fatal event)	Assumption. The same split between first event and all events as used in a previous manufacturer's STA submission[117] is assumed for first/subsequent	UK population	0.53	0.92	1.71	0.06	0.88	2.23
CHD (any non-fatal event)	BHF 2018[120]	UK population	0.70	1.37	2.90	0.08	0.88	3.05

STA, single technology appraisal.

TABLE 27 Annual mortality for smokers by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.00	3.05	7.28	0.00	2.88	7.89
Lung cancer	0.00	29.30	48.80	0.00	23.80	34.30
CHD (first non-fatal event)	0.53	1.85	2.37	0.06	2.14	3.46
CHD (any non-fatal event)	0.70	2.76	4.02	0.08	2.14	4.74
Stroke (first non-fatal event)	0.41	1.24	3.00	0.14	1.64	4.75
Stroke (any non-fatal event)	0.60	1.65	4.61	0.20	2.29	7.92

TABLE 28 Annual mortality for recent quitters by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.00	2.79	6.65	0.00	2.81	7.71
Lung cancer	0.00	29.30	48.80	0.00	23.80	34.30
CHD (first non-fatal event)	0.53	0.99	1.78	0.06	0.98	2.37
Stroke (first non-fatal event)	0.41	0.36	1.73	0.14	0.47	2.80
CHD (any non-fatal event)	0.70	0.99	2.51	0.08	0.98	3.25
Stroke (any non-fatal event)	0.60	0.48	2.67	0.20	0.66	4.67

TABLE 29 Annual mortality for long-run quitters by age and sex category

Disease	Age and sex category (%)					
	Male aged 18–34 years	Male aged 35–64 years	Male aged ≥ 65 years	Female aged 18–34 years	Female aged 35–64 years	Female aged ≥ 65 years
COPD	0.0	0.2	0.4	0.0	0.2	0.7
Lung cancer	0.00	29.30	48.80	0.00	23.80	34.30
CHD (first non-fatal event)	0.5	0.6	1.5	0.1	0.5	2.0
Stroke (first non-fatal event)	0.4	0.3	1.6	0.1	0.4	2.4
CHD (any non-fatal event)	0.7	0.8	2.5	0.1	0.5	2.7
Stroke (any non-fatal event)	0.6	0.4	2.4	0.2	0.5	4.1

TABLE 30 Annual relapse rates

Data	Original source	Mean probability	95% CI	Distribution over relapse category time period
Annual relapse probability, > 1 and < 5 years post cessation (time period 4 years)	Hawkins *et al.* 2010[121]	0.1291	0.1174 to 0.1414	Beta(395, 35)
Annual relapse probability, ≥ 5 and < 10 years post cessation (time period 5 years)	Hawkins *et al.* 2010[121]	0.0331	0.0230 to 0.0452	Beta(33, 180)
Annual relapse probability, > 10 years post cessation (time period 26 years)	Krall *et al.* 2002[122]	0.0009	0.0004 to 0.0015	Beta(9, 360)

TABLE 31 Health state costs

Data	Original source	*n*	Mean cost from paper (currency)	95% CrI (currency)	Cost for model (£)	Distribution
COPD	Hospital Inpatient Enquiry Database 2015.[663] Cost per prevalent case of inpatient and day case treatment	73,901	868 (euros)	664 to 1097 (euros)	1468 (exchange rate £1 = €1.14)[125]	Gamma (7,390,100, 0.0002)
	Primary Care Reimbursement Service 2014.[664] Cost per prevalent case of primary care treatment	73,657	662 (euros)	504 to 831 (euros)		
	Total of inpatient and primary care		1530 (euros)			
Lung cancer	Hospital Inpatient Enquiry Database 2015.[663] Cost per prevalent case of inpatient and day-case treatment	4666	5107 (euros)	3915 to 6499 (euros)	5429 (exchange rate £1 = €1.14)[125]	Gamma (466,600, 0.01)
	Primary Care Reimbursement Service 2014.[664] Cost per prevalent case of primary care treatment	4666	555 (euros)	423 to 698 (euros)		
	Total of inpatient and primary care		5662 (euros)			
CHD (non-fatal event)	British Heart Foundation. 2014[128]		1323 (GBP)		1460	Gamma (100, 14.60)
Stroke (non-fatal event)	Xu *et al.* 2018[130]	84,184	13,452 at 1 year (GBP)		13,788	Gamma (8,418,400, 0.002)
Asthma exacerbation	Tan *et al.* 2016[132]	939	341 (GBP)	SE 12.94 (GBP)	367	Gamma (805, 0.46)
Depression	Hunter *et al.* 2014[134]		340.35 (GBP)		395	Gamma (100, 3.95)
Self-harm	Tsiachristas *et al.* 2017[135]	1140	809 (GBP)	SE 26.78 (GBP)	850	Gamma (1007, 0.84)

GBP, Great British pounds.

TABLE 32 Intervention costs

Treatment	Assumed mean cost (£)	Source	Assumption
NRT low	83.84	BNF[137]	4 weeks of 10-mg/16-hour patches and 4 weeks of 5-mg/16-hour patches
NRT standard	105.65	BNF[137]	High-strength patch daily for 6–8 weeks, followed by medium-strength patch for 2 weeks, and low-strength patch for final 2 weeks
NRT high	77.46	BNF[137]	4-week supply of 21 mg NicoDerm transdermal patches, followed by 2 weeks of 14 mg and 2 weeks of 7 mg
Bupropion low	62.64	BNF[137]	One 150-mg tablet a day for an average of 13 weeks
Bupropion standard	83.52	BNF[137]	150 mg daily for 6 days, then 150 mg twice daily for a period of treatment of 7–9 weeks
Varenicline low	163.80	BNF[137]	0.5 mg once daily for 3 days, increased to 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks
Varenicline standard	163.80	BNF[137]	1 mg once daily for 3 days, increased to 1 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks
E-cigarette	82	Liber *et al.* 2017[139]	12-week supply of e-cigarettes (e-cigarette + 3.55 ml liquid per day including a replacement atomiser in months 2 and 3)
Bupropion standard plus NRT high	160.98	BNF[137]	
Varenicline low plus NRT standard	269.45	BNF[137]	
Varenicline standard plus NRT standard	269.45	BNF[137]	
Varenicline standard plus NRT high	241.26	BNF[137]	
Varenicline standard plus bupropion standard	247.32	BNF[137]	

TABLE 33 Health state mean utility values

Health state	Utility source	*n*	Mean utility	SE
NCM, male, 18–34 years	Ara and Brazier 2010[140]	26,679	0.94	
NCM, male, 35–64 years	Ara and Brazier 2010[140]	26,679	0.88	
NCM, male, 65–100 years	Ara and Brazier 2010[140]	26,679	0.72	
NCM, female, 18–34 years	Ara and Brazier 2010[140]	26,679	0.92	
NCM, female, 35–64 years	Ara and Brazier 2010[140]	26,679	0.86	
NCM, female, 65–100 years	Ara and Brazier 2010[140]	26,679	0.70	
Lung cancer	Bertranou *et al.* 2018[142]	464	0.72	0.001
COPD	Pickard *et al.* 2008[144]		0.69	0.043
CHD	Stevanović *et al.* 2016[146]	30,575	0.76	0.01
Stroke (first event)	Haacke *et al.* 2006[148]	77	0.73	0.036
Stroke (second event)	Ara and Brazier 2010[140]	18	0.48	0.087
Asthma exacerbation	Lloyd *et al.* 2007[151]	112	0.57	0.026
Depression	Hunter *et al.* 2014[134]		0.58	0.015
Self-harm	Byford *et al.* 2003[157]	480	0.50	0.016

NCM, No comorbidity.

TABLE 34 Absolute probability of 1-year continuous cessation based on NRT standard taken from Taylor *et al.*[158] and ORs estimated from the NMA (see *Chapter 5*)

	1-year continuous abstinence probability		
Treatment	**Mean**	**2.5%**	**97.5%**
Varenicline low plus NRT standard	0.43	0.17	0.73
Varenicline standard plus NRT standard	0.43	0.23	0.66
E-cigarette low	0.32	0.12	0.63
Varenicline plus bupropion standard	0.31	0.15	0.51
E-cigarette high	0.30	0.18	0.45
Varenicline standard	0.27	0.23	0.32
Varenicline standard plus NRT high	0.24	0.12	0.38
NRT high	0.23	0.19	0.27
NRT standard	0.21	0.21	0.21
Varenicline low	0.19	0.12	0.28
Bupropion standard plus NRT high	0.19	0.10	0.32
Bupropion low	0.19	0.12	0.28
Bupropion standard	0.18	0.15	0.22
NRT low	0.07	0.02	0.16

TABLE 35 Absolute probability of depression based on NRT not specified taken from Kotz *et al.*[57] and ORs estimated from the NMA (see *Chapter 5*)

	Depression probability		
Treatment	**Mean**	**2.5%**	**97.5%**
NRT standard	0.07	0.00	0.39
Bupropion standard plus NRT high	0.08	0.01	0.22
NRT not specified	0.15	0.15	0.15
Bupropion standard	0.17	0.11	0.24
Varenicline standard plus NRT high	0.17	0.06	0.37
NRT high	0.19	0.10	0.30
Varenicline standard	0.22	0.16	0.31
Varenicline low	0.29	0.02	0.78
Varenicline standard plus NRT standard	0.36	0.09	0.77

TABLE 36 Absolute probability of self-harm based on NRT not specified taken from Kotz *et al.*[57] and ORs estimated from the NMA (see *Chapter 5*)

	Self-harm probability		
Treatment	**Mean**	**2.5%**	**97.5%**
Varenicline plus bupropion standard	0.004	0.000	0.018
Bupropion standard plus NRT high	0.005	0.001	0.016
NRT standard	0.006	0.000	0.036
NRT not specified	0.010	0.010	0.011
Bupropion standard	0.012	0.007	0.018
Varenicline standard plus NRT high	0.013	0.003	0.033
NRT high	0.013	0.006	0.024
Varenicline standard	0.016	0.011	0.025
Varenicline low	0.034	0.001	0.171
Varenicline standard plus NRT standard	0.042	0.006	0.158

TABLE 37 Relative risks of disease prevalence in smokers relative to never-smokers

Disease	RR in smokers	RR in former smokers	RR in never-smokers
COPD[a]			
Male aged 18–34 years	1	1	1
Male aged 35–64 years	17.1	15.64	1
Male aged ≥ 65 years	17.1[b]	15.64[b]	1
Female aged 18–34 years	1	1	1
Female aged 35–64 years	12.04	11.77	1
Female aged ≥ 65 years	12.04[b]	11.77[b]	1
Lung cancer[a]			
Male aged 18–34 years	1	1	1
Male aged 35–64 years	23.26	8.7	1
Male aged ≥ 65 years	23.26[b]	8.7[b]	1
Female aged 18–34 years	1	1	1
Female aged 35–64 years	12.69	4.53	1
Female aged ≥ 65 years	12.69[b]	4.53[b]	1
CHD[c]			
Male aged 18–34 years	1	1	1
Male aged 35–64 years	3.35	1.80	1
Male aged ≥ 65 years	1.60	1.20	1
Female aged 18–34 years	1	1	1
Female aged 35–64 years	4.05	1.85	1
Female aged ≥ 65 years	1.75	1.20	1

TABLE 37 Relative risks of disease prevalence in smokers relative to never-smokers (*continued*)

Disease	RR in smokers	RR in former smokers	RR in never-smokers
Stroke[c]			
Male aged 18–34 years	1	1	1
Male aged 35–64 years	3.75	1.1	1
Male aged ≥ 65 years	1.9	1.1[b]	1
Female aged 18–34 years	1	1	1
Female aged 35–64 years	4.55	1.3	1
Female aged ≥ 65 years	1.95	1.15	1

a Health Profile for England 2007, Department of Health, Tobacco in London, The Preventable Burden, Smokefree London & The London Health Observatory, 2004.
b Relative risk assumed to be the same as that in persons aged 35–64 years.
c Based on data from CPS-II 1982–8, which was a prospective study of smoking and death in more than 1 million Americans aged ≥ 30 years.

Appendix 3 Formulae to calculate the expected number of cases of disease in the cohort of smokers

Total disease prevalence (P_T) within the overall population is the weighted sum of the prevalence within the three subgroups [current smokers (P_{CS}), former smokers (P_{FS}) and never smokers (P_{NS})], with the weights being the proportion of people in each group [current smokers (π_{CS}), former smokers (π_{FS}) or never smokers ($1 - \pi_{CS} - \pi_{FS}$); *Equation 3*].

$$P_T = P_{NS} \times (1 - \pi_{CS} - \pi_{FS}) + P_{FS} \times \pi_{FS} + P_{CS} \times \pi_{CS}. \quad (3)$$

Disease prevalence within the group of current and former smokers can be expressed in terms of the prevalence among never smokers using the RR of the disease in current and former smokers (RR_{CS} and RR_{FS}, respectively).

$$P_{FS} = P_{NS} \times RR_{FS}. \quad (4)$$

$$P_{CS} = P_{NS} \times RR_{CS}. \quad (5)$$

Substituting these into *Equation 3* gives *Equation 6*, which on rearrangement allows the disease prevalence among never-smokers (P_{NS}) to be expressed in terms of the total population prevalence (P_T), the proportion of people who are current smokers (π_{CS}), former smokers (π_{FS}), and the RR associated with being a current or former smoker (RR_{CS}, RR_{FS}), all of which are known (*Equation 7*):

$$P_T = P_{NS} \times (1 - \pi_{FS} - \pi_{CS}) + P_{NS} \times RR_{FS} \times \pi_{FS} + P_{NS} \times RR_{CS} \times \pi_{CS}. \quad (6)$$

$$P_{NS} = \frac{P_T}{((1 - \pi_{FS} - \pi_{CS}) + RR_{FS} \times \pi_{FS} + RR_{CS} \times \pi_{CS})}. \quad (7)$$

Solving for P_{NS} then allows us to calculate P_{FS} (prevalence rate in former smokers) and P_{CS} (prevalence rate in current smokers) using *Equations 4* and *5*.

Appendix 4 Risk-of-bias summary figures

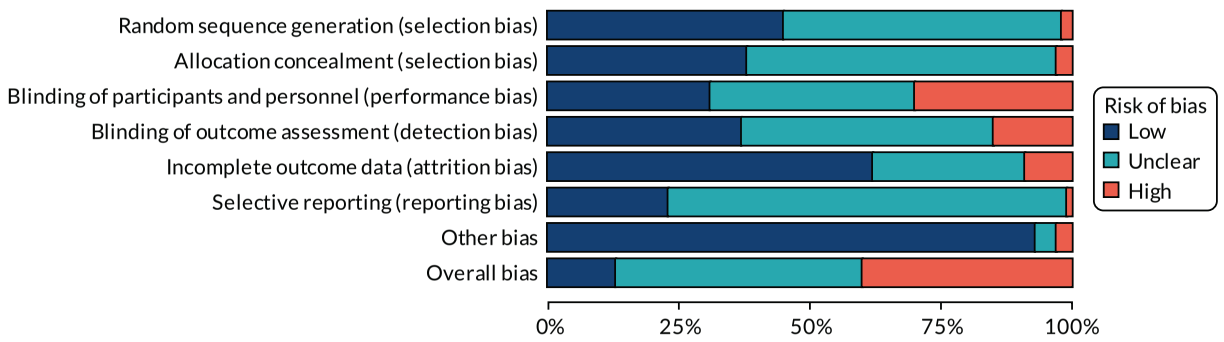

FIGURE 34 Risk-of-bias summary figure for RCTs reporting one or more effectiveness outcomes. This figure is reproduced with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

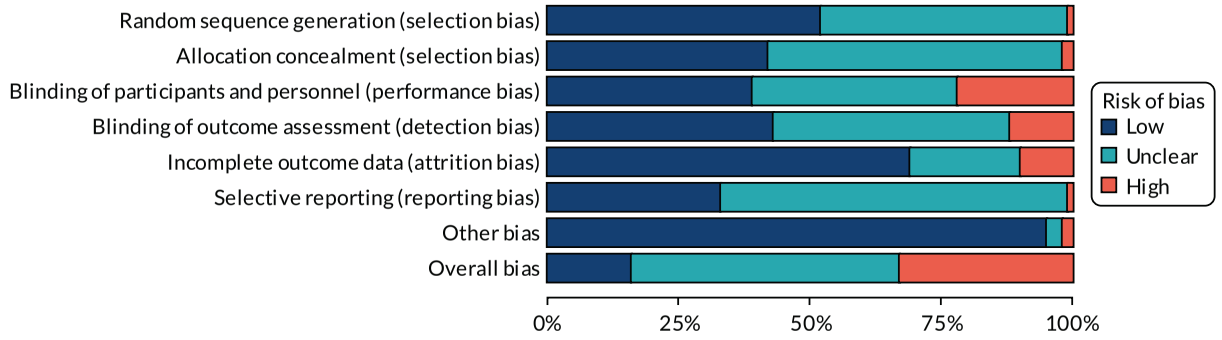

FIGURE 35 Risk-of-bias summary figure for RCTs reporting one or more safety outcomes. This figure is reproduced with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

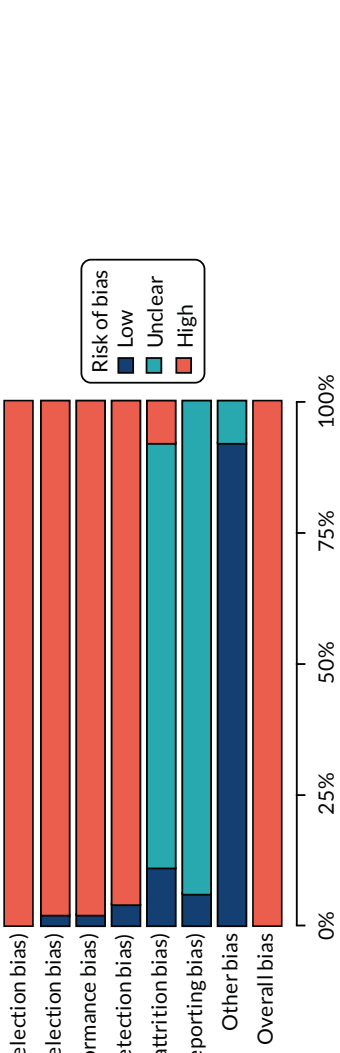

FIGURE 36 Risk-of-bias summary figure for non-randomised studies reporting one or more safety outcomes.

Appendix 5 Effectiveness analyses

TABLE 38 List and frequency of treatments delivered in trials included in effectiveness analyses

Treatment	Frequency
Bupropion low	10
Bupropion high plus NRT combination high	1
Bupropion not specified	2
Bupropion not specified plus NRT choice not specified	1
Bupropion not specified plus NRT patch (24 hours) not specified	1
Bupropion standard	73
Bupropion standard plus NRT choice not specified	1
Bupropion standard plus NRT combination high	1
Bupropion standard plus NRT gum high	1
Bupropion standard plus NRT gum not specified	4
Bupropion standard plus NRT gum standard	1
Bupropion standard plus NRT inhalator not specified	1
Bupropion standard plus NRT lozenge not specified	2
Bupropion standard plus NRT patch (24 hours) high	8
Bupropion standard plus NRT patch (24 hours) not specified	2
E-cigarette high	2
E-cigarette high plus NRT patch (24 hours) not specified	1
E-cigarette high	4
No drug treatment	97
NRT choice high	1
NRT choice not specified	29
NRT choice standard	1
NRT combination high	8
NRT combination not specified	7
NRT combination standard	6
NRT gum high	13
NRT gum high	1
NRT gum not specified	14
NRT gum standard	79
NRT inhalator standard	10
NRT lozenge high	7
NRT lozenge high	1
NRT lozenge not specified	9
NRT lozenge standard	2
NRT mouth spray standard	3
NRT nasal spray standard	6
NRT not specified	55

continued

TABLE 38 List and frequency of treatments delivered in trials included in effectiveness analyses (*continued*)

Treatment	Frequency
NRT patch (16 hours) high	3
NRT patch (16 hours) high	3
NRT patch (16 hours) standard	14
NRT patch (24 hours) high	63
NRT patch (24 hours) high	1
NRT patch (24 hours) not specified	48
NRT patch (24 hours) standard	2
NRT sublingual tablet not specified	4
Placebo	210
Usual care	30
Varenicline standard plus bupropion standard	2
Varenicline high	6
Varenicline high plus NRT gum standard	1
Varenicline not specified	4
Varenicline standard	64
Varenicline standard plus NRT gum standard	1
Varenicline standard plus NRT patch (16 hours) standard	1
Varenicline standard plus NRT patch (24 hours) high	3
Waitlist	4

Sustained abstinence

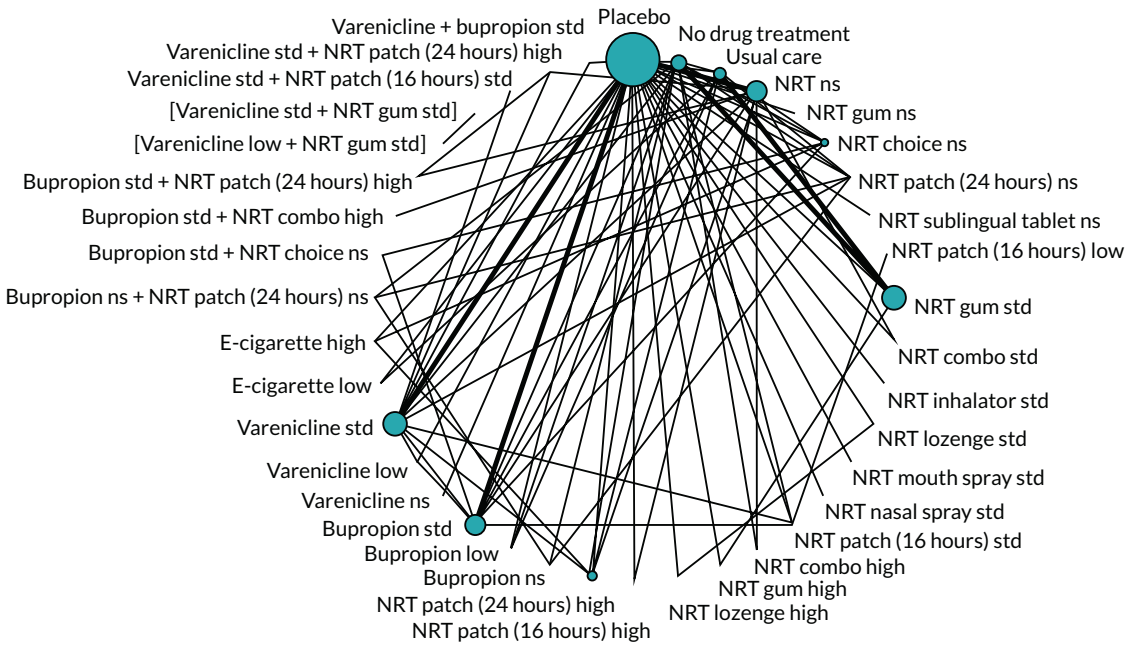

FIGURE 37 Network plot for sustained abstinence at treatment level. Square brackets denote disconnected interventions. Ns, not specified; std, standard.

TABLE 39 Comparison of different NMA models for sustained abstinence (349 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	340.0	2194	0.41 (0.34 to 0.49)	–
Random-class model, consistency	338.3	2187	0.40 (0.34 to 0.48)	0.12 (0.01 to 0.32)
Fixed-class model, consistency	338.5	2186	0.41 (0.34 to 0.49)	–
Fixed-class model, inconsistency	353.7	2209	0.32 (0.25 to 0.40)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.
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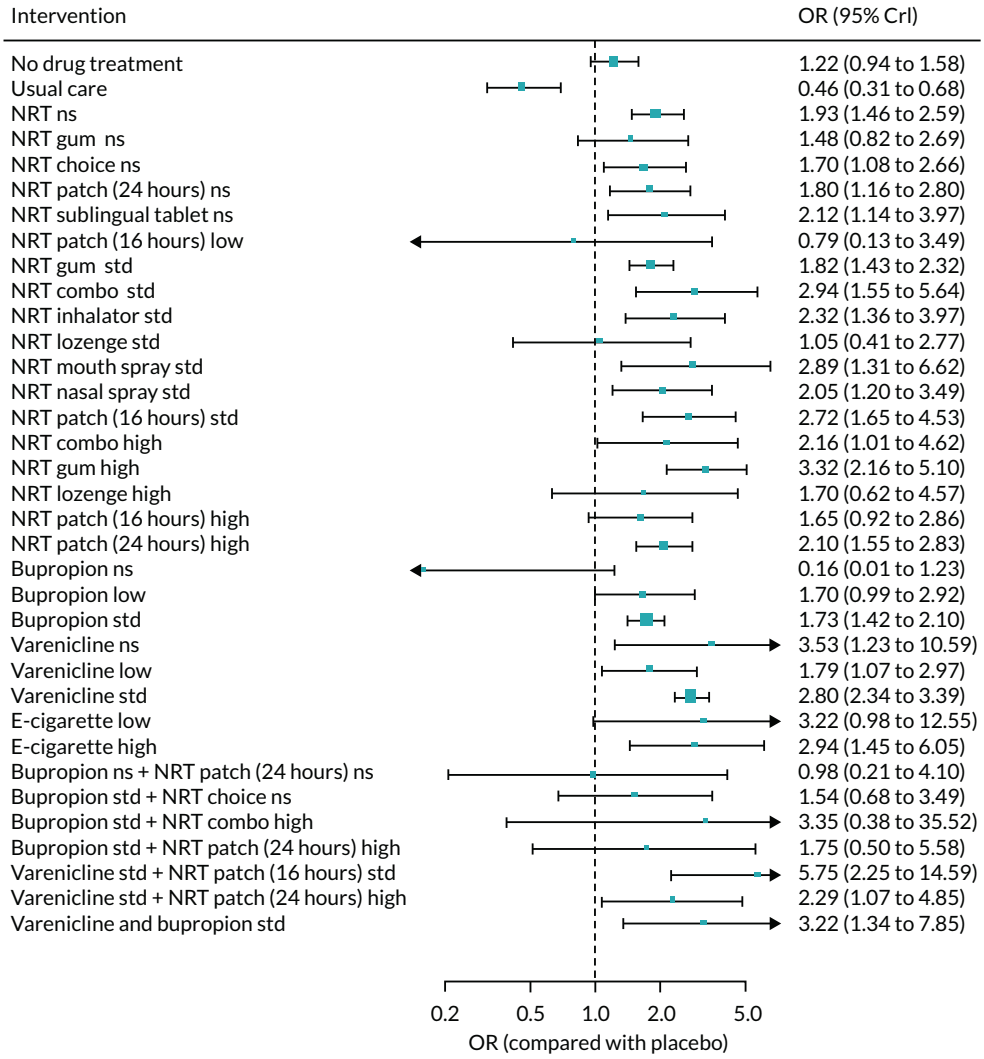

FIGURE 38 Forest plot with full interaction NMA model results for sustained abstinence. Ns, not specified; std, standard.

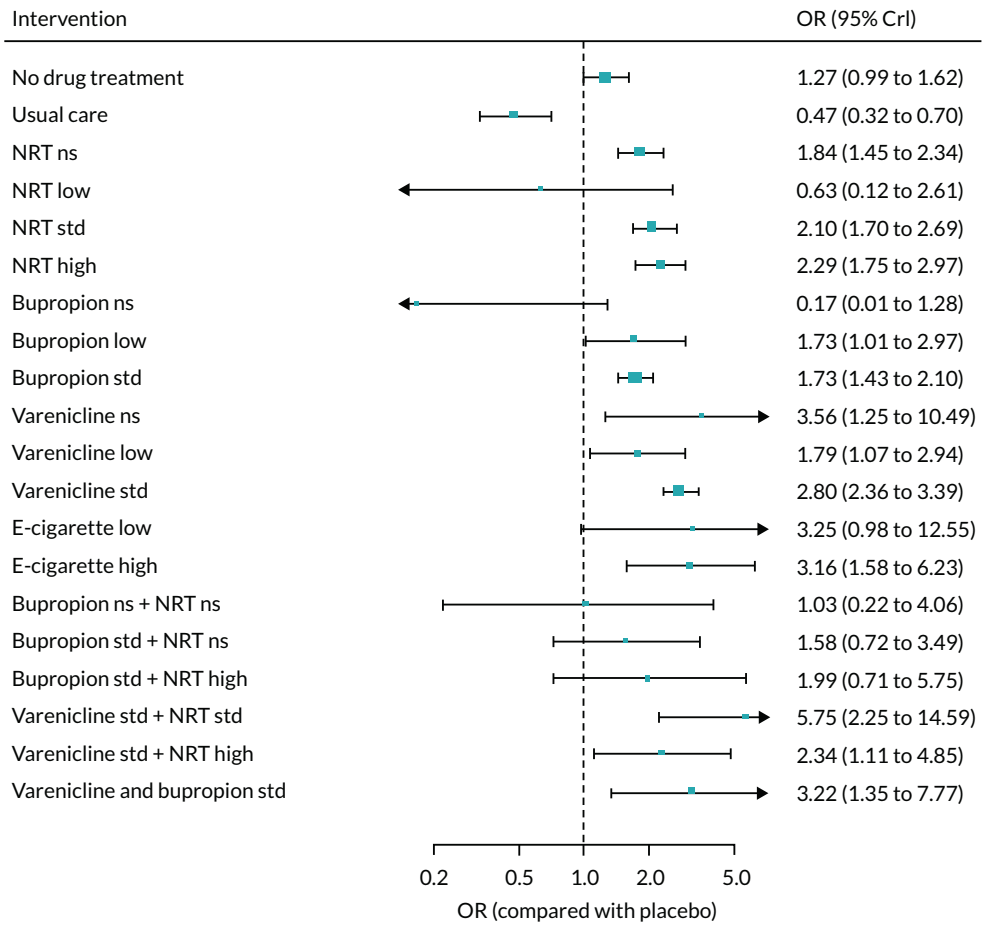

FIGURE 39 Forest plot with random-class NMA model results for sustained abstinence. Ns, not specified; std, standard.

Sensitivity analyses

Analysis excluding studies at high risk of bias

This analysis was based on 111 studies. The estimate of the SDs between class effects was 0.34 (95% CrI 0.27 to 0.43).

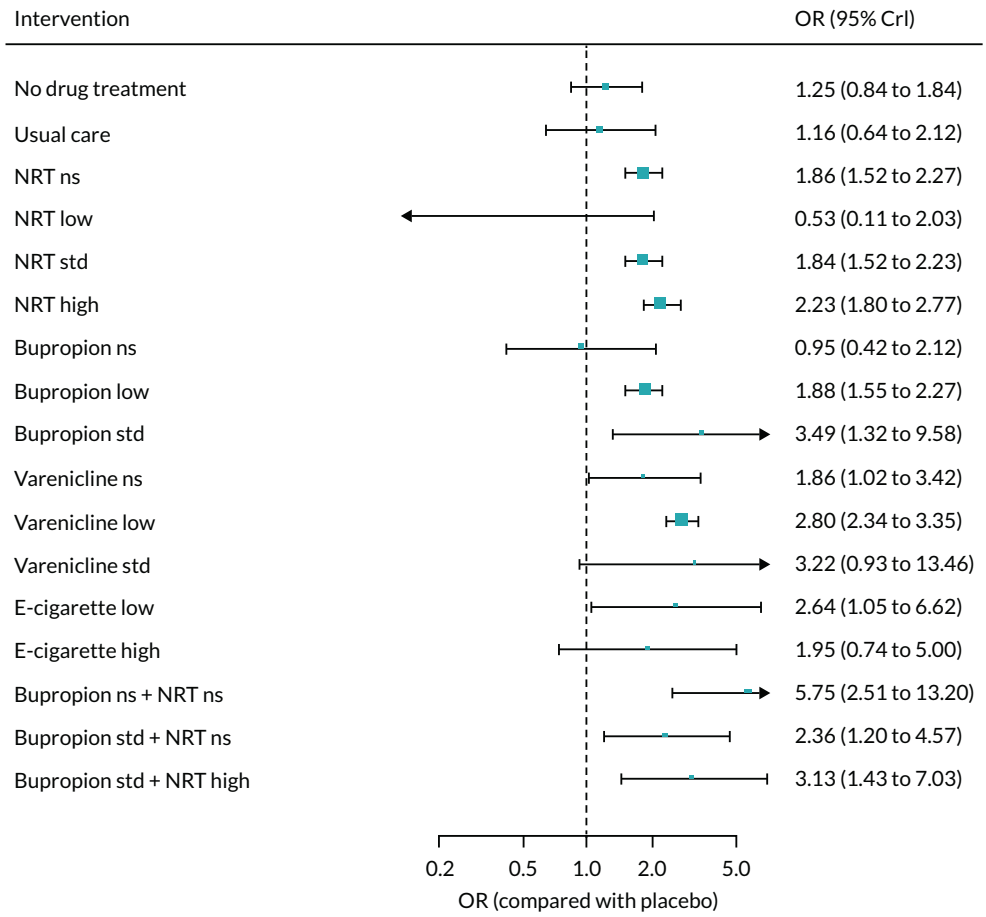

FIGURE 40 Forest plot with fixed-class NMA model results for sustained abstinence without studies at high risk of bias. Ns, not specified; std, standard.

Sensitivity analysis excluding studies of pharmacological treatment plus counselling (if counselling is not given in all study arms)

This analysis was based on 143 studies. The estimate of the SD between class effects was 0.31 (95% CrI 0.31 to 0.39), which is nearly identical to that for the main analysis.

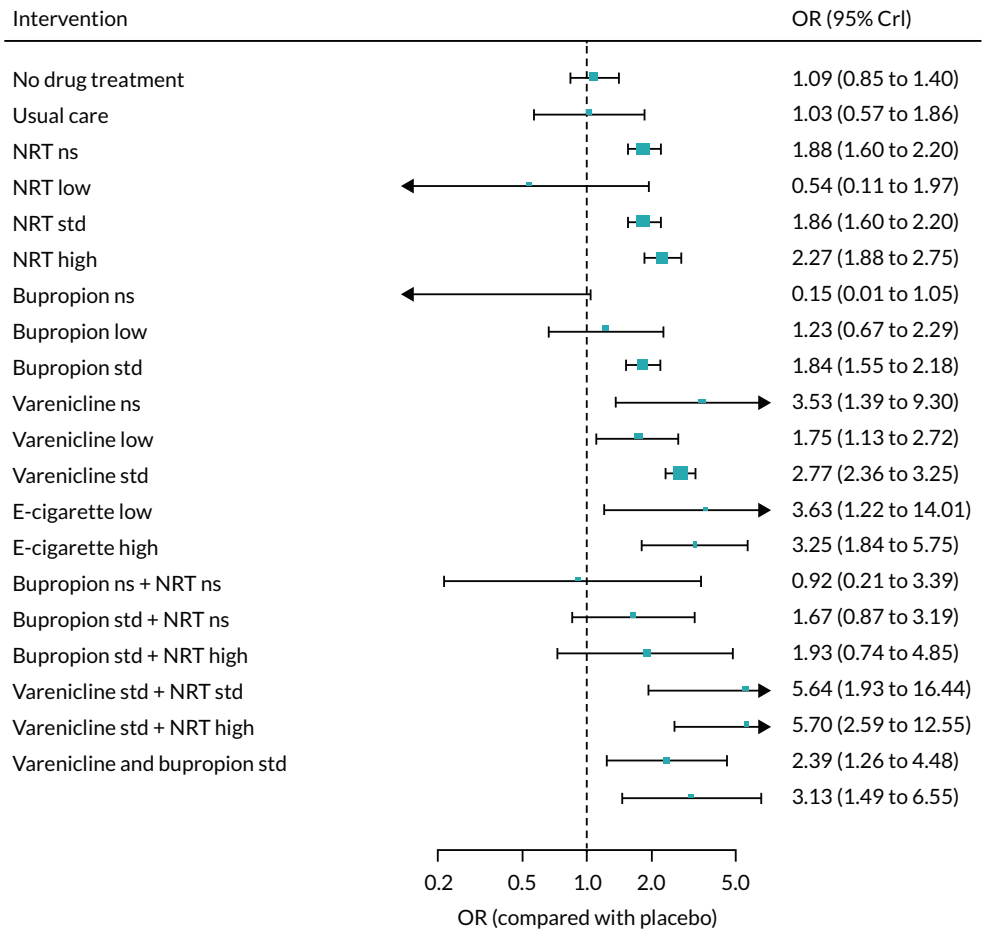

FIGURE 41 Forest plot with fixed-class NMA model results for sustained abstinence without studies that include pharmacological treatment plus counselling (unless counselling included on all arms). Ns, not specified; std, standard.

Meta-regressions

Industry sponsorship as covariate

This analysis was based on 145 studies. There was inconclusive evidence of effect modification based on industry sponsorship (B = 0.42, −197.0 to 198.3). The estimate of the SD between class effects was 0.42 (95% CrI 0.35 to 0.50).

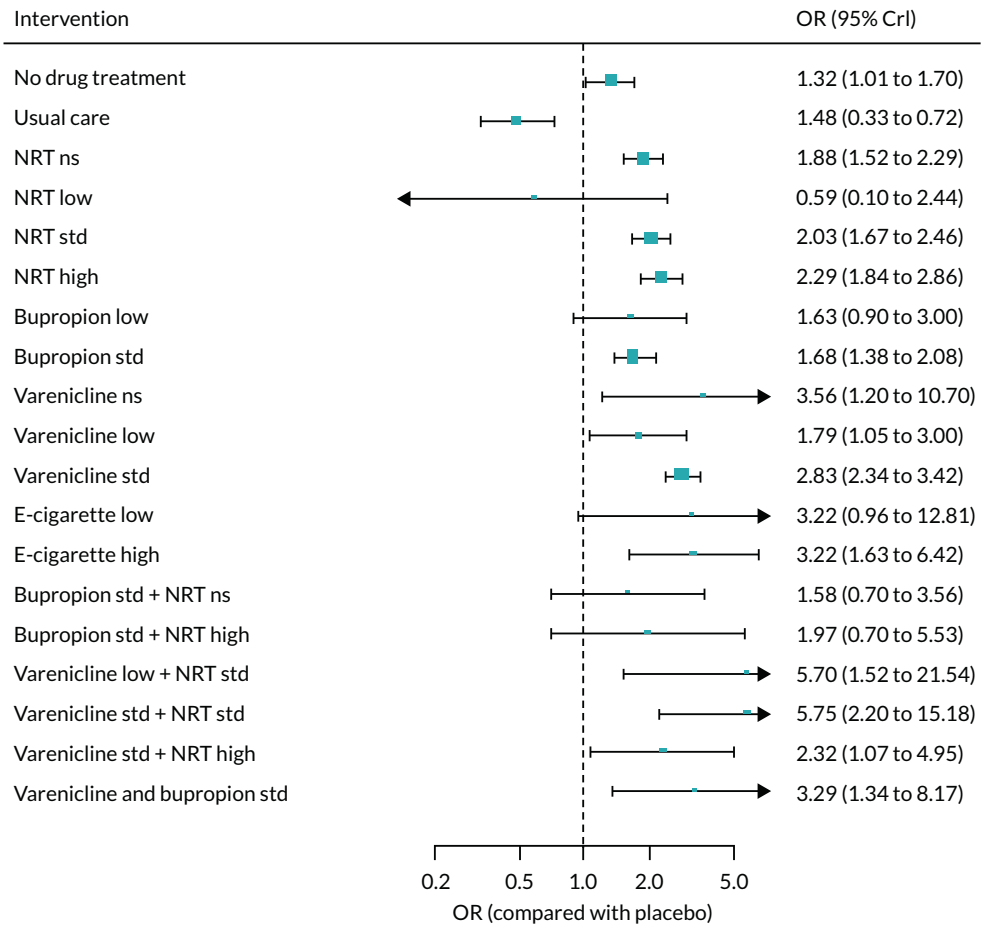

FIGURE 42 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for sponsorship. Ns, not specified; std, standard.

Placebo type as covariate

This analysis was based on 113 studies. There was inconclusive evidence of effect modification based on type of placebo (B = 0.34, −196.8 to 196.2). The estimate of the SD between class effects was 0.34 (95% CrI 0.26 to 0.43).

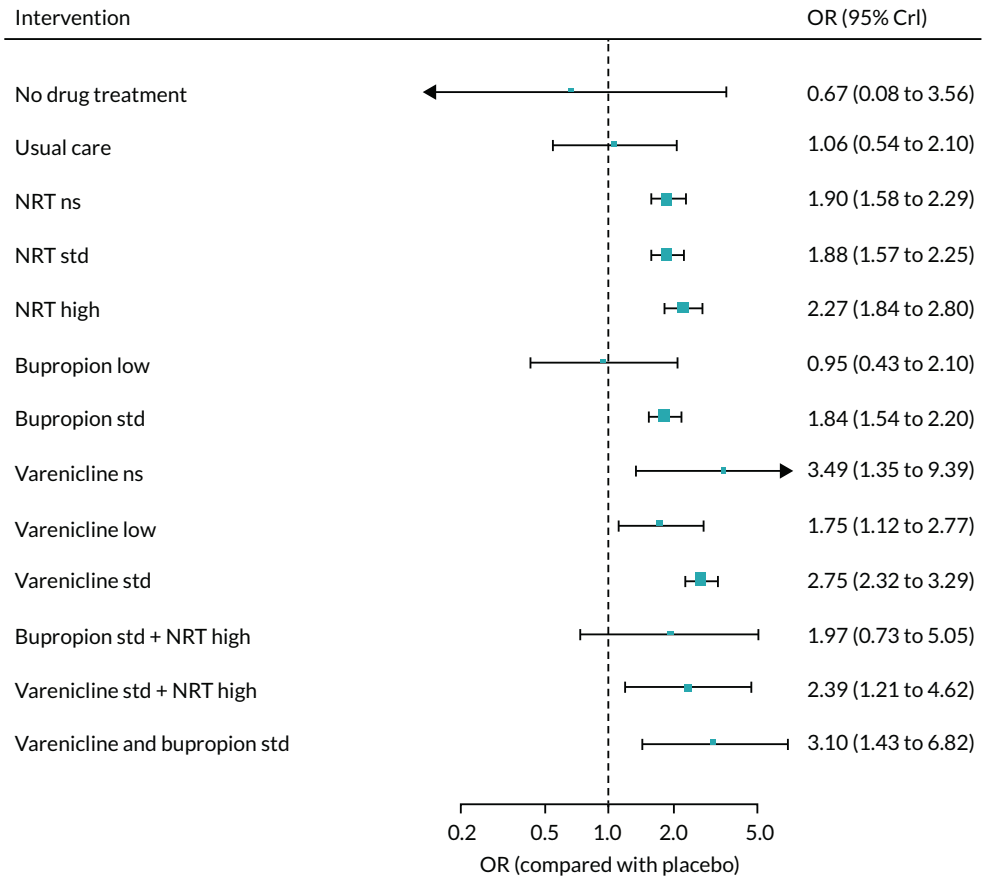

FIGURE 43 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for type of placebo. Ns, not specified; std, standard.

Treatment duration as covariate

This analysis was based on 150 studies. There was inconclusive evidence of effect modification as a function of treatment duration (B = –0.01, –0.05 to 0.04). The estimate of the SD between class effects was 0.32 (95% CrI 0.13 to 0.56).

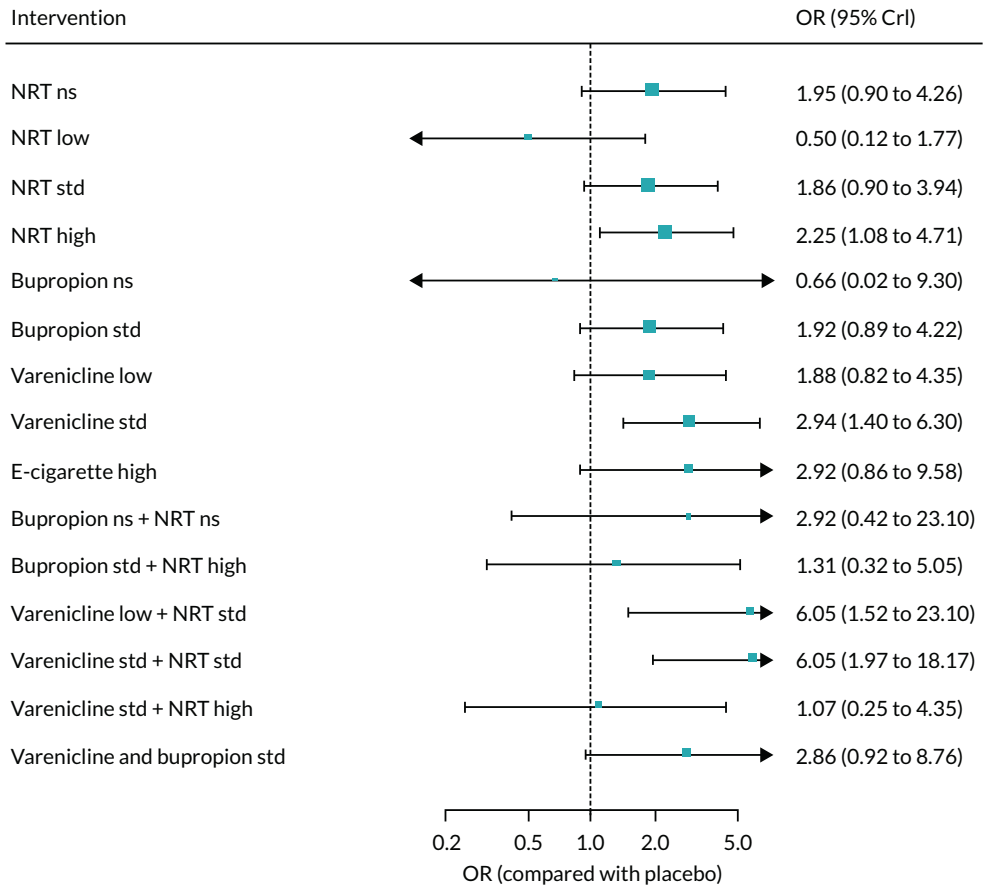

FIGURE 44 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for treatment duration. Ns, not specified; std, standard.

Counselling as covariate

This analysis was based on 161 studies. There was evidence of effect modification as a function of counselling, with interventions including counselling associated with a higher proportion of smokers achieving sustained abstinence (B = 0.86, 0.450 to 1.27). The estimate of the SD between class effects was 0.36 (95% CrI 0.29 to 0.44).

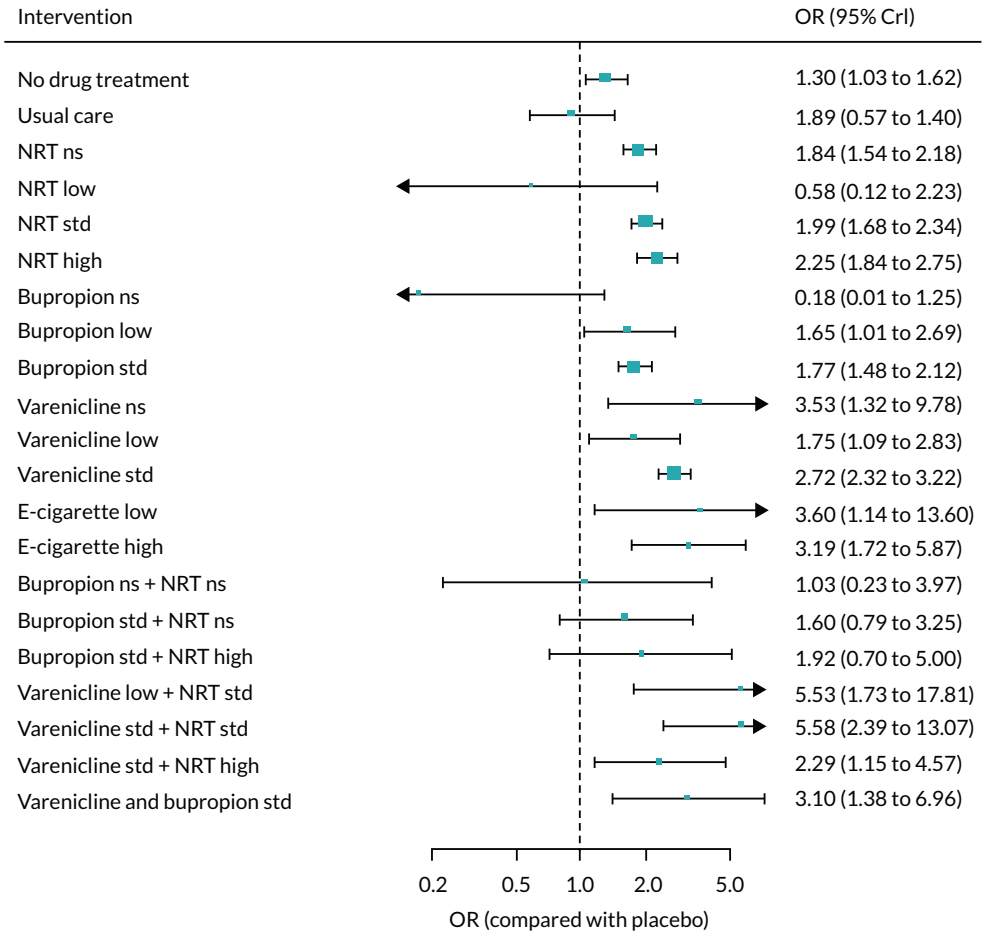

FIGURE 45 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for counselling. Ns, not specified; std, standard.

Counselling as covariate (excluding pharma vs. psychiatric studies)

This analysis was based on 143 studies. There was inconclusive evidence of effect modification as a function of counselling (B = 0.16, –0.05 to 0.37). The estimate of the SD between class effects was 0.31 (95% CrI 0.24 to 0.39).

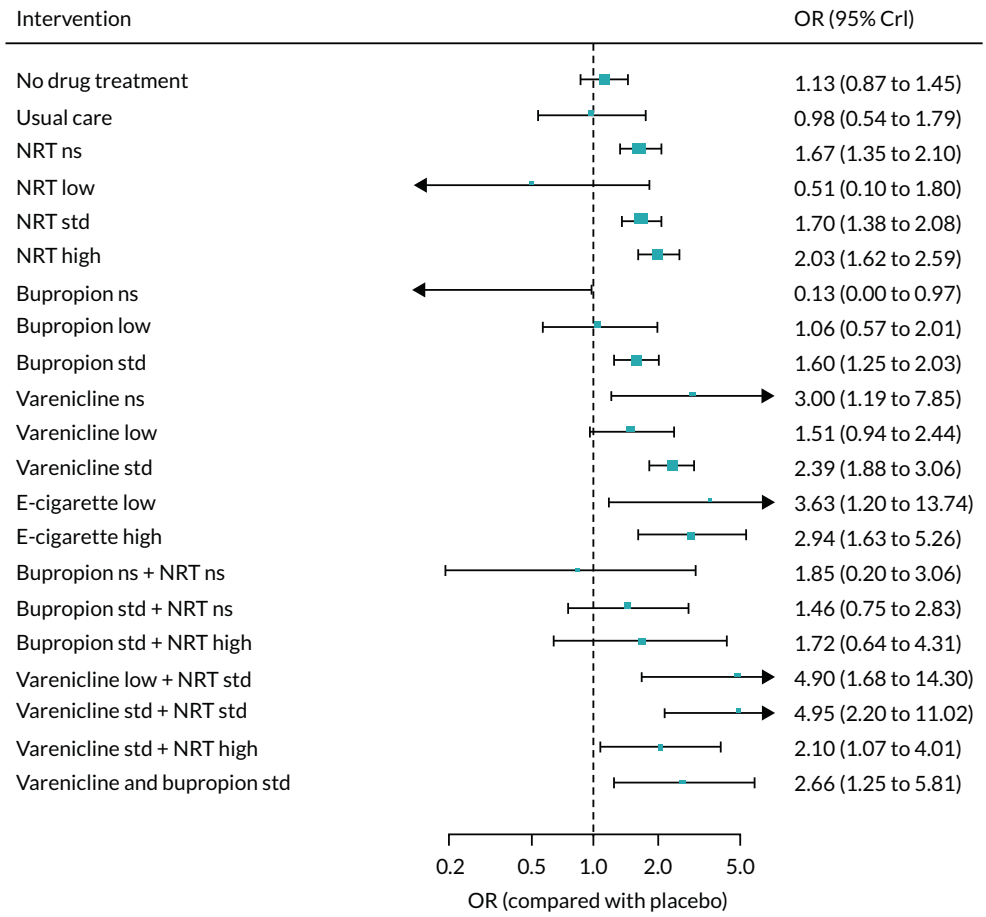

FIGURE 46 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for counselling (excluding pharma vs. psychiatric studies). Ns, not specified; std, standard.

Dependence as covariate

This analysis was based on 94 studies. There was evidence of effect modification as a function of dependence, with higher odds of quitting among smokers with higher dependence scores (B = 0.23, 0.02 to 0.43). The estimate of the SD between class effects was 0.35 (95% CrI 0.27 to 0.44).

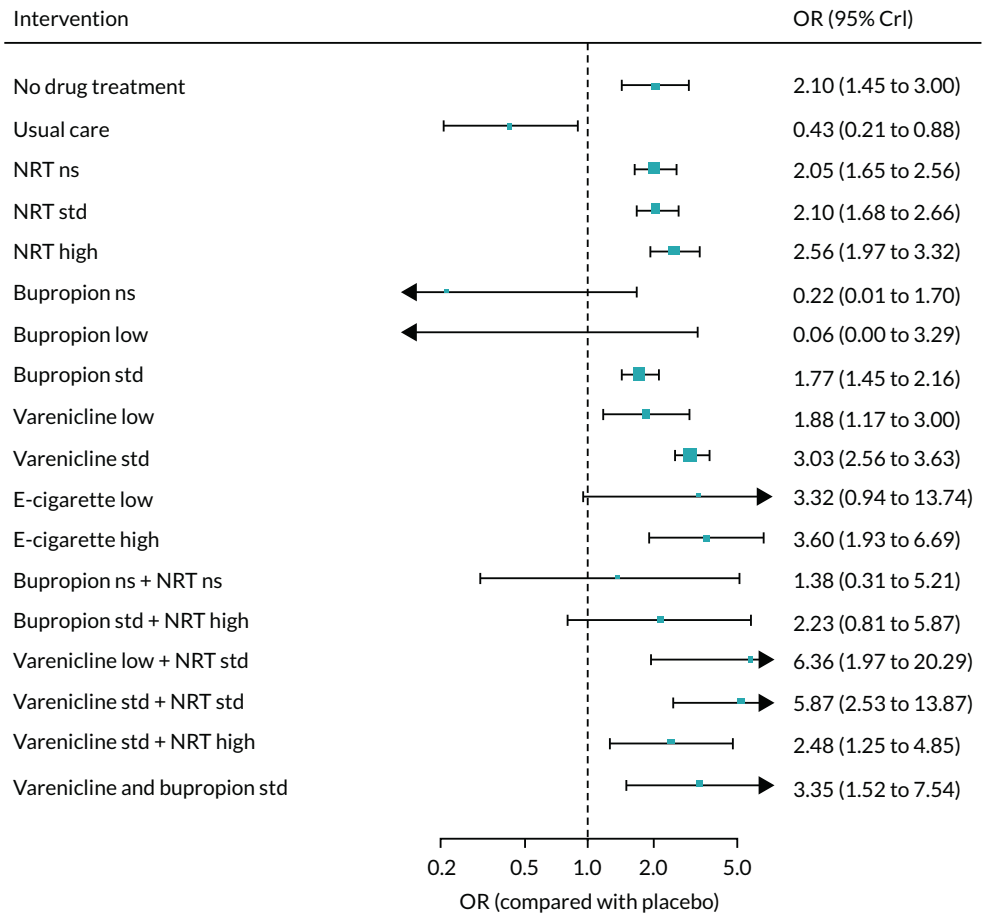

FIGURE 47 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for dependence. Ns, not specified; std, standard.

Comorbidities as covariate

This analysis was based on 161 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = 0.18, −195.6 to 196.0). The estimate of the SD between class effects was 0.41 (95% CrI 0.34 to 0.49).

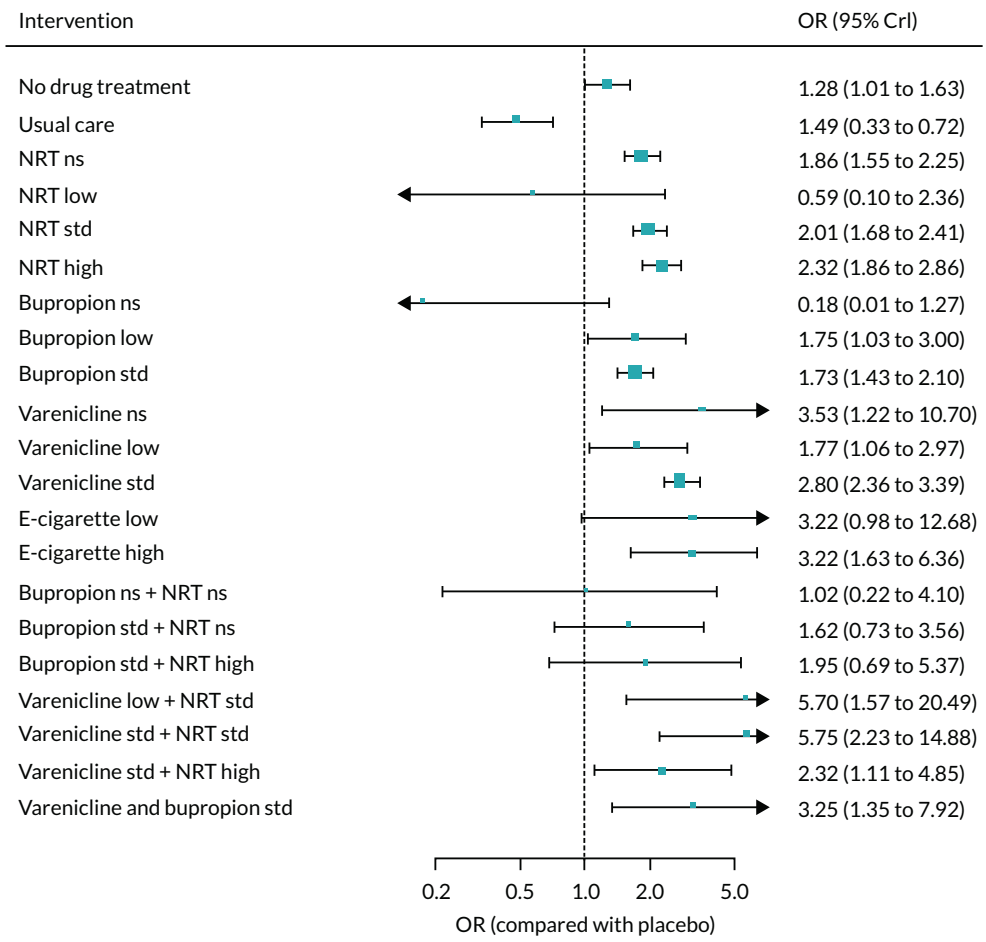

FIGURE 48 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for comorbidities. Ns, not specified; std, standard.

Psychiatric comorbidities as covariate

This analysis was based on 161 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = 0.18, −195.6 to −196.0). The estimate of the SD between class effects was 0.41 (95% CrI 0.34 to 0.49).

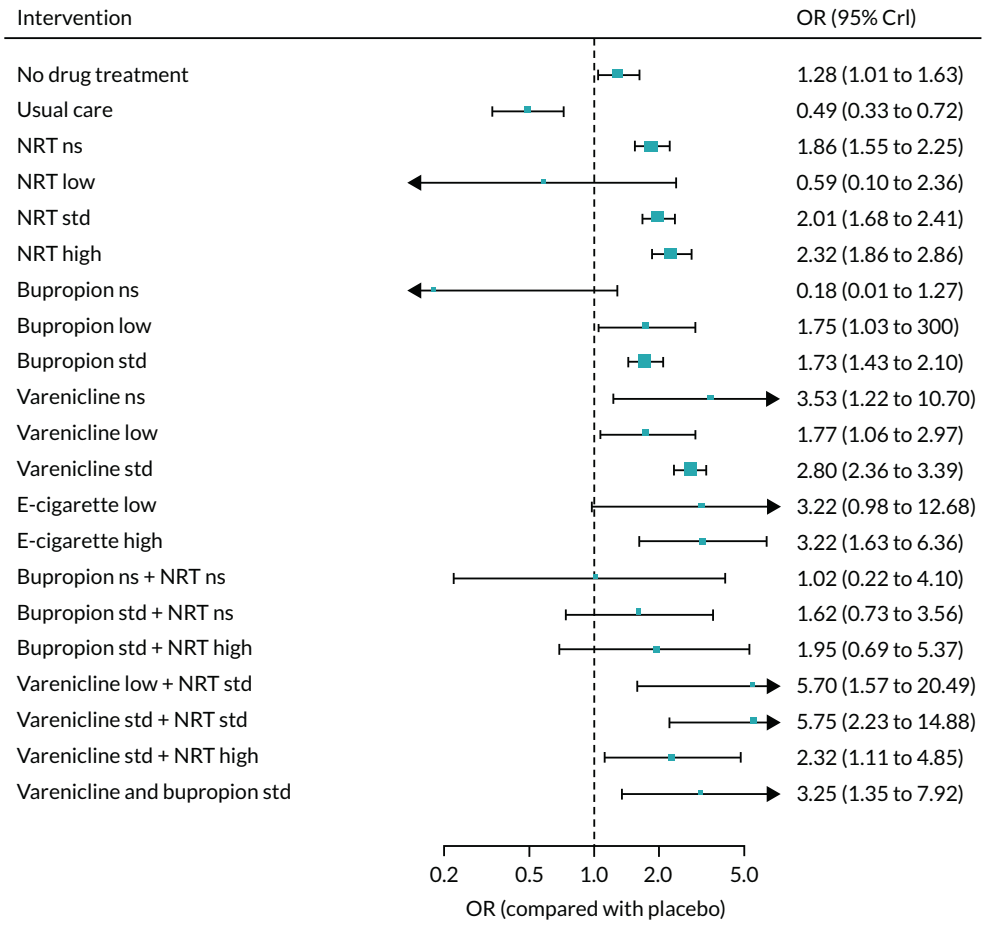

FIGURE 49 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for psychiatric comorbidities. Ns, not specified; std, standard.

Requirement for patients to be willing to quit as covariate

This analysis was based on 161 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = 0.18, −195.6 to −196.0). The estimate of the SD between class effects was 0.41 (95% CrI 0.34 to 0.49).

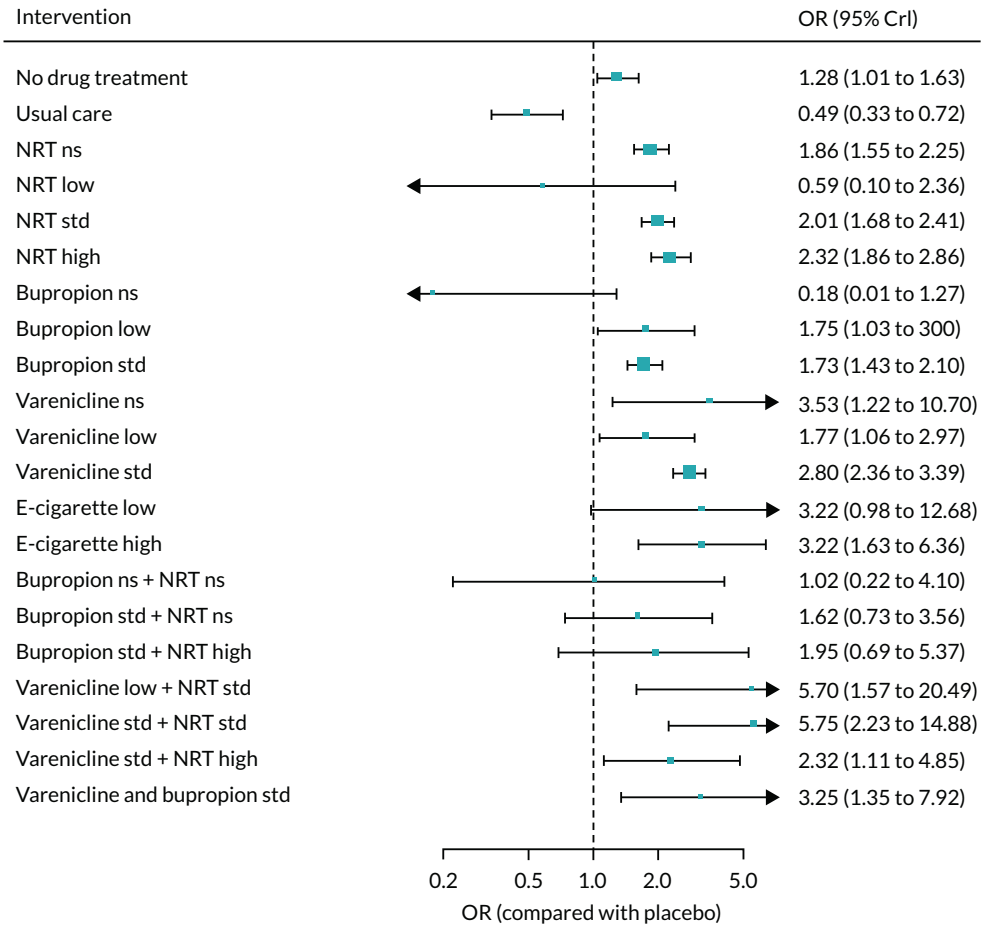

FIGURE 50 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for willingness to quit. Ns, not specified; std, standard.

Smokeless tobacco as covariate

This analysis was based on 161 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = 0.18, −195.6 to −196.0). The estimate of the SD between class effects was 0.41 (95% CrI 0.34 to 0.49).

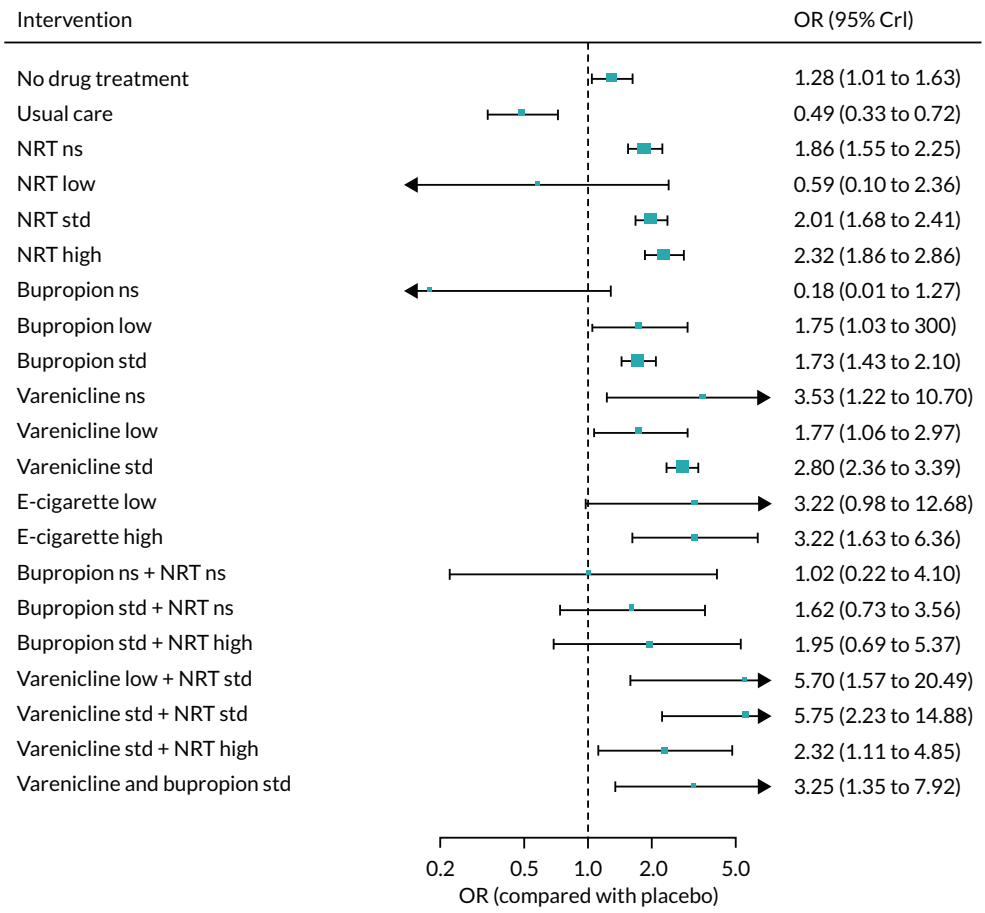

FIGURE 51 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for use of smokeless tobacco. Ns, not specified; std, standard.

Smoking level as covariate

This analysis was based on 108 studies. There was inconclusive evidence of effect modification as a function of smoking level (B = –0.06, –0.21 to 0.33). The estimate of the SD between class effects was 0.29 (95% CrI 0.33 to 0.37).

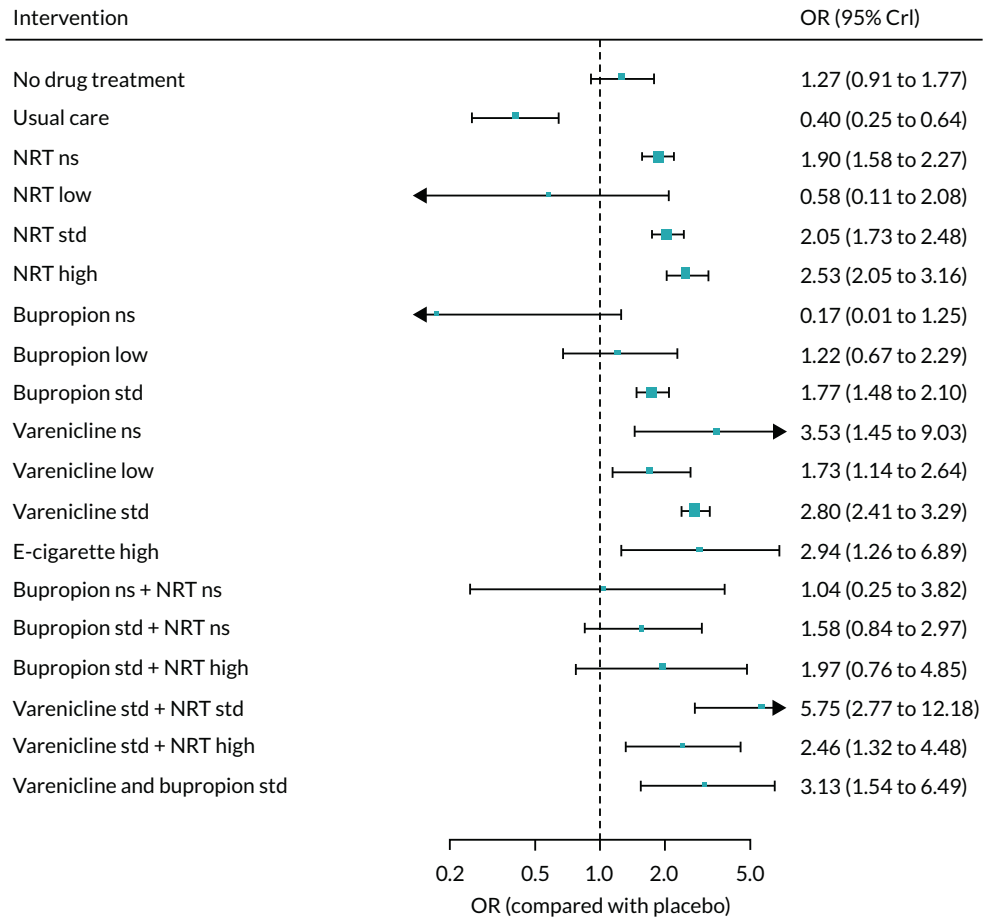

FIGURE 52 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for smoking level. Ns, not specified; std, standard.

Publication year as covariate

This analysis was based on 161 studies. There was inconclusive evidence of effect modification based on publication year (B = 0.14, −195.6 to 196.9). The estimate of the SD between class effects was 0.40 (95% CrI 0.34 to 0.48).

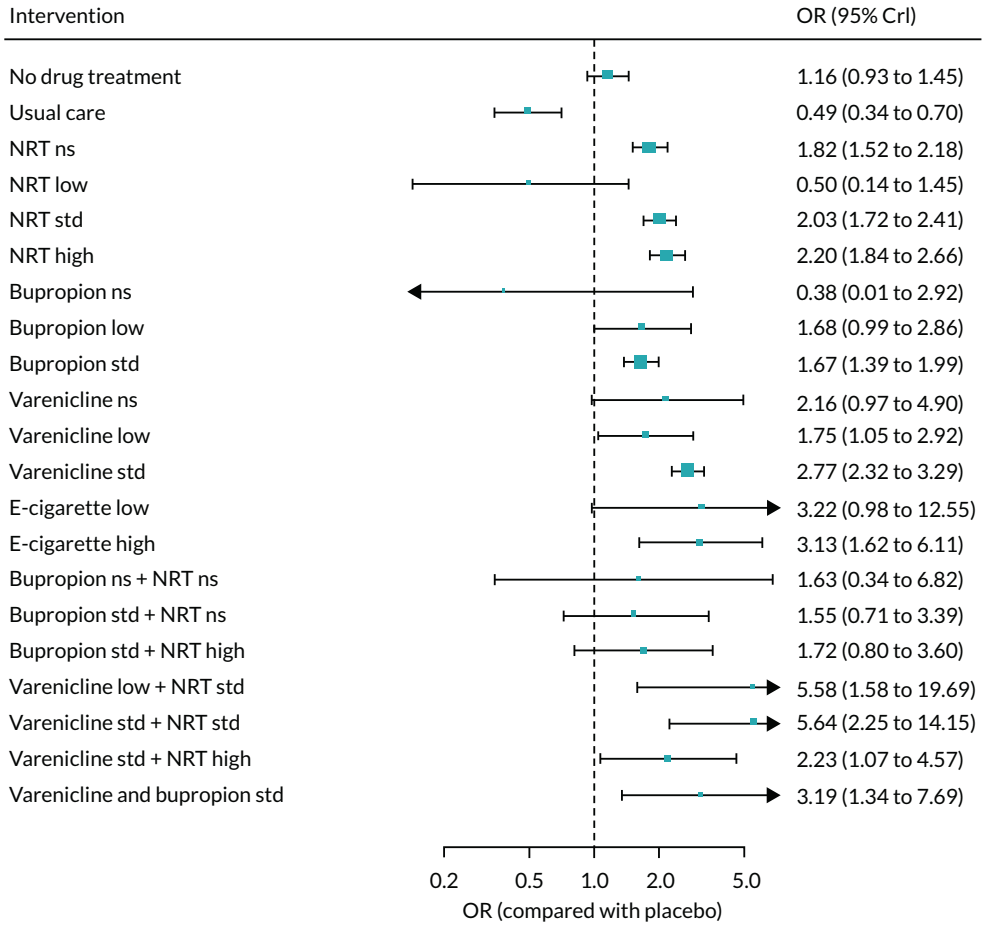

FIGURE 53 Forest plot with fixed-class NMA model results for sustained abstinence adjusted for publication year. Ns, not specified; std, standard.

Prolonged abstinence

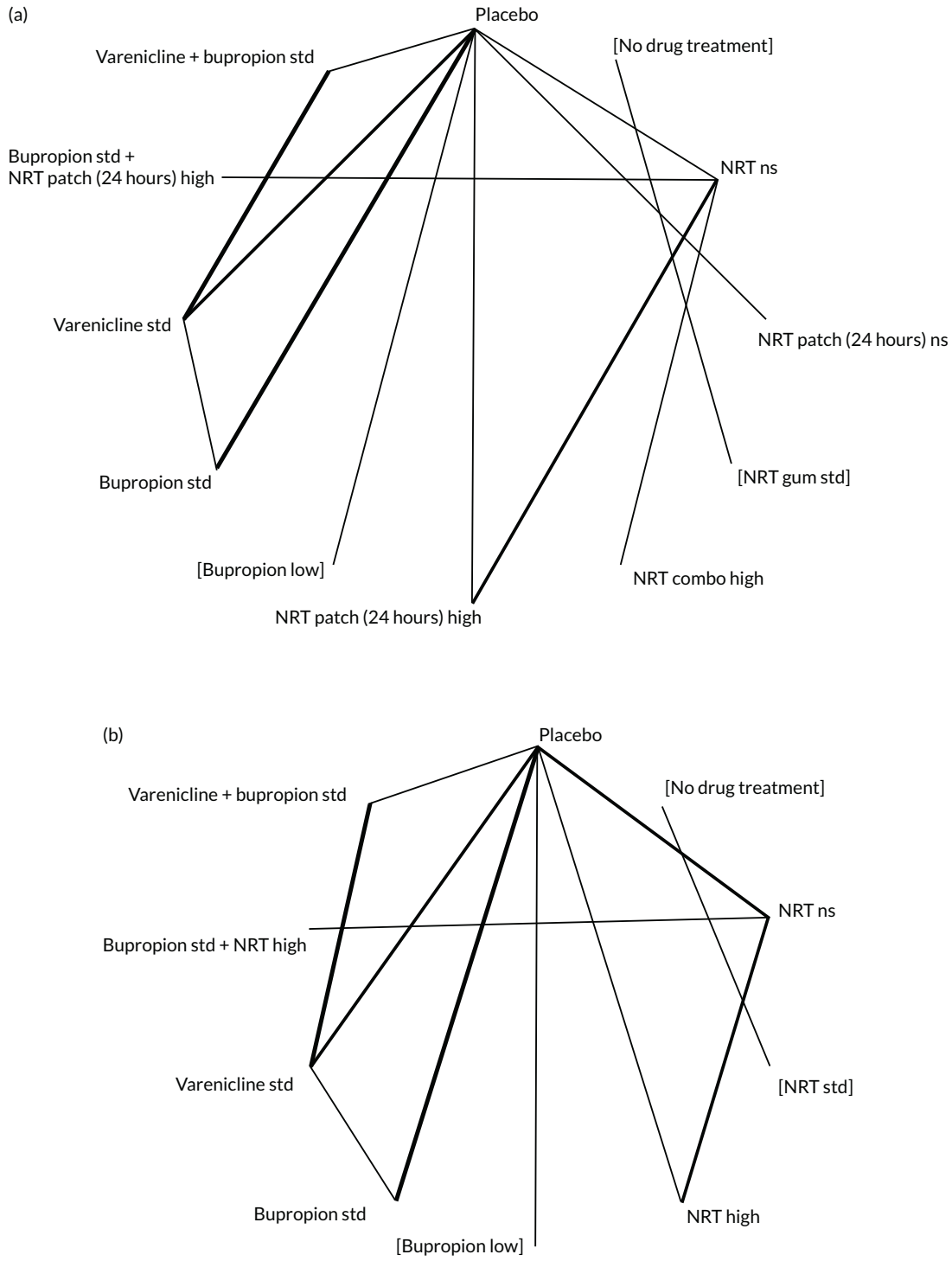

FIGURE 54 Network plots for prolonged abstinence at (a) treatment and (b) class level. Squared brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

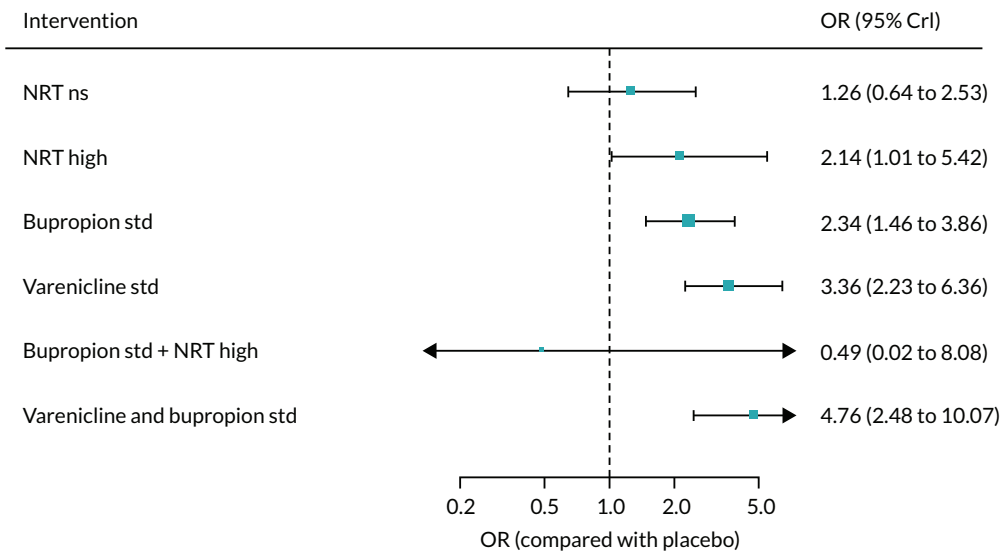

FIGURE 55 Forest plot with results of the fixed-class NMA model for prolonged abstinence. Ns, not specified; std, standard. This figure has been adapted with permission from Thomas *et al.*[67] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by/4.0/. The figure includes minor additions and formatting changes to the original figure.

TABLE 40 Results for prolonged abstinence: comparisons with placebo

	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
NRT not specified	1.31 (0.53 to 3.29)	1.18 (0.38 to 3.67)	1.26 (0.64 to 2.53)
NRT high	2.18 (0.43 to 11.0)	2.12 (0.79 to 5.69)	2.14 (1.01 to 5.42)
Bupropion standard	2.39 (1.31 to 4.39)	2.26 (1.03 to 4.95)	2.34 (1.46 to 3.86)
Varenicline standard	3.67 (1.93 to 7.17)	3.56 (1.42 to 8.94)	3.63 (2.23 to 6.36)
Bupropion standard plus NRT high	–	0.49 (0.02 to 8.08)	0.49 (0.02 to 8.08)
Varenicline standard plus bupropion standard	5.05 (1.75 to 24.1)	4.64 (2.00 to 10.8)	4.76 (2.48 to 10.1)

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TABLE 41 Results for prolonged abstinence: pairwise comparisons of interventions

	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Varenicline standard vs. bupropion standard	–	1.57 (0.86 to 2.92)	1.57 (0.86 to 2.92)
Varenicline standard plus bupropion standard vs. bupropion standard	–	2.03 (0.97 to 4.61)	2.03 (0.97 to 4.61)
Varenicline standard plus bupropion standard vs. varenicline standard	1.39 (0.49 to 3.94)	1.28 (0.71 to 2.33)	1.31 (0.80 to 2.26)

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TABLE 42 Comparison of different NMA models for prolonged abstinence (32 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	30.0	182.8	0.18 (0.01 to 0.69)	–
Random-class model, consistency	29.5	182.6	0.18 (0.01 to 0.7)	1.33 (0.07 to 4.58)
Fixed-class model, consistency	32.0	182.9	0.18 (0.01 to 0.71)	–
Fixed-class model, inconsistency	32.2	186.7	0.30 (0.01 to 1.05)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.

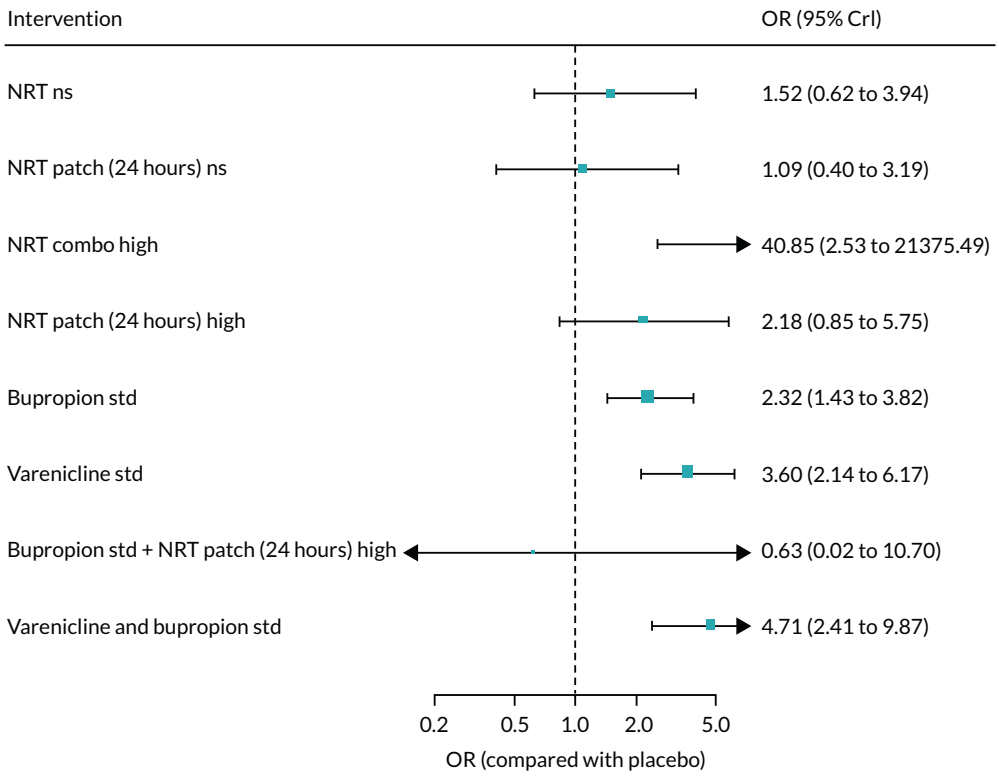

FIGURE 56 Forest plot with full interaction NMA model results for prolonged abstinence. Ns, not specified; std, standard.

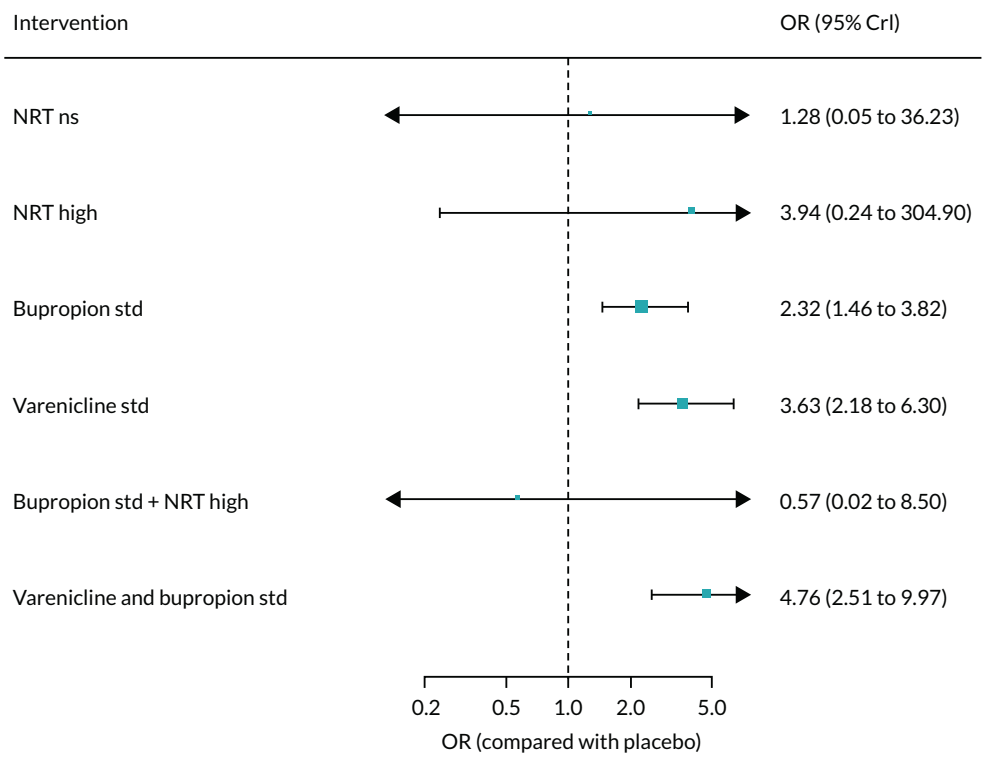

FIGURE 57 Forest plot with random-class NMA model results for prolonged abstinence. Ns, not specified; std, standard.

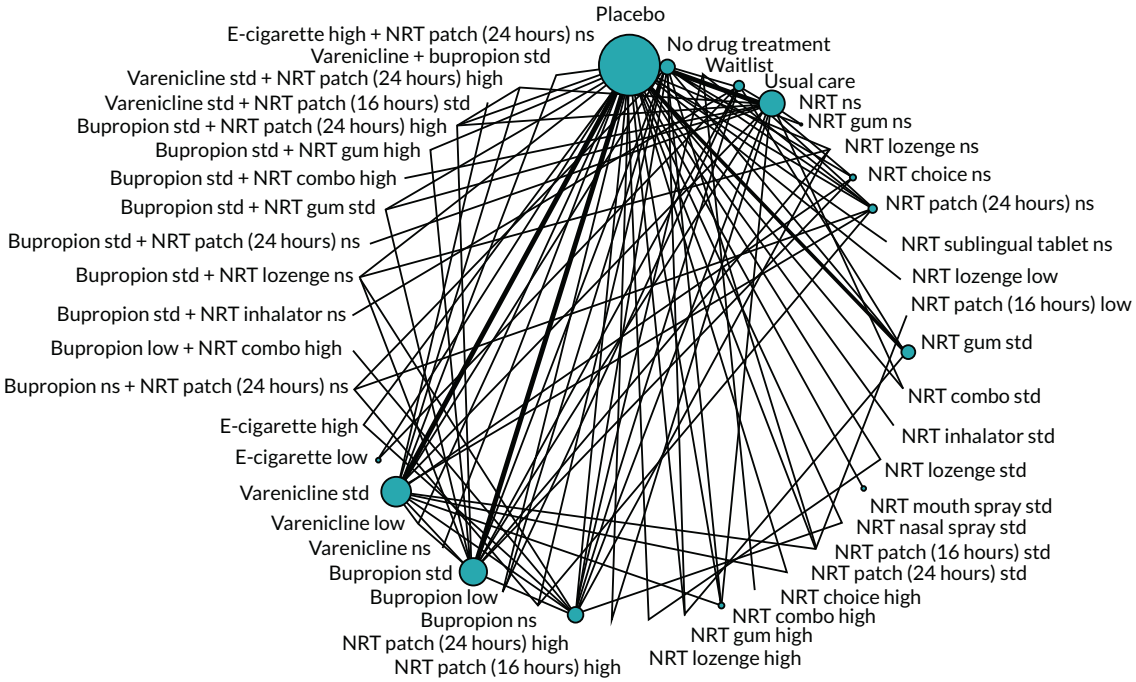

FIGURE 58 Network plot for any abstinence at treatment level. Ns, not specified; std, standard.

TABLE 43 Results for any abstinence: comparisons with placebo

Intervention	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	1.01 (0.58 to 1.75)	1.61 (1.24 to 2.09)	1.48 (1.19 to 1.86)
Waitlist	–	1.09 (0.51 to 2.29)	1.09 (0.51 to 2.29)
Usual care	0.93 (0.47 to 1.82)	0.58 (0.37 to 0.90)	0.66 (0.46 to 0.96)
NRT not specified	1.93 (1.60 to 2.36)	1.57 (1.05 to 2.35)	1.86 (1.57 to 2.20)
NRT low	1.51 (0.61 to 3.86)	1.17 (0.26 to 5.20)	1.40 (0.63 to 3.06)
NRT standard	2.03 (1.72 to 2.44)	–	2.03 (1.72 to 2.44)
NRT high	2.39 (1.92 to 2.97)	2.84 (1.77 to 4.54)	2.46 (2.03 to 2.94)
Bupropion not specified	–	0.19 (0.01 to 1.43)	0.19 (0.01 to 1.43)
Bupropion low	5.58 (0.15 to 3041)	2.84 (1.31 to 6.15)	2.89 (1.34 to 6.23)
Bupropion standard	1.84 (1.57 to 2.16)	–	1.84 (1.57 to 2.16)
Varenicline not specified	4.06 (1.40 to 11.9)	–	4.06 (1.40 to 11.9)
Varenicline low	1.52 (0.84 to 2.75)	–	1.52 (0.84 to 2.75)
Varenicline standard	2.69 (2.27 to 3.19)	–	2.69 (2.27 to 3.19)
E-cigarette low	2.51 (0.78 to 9.12)	11.1 (0.81 to 153)	3.29 (1.13 to 10.8)
E-cigarette high	2.64 (0.88 to 7.85)	3.79 (0.24 to 59.1)	2.77 (1.01 to 7.69)
Bupropion not specified plus NRT not specified	–	1.12 (0.24 to 4.44)	1.12 (0.24 to 4.44)
Bupropion low plus NRT high	–	5.75 (1.79 to 19.1)	5.75 (1.79 to 19.1)
Bupropion standard plus NRT not specified	1.88 (0.87 to 4.06)	2.36 (1.07 to 5.18)	2.10 (1.22 to 3.60)
Bupropion standard plus NRT standard	1.48 (0.61 to 3.63)	0.74 (0.01 to 51.7)	1.43 (0.60 to 3.46)
Bupropion standard plus NRT high	2.48 (1.39 to 4.48)	2.70 (1.23 to 5.91)	2.56 (1.60 to 4.14)
Varenicline standard plus NRT standard	–	5.53 (2.12 to 14.4)	5.53 (2.12 to 14.4)
Varenicline standard plus NRT high	–	2.36 (1.12 to 4.90)	2.36 (1.12 to 4.90)
Varenicline standard plus bupropion standard	3.32 (1.28 to 8.94)	3.78 (1.52 to 9.38)	3.56 (1.84 to 6.89)
E-cigarette high plus NRT not specified	–	4.76 (0.62 to 47.8)	4.76 (0.62 to 47.8)

TABLE 44 Results for any abstinence: pairwise comparisons of interventions

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	–	0.90 (0.72 to 1.13)	0.90 (0.72 to 1.13)
Varenicline standard vs. NRT standard	–	1.32 (1.05 to 1.65)	1.32 (1.05 to 1.65)
E-cigarette low vs. NRT standard	–	1.60 (0.55 to 5.38)	1.60 (0.55 to 5.38)
E-cigarette high vs. NRT standard	–	1.35 (0.49 to 3.76)	1.35 (0.49 to 3.76)
Bupropion standard plus NRT standard vs. NRT standard	–	0.71 (0.29 to 1.72)	0.71 (0.29 to 1.72)
Varenicline standard plus NRT standard vs. NRT standard	–	2.70 (1.02 to 7.13)	2.70 (1.02 to 7.13)
Varenicline standard plus bupropion standard vs. NRT standard	–	1.75 (0.88 to 3.45)	1.75 (0.88 to 3.45)
Varenicline standard vs. bupropion standard	–	1.46 (1.18 to 1.81)	1.46 (1.18 to 1.81)
E-cigarette low vs. bupropion standard	–	1.78 (0.61 to 5.95)	1.78 (0.61 to 5.95)

continued

TABLE 44 Results for any abstinence: pairwise comparisons of interventions (*continued*)

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
E-cigarette high vs. bupropion standard	–	1.50 (0.54 to 4.19)	1.50 (0.54 to 4.19)
Bupropion standard plus NRT standard vs. bupropion standard	–	0.78 (0.33 to 1.89)	0.78 (0.33 to 1.89)
Varenicline standard plus NRT standard vs. bupropion standard	–	2.99 (1.13 to 7.88)	2.99 (1.13 to 7.88)
Varenicline standard plus bupropion standard vs. bupropion standard	–	1.93 (0.98 to 3.79)	1.93 (0.98 to 3.79)
E-cigarette low vs. varenicline standard	–	1.22 (0.42 to 4.07)	1.22 (0.42 to 4.07)
E-cigarette high vs. varenicline standard	–	1.03 (0.37 to 2.86)	1.03 (0.37 to 2.86)
Bupropion standard plus NRT standard vs. varenicline standard	–	0.53 (0.22 to 1.30)	0.53 (0.22 to 1.30)
Varenicline standard plus NRT standard vs. varenicline standard	2.05 (0.80 to 5.25)	–	2.05 (0.80 to 5.25)
Varenicline standard plus bupropion standard vs. varenicline standard	1.50 (0.70 to 3.27)	0.95 (0.28 to 3.21)	1.32 (0.69 to 2.52)
E-cigarette high vs. e-cigarette low	–	0.84 (0.18 to 3.69)	0.84 (0.18 to 3.69)
Bupropion standard plus NRT standard vs. e-cigarette low	–	0.44 (0.10 to 1.74)	0.44 (0.10 to 1.74)
Varenicline standard plus NRT standard vs. e-cigarette low	–	1.67 (0.37 to 6.99)	1.67 (0.37 to 6.99)
Varenicline standard plus bupropion standard vs. e-cigarette low	–	1.08 (0.28 to 3.82)	1.08 (0.28 to 3.82)
Bupropion standard plus NRT standard vs. e-cigarette high	–	0.52 (0.14 to 1.98)	0.52 (0.14 to 1.98)
Varenicline standard plus NRT standard vs. e-cigarette high	–	2.00 (0.49 to 8.02)	2.00 (0.49 to 8.02)
Varenicline standard plus bupropion standard vs. e-cigarette high	–	1.29 (0.38 to 4.27)	1.29 (0.38 to 4.27)
Varenicline standard plus NRT standard vs. bupropion standard plus NRT standard	–	3.83 (1.05 to 14.0)	3.83 (1.05 to 14.0)
Varenicline standard plus bupropion standard vs. bupropion standard plus NRT standard	–	2.48 (0.83 to 7.34)	2.48 (0.83 to 7.34)
Varenicline standard plus bupropion standard vs. varenicline standard plus NRT standard	–	0.65 (0.21 to 2.04)	0.65 (0.21 to 2.04)

TABLE 45 Comparison of different NMA models for any abstinence (431 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	428.6	2720	0.42 (0.35 to 0.50)	–
Random-class model, consistency	426.7	2711	0.14 (0.35 to 0.48)	0.14 (0.01 to 0.31)
Fixed-class model, consistency	426.1	2710	0.42 (0.36 to 0.50)	–
Fixed-class model, inconsistency	443.9	2723	0.34 (0.27 to 0.41)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.

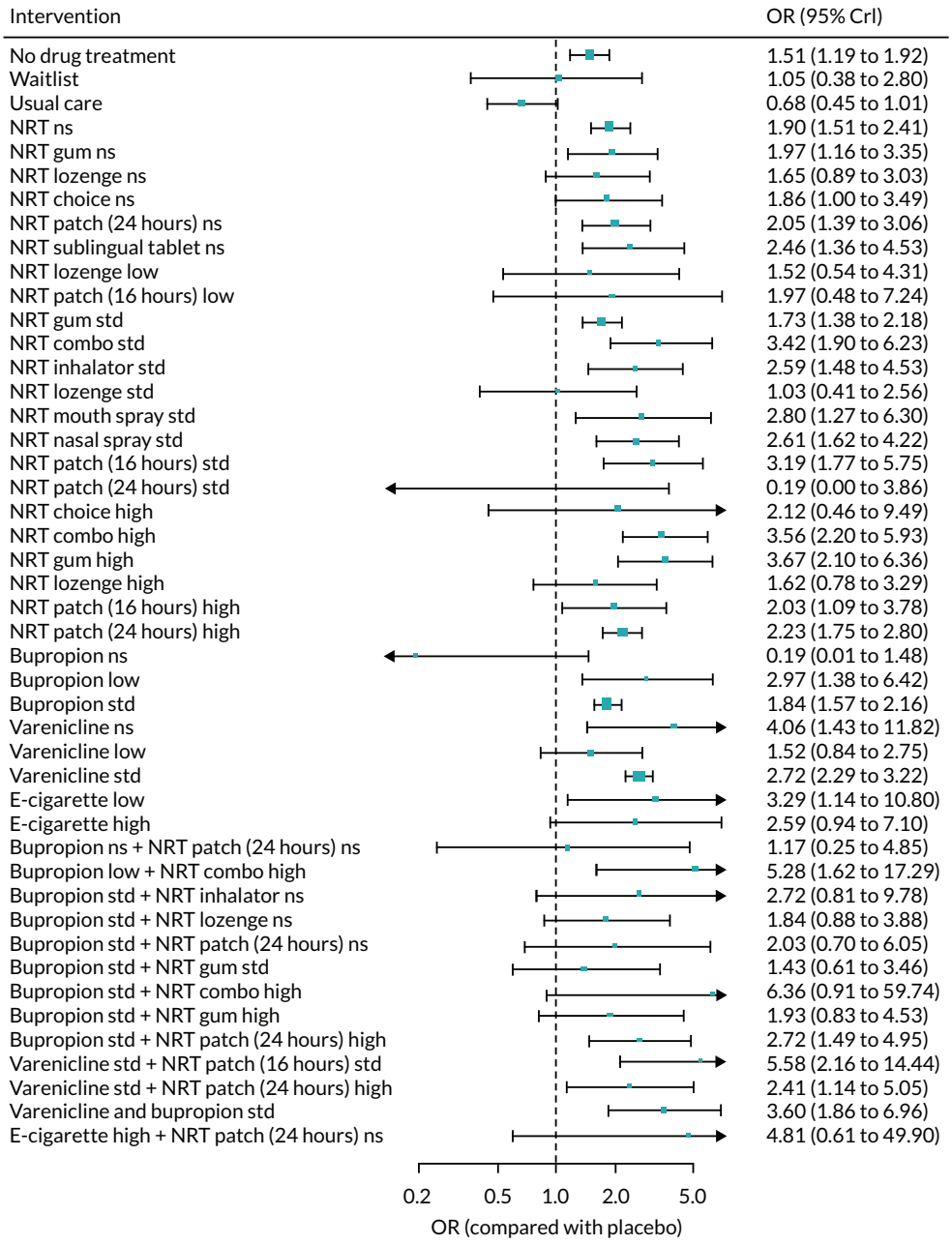

FIGURE 59 Forest plot with full interaction NMA model results for any abstinence. Ns, not specified; std, standard.

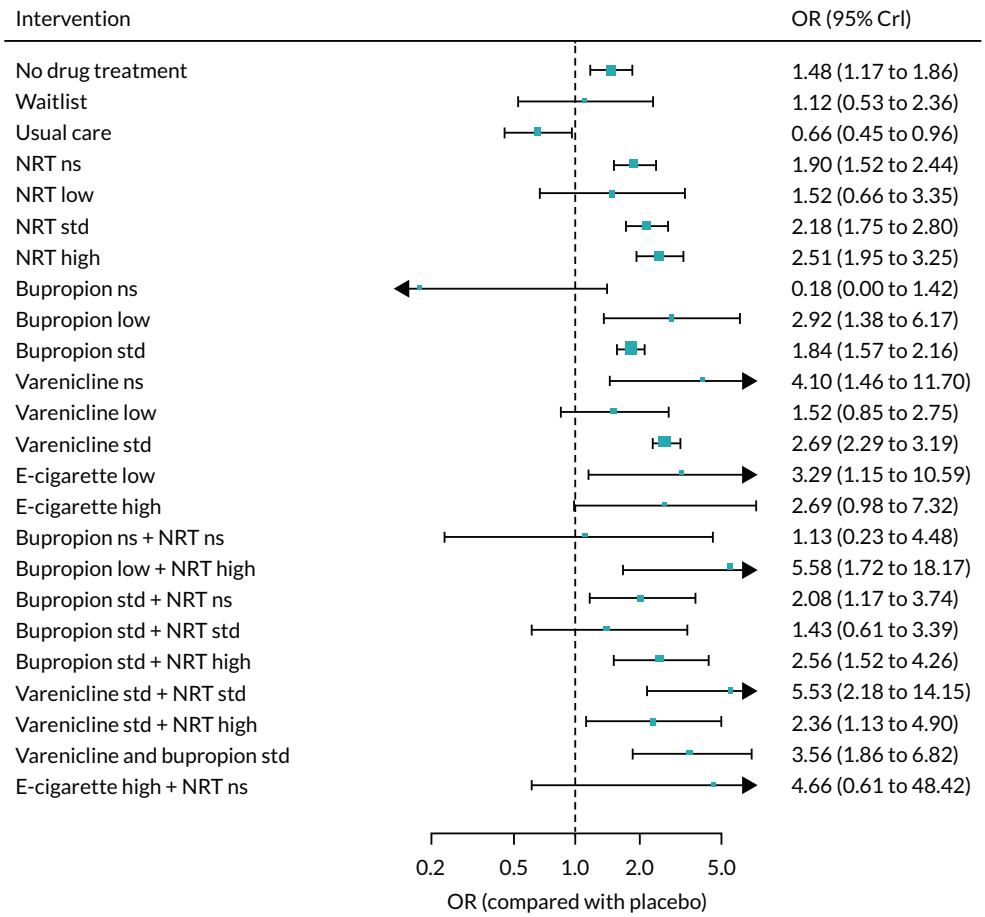

FIGURE 60 Forest plot with random-class NMA model results for any abstinence. Ns, not specified; std, standard.

Seven-day point prevalence abstinence

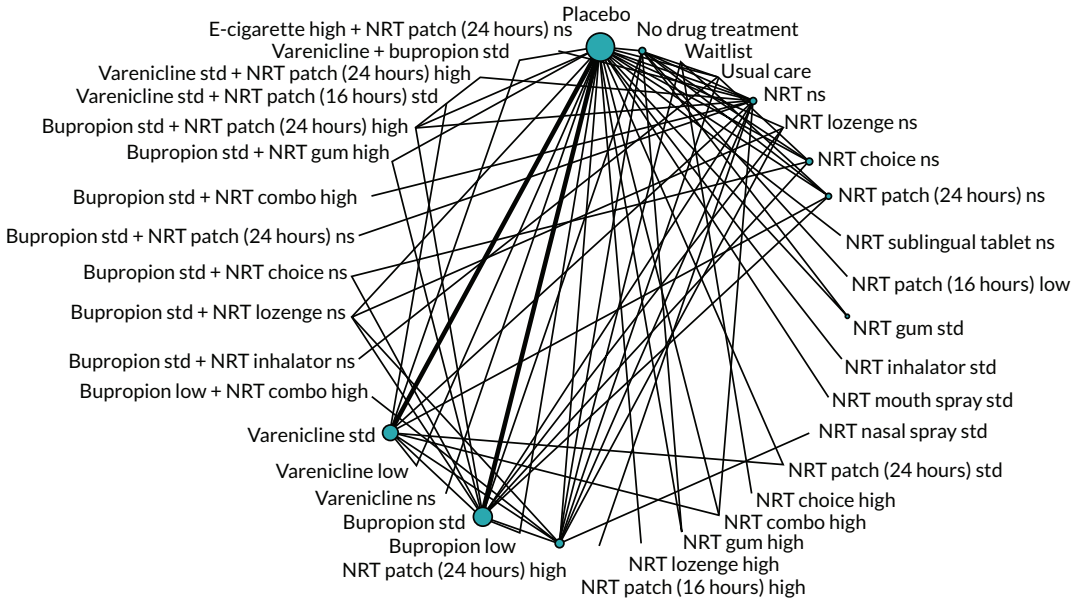

FIGURE 61 Network plot for 7-day PPA at treatment level. Ns, not specified; std, standard.

TABLE 46 Results for PPA: comparisons with placebo

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
No drug treatment	1.02 (0.64 to 1.62)	1.18 (0.87 to 1.61)	1.13 (0.87 to 1.45)
Waitlist	–	0.98 (0.53 to 1.79)	0.98 (0.53 to 1.79)
Usual care	0.84 (0.15 to 3.32)	1.10 (0.67 to 1.80)	1.07 (0.66 to 1.72)
NRT not specified	1.60 (1.22 to 2.12)	1.87 (1.48 to 2.35)	1.75 (1.48 to 2.08)
NRT low	–	1.48 (0.70 to 3.13)	1.48 (0.70 to 3.13)
NRT standard	1.58 (1.21 to 2.12)	–	1.58 (1.21 to 2.12)
NRT high	2.20 (1.73 to 2.80)	1.75 (1.34 to 2.29)	1.99 (1.67 to 2.39)
Bupropion low	1.21 (0.78 to 1.90)	–	1.21 (0.78 to 1.90)
Bupropion standard	1.67 (1.48 to 1.88)	–	1.67 (1.48 to 1.88)
Varenicline not specified	2.56 (1.21 to 5.42)	–	2.56 (1.21 to 5.42)
Varenicline low	1.70 (0.90 to 3.19)	2.18 (0.40 to 11.8)	1.75 (0.97 to 3.13)
Varenicline standard	2.14 (1.86 to 2.46)	–	2.14 (1.86 to 2.46)
Bupropion low plus NRT high	–	4.76 (1.82 to 12.7)	4.76 (1.82 to 12.7)
Bupropion standard plus NRT not specified	1.77 (1.01 to 3.13)	1.87 (1.29 to 2.73)	1.84 (1.35 to 2.53)
Bupropion standard plus NRT high	2.46 (1.57 to 3.90)	1.91 (1.24 to 2.96)	2.16 (1.57 to 2.97)
Varenicline standard plus NRT standard	–	4.01 (2.16 to 7.54)	4.01 (2.16 to 7.54)
Varenicline standard plus NRT high	–	2.14 (0.91 to 4.85)	2.14 (0.91 to 4.85)
Varenicline plus bupropion standard	1.75 (0.90 to 3.53)	2.79 (1.58 to 4.90)	2.29 (1.48 to 3.56)
E-cigarette high plus NRT not specified	–	4.10 (0.63 to 37.7)	4.10 (0.63 to 37.7)

TABLE 47 Results for PPA: pairwise comparisons of interventions

Comparison	Direct evidence, OR (95% CrI)	Indirect evidence, OR (95% CrI)	NMA, OR (95% CrI)
Bupropion standard vs. NRT standard	–	1.05 (0.78 to 1.41)	1.05 (0.78 to 1.41)
Varenicline standard vs. NRT standard	–	1.35 (0.99 to 1.82)	1.35 (0.99 to 1.82)
Varenicline standard plus NRT standard vs. NRT standard	–	2.54 (1.28 to 4.98)	2.54 (1.28 to 4.98)
Varenicline plus bupropion standard vs. NRT standard	–	1.44 (0.86 to 2.42)	1.44 (0.86 to 2.42)
Varenicline standard vs. bupropion standard	–	1.28 (1.08 to 1.53)	1.28 (1.08 to 1.53)
Varenicline standard plus NRT standard vs. bupropion standard	–	2.42 (1.28 to 4.57)	2.42 (1.28 to 4.57)
Varenicline plus bupropion standard vs. bupropion standard	–	1.38 (0.88 to 2.17)	1.38 (0.88 to 2.17)
Varenicline standard plus NRT standard vs. varenicline standard	1.88 (1.02 to 3.46)	–	1.88 (1.02 to 3.46)
Varenicline plus bupropion standard vs. varenicline standard	1.40 (0.79 to 2.49)	0.81 (0.44 to 1.46)	1.07 (0.70 to 1.63)
Varenicline plus bupropion standard vs. varenicline standard plus NRT standard	–	0.57 (0.27 to 1.20)	0.57 (0.27 to 1.20)

TABLE 48 Comparison of different NMA models for 7-day PPA (265 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	272.3	1672	0.23 (0.14 to 0.33)	–
Random-class model, consistency	275.0	1663	0.22 (0.13 to 0.31)	0.12 (0.01 to 0.34)
Fixed-class model, consistency	274.8	1662	0.23 (0.15 to 0.32)	–
Fixed-class model, inconsistency	276.0	1671	0.21 (0.12 to 0.31)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.

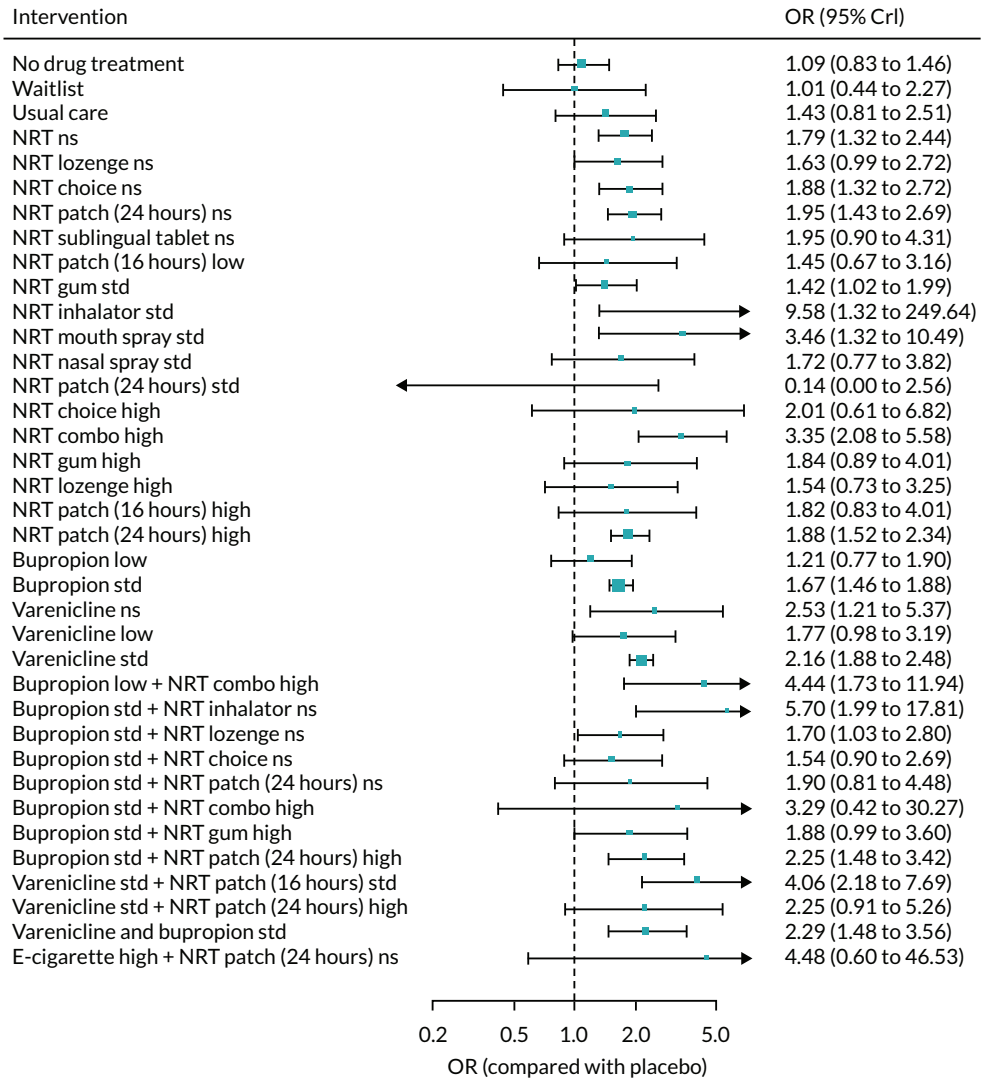

FIGURE 62 Forest plot with full interaction NMA model results for 7-day PPA. Ns, not specified; std, standard.

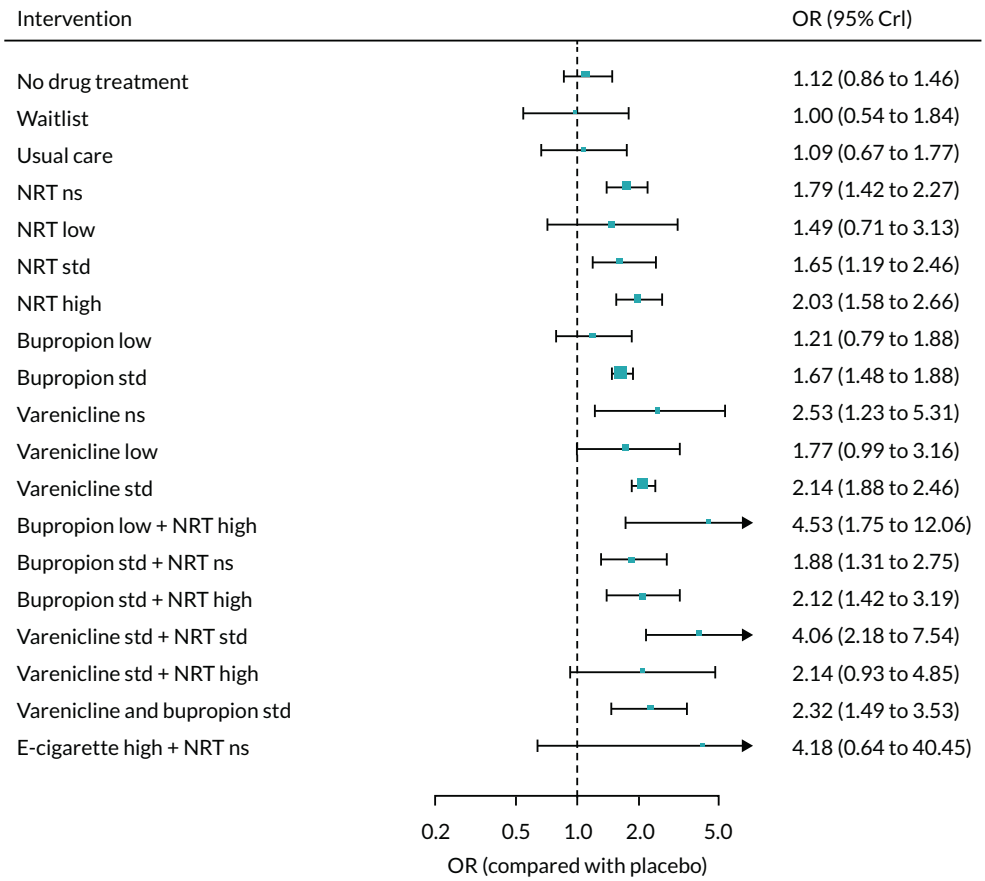

FIGURE 63 Forest plot with random-class NMA model results for 7-day PPA. Ns, not specified; std, standard.

Appendix 6 Threshold analyses

List of treatment codes

Treatment classes in bold are the subset used for ranking and threshold analysis.

1. **Placebo.**
2. No drug treatment.
3. Waitlist.
4. Usual care.
5. NRT not specified.
6. NRT low.
7. **NRT standard.**
8. NRT high.
9. Bupropion not specified.
10. Bupropion low.
11. **Bupropion standard.**
12. Varenicline not specified.
13. Varenicline low.
14. **Varenicline standard.**
15. Varenicline high.
16. E-cigarette not specified.
17. **E-cigarette low.**
18. **E-cigarette high.**
19. Bupropion not specified plus NRT not specified.
20. Bupropion low plus NRT high.
21. Bupropion standard plus NRT not specified.
22. Bupropion standard plus NRT standard.
23. Bupropion standard plus NRT high.
24. Varenicline low plus NRT standard.
25. Null.
26. **Varenicline standard plus NRT standard.**
27. Varenicline standard plus NRT high.
28. **Varenicline plus bupropion standard.**
29. E-cigarette high plus NRT not specified.

Appendix 7 Primary and secondary safety outcome analyses

TABLE 49 List and frequency of treatments delivered in randomised trials included in safety analyses

Treatment	Frequency
Bupropion low	9
Bupropion low plus NRT combination high	1
Bupropion not specified plus NRT choice not specified	1
Bupropion standard	79
Bupropion standard plus NRT choice not specified	1
Bupropion standard plus NRT combination high	1
Bupropion standard plus NRT gum not specified	4
Bupropion standard plus NRT gum standard	1
Bupropion standard plus NRT inhalator not specified	1
Bupropion standard plus NRT lozenge not specified	2
Bupropion standard plus NRT patch (24 hours) high	8
E-cigarette high	3
E-cigarette high plus NRT patch (24 hours) not specified	1
E-cigarette low	5
E-cigarette not specified	1
No drug treatment	40
NRT choice not specified	20
NRT choice standard	1
NRT combination high	7
NRT combination not specified	9
NRT combination standard	6
NRT gum high	10
NRT gum not specified	8
NRT gum standard	28
NRT inhalator standard	7
NRT lozenge high	8
NRT lozenge low	2
NRT lozenge not specified	9
NRT lozenge standard	4
NRT mouth spray standard	2
NRT nasal spray not specified	1
NRT nasal spray standard	6

continued

TABLE 49 List and frequency of treatments delivered in randomised trials included in safety analyses (*continued*)

Treatment	Frequency
NRT not specified	52
NRT patch (16 hours) high	1
NRT patch (16 hours) low	5
NRT patch (16 hours) not specified	1
NRT patch (16 hours) standard	15
NRT patch (24 hours) high	61
NRT patch (24 hours) low	1
NRT patch (24 hours) not specified	30
NRT patch (24 hours) standard	1
NRT sublingual tablet not specified	4
Placebo	244
Usual care	23
Varenicline standard plus bupropion standard	4
Varenicline high	1
Varenicline low	13
Varenicline low plus NRT gum standard	1
Varenicline not specified	2
Varenicline standard	91
Varenicline standard plus NRT gum standard	1
Varenicline standard plus NRT patch (16 hours) standard	2
Varenicline standard plus NRT patch (24 hours) high	3
Waitlist	2

TABLE 50 List and frequency of treatments delivered in non-randomised studies included in safety analyses

Treatment	Frequency
Bupropion low	2
Bupropion not specified plus NRT choice not specified	2
Bupropion not specified	12
Bupropion standard plus NRT choice not specified	2
Bupropion standard plus NRT patch (24 hours) not specified	1
Bupropion standard plus NRT patch (24 hours) standard	1
Bupropion standard	4
Dual use standard	1
E-cigarette standard	1
No treatment	17
NRT choice not specified	12
NRT combination high	2
NRT combination not specified	4
NRT gum high	2
NRT gum not specified	2
NRT gum standard	2
NRT inhalator low	1
NRT inhalator not specified	1
NRT lozenge not specified	1
NRT not specified	8
NRT patch (16 hours) standard	2
NRT patch (24 hours) not specified	15
Usual care	1
Varenicline low	1
Varenicline not specified plus NRT choice not specified	1
Varenicline not specified	20
Varenicline standard plus bupropion standard	1
Varenicline standard plus NRT choice not specified	1
Varenicline standard plus NRT combination not specified	1
Varenicline standard	8

Serious adverse events

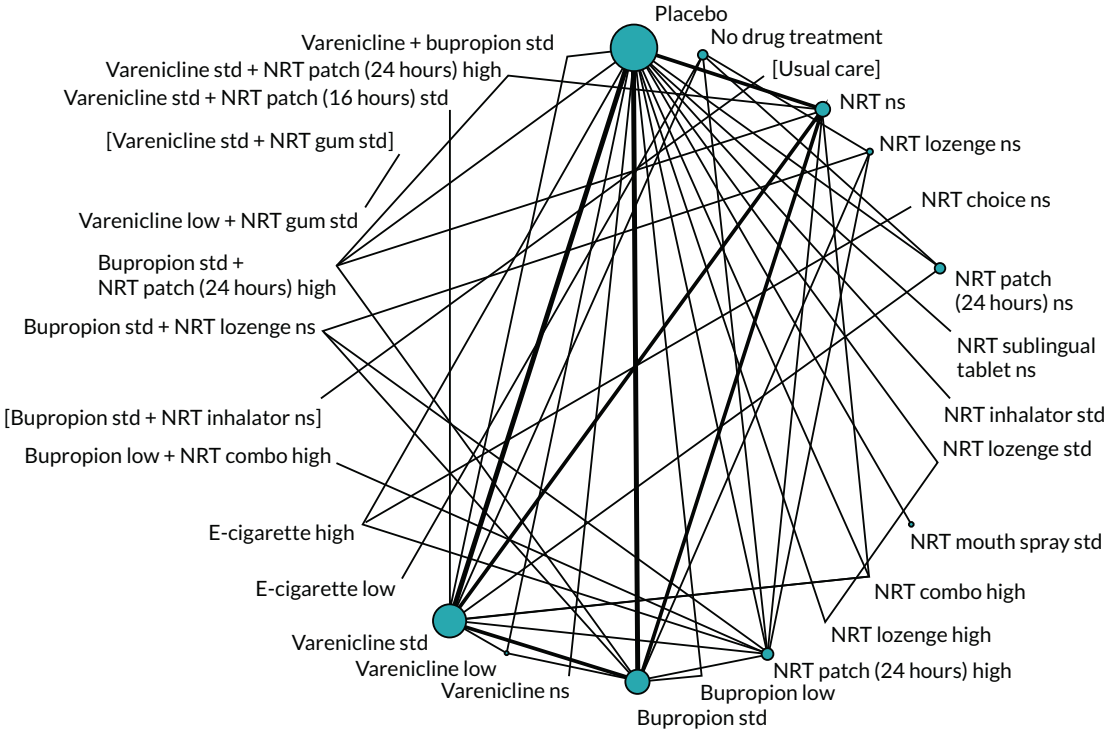

FIGURE 64 Network plot for SAEs at treatment level. Square brackets denote interventions that were excluded from the NMA. Ns, not specified; std, standard.

Incorporating non-randomised evidence

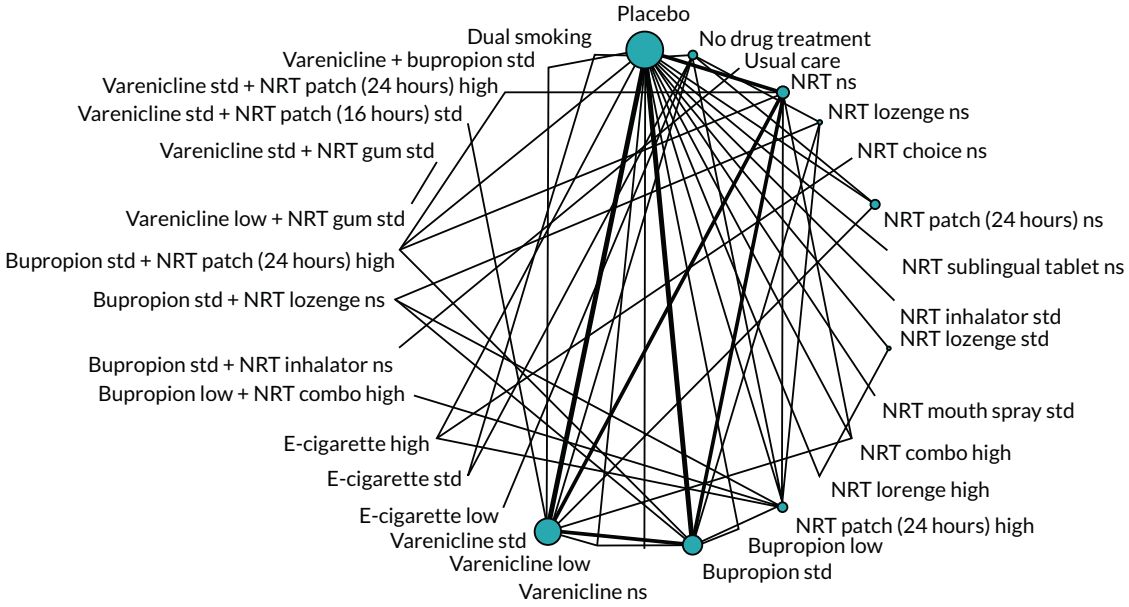

FIGURE 65 Network plot for SAEs incorporating non-randomised evidence at treatment level. Ns, not specified; std, standard.

TABLE 51 Comparison of different NMA models for serious AEs (219 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	207.1	1021	0.09 (0.01 to 0.29)	–
Random-class model, consistency	205.6	1014	0.07 (0 to 0.28)	0.2 (0.01 to 0.68)
Fixed-class model, consistency	205.8	1012	0.09 (0 to 0.28)	–
Fixed-class model, inconsistency	211.1	1027	0.09 (0.01 to 0.29)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.

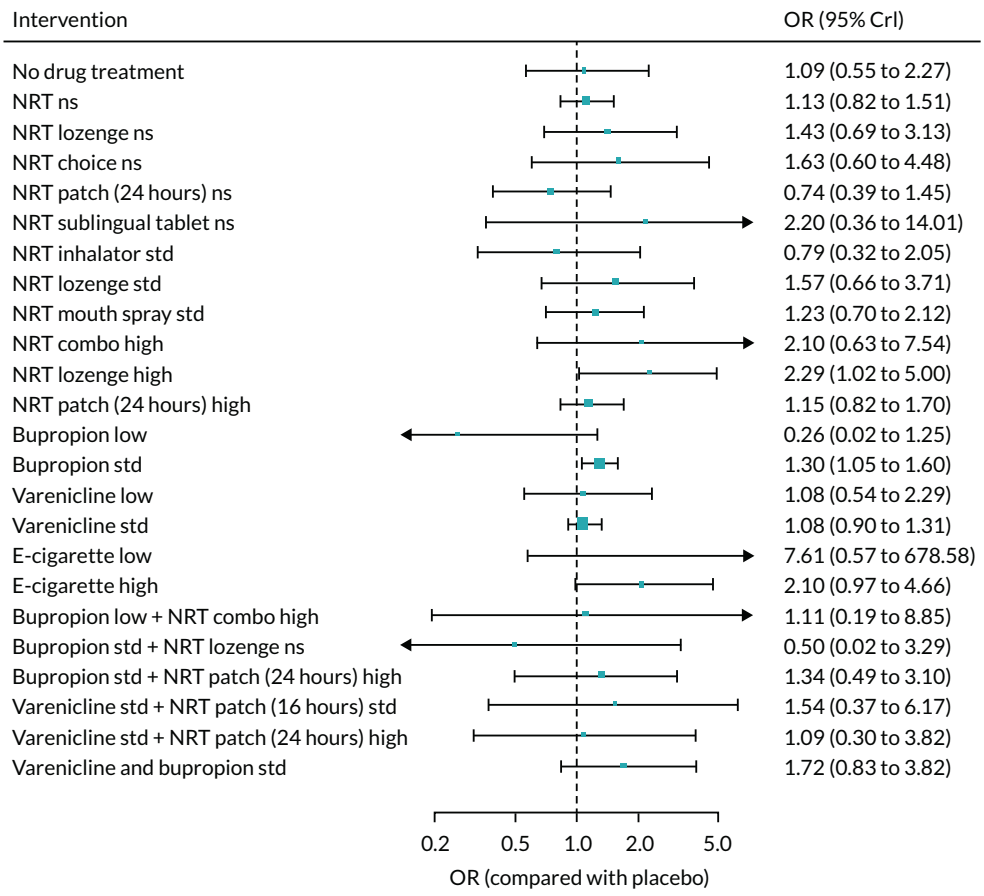

FIGURE 66 Forest plot with full interaction NMA model results for SAEs. Ns, not specified; std, standard.

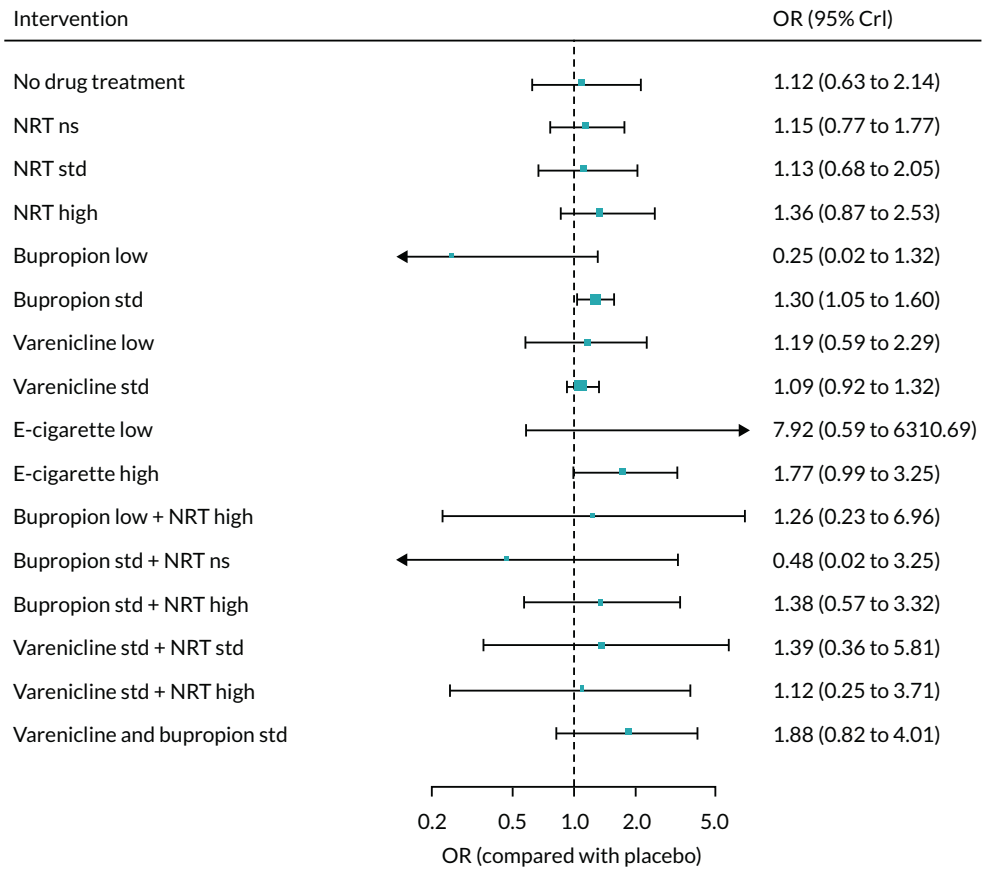

FIGURE 67 Forest plot with random-class NMA model results for SAEs. Ns, not specified; std, standard.

Sensitivity analyses

Analysis excluding studies at high risk of bias

This analysis was based on 76 studies. The estimate of the SD between class effects was 0.11 (0.01, 0.33).

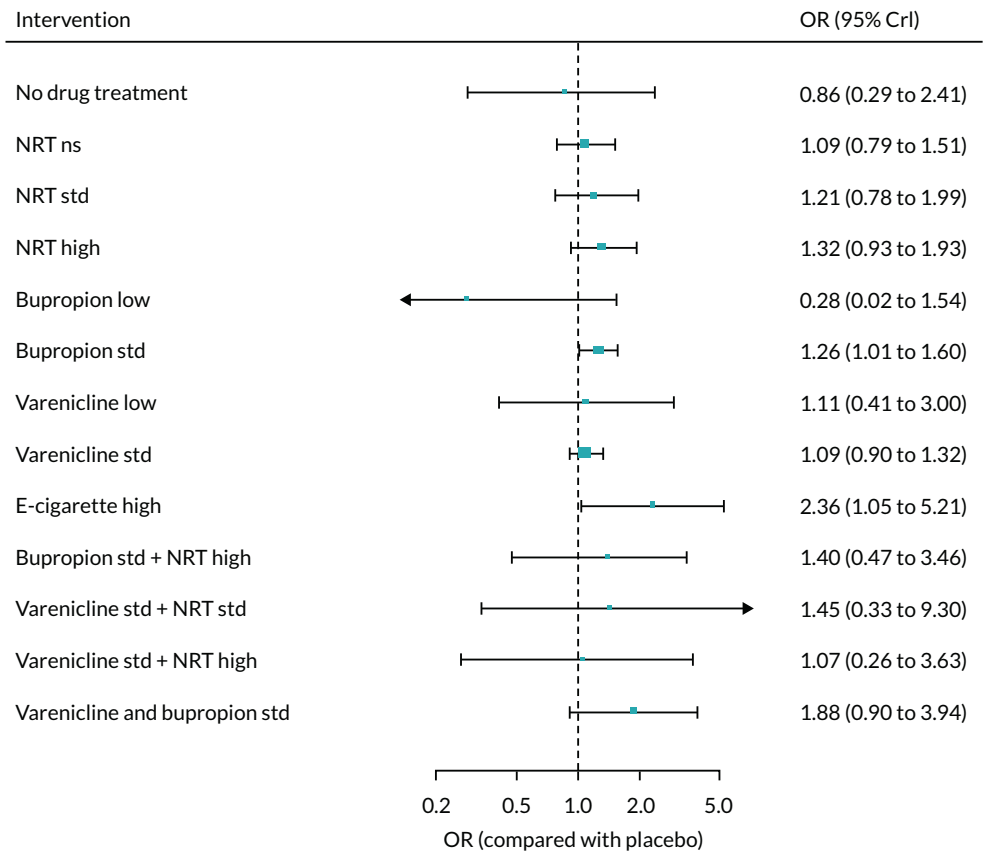

FIGURE 68 Forest plot with fixed-class NMA model results for SAEs without studies at high risk of bias. Ns, not specified; std, standard.

Sensitivity analysis excluding studies of pharmacological treatment plus counselling (if counselling is not given in all study arms)

This analysis was based on 97 studies. The estimate of the SD between class effects was 0.09 (0.01, 0.27), which is nearly identical to that for the main analysis.

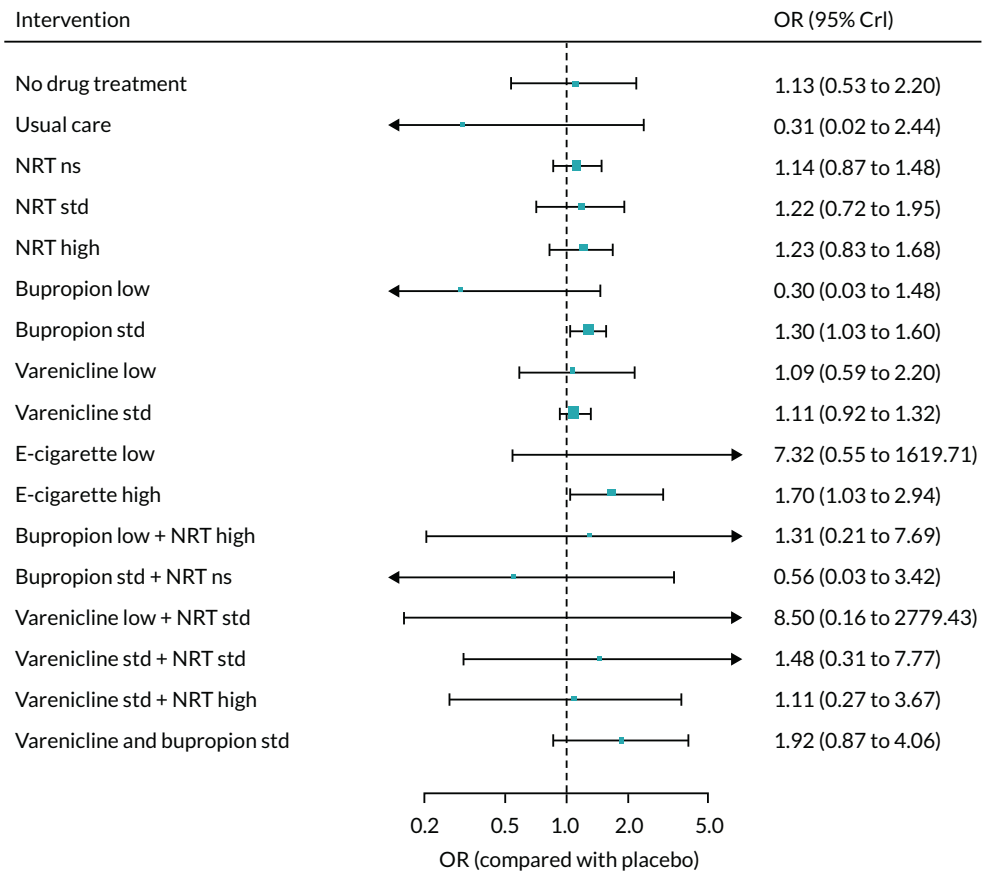

FIGURE 69 Forest plot with fixed-class NMA model results for SAEs without studies that include pharmacological treatment plus counselling (unless counselling included in all arms). Ns, not specified; std, standard.

Meta-regressions

Industry sponsorship as covariate

This analysis was based on 96 studies. There was inconclusive evidence of effect modification based on industry sponsorship (B = –0.87, –195.4 to 197.5). The estimate of the SD between class effects was 0.09 (0.00, 0.29).

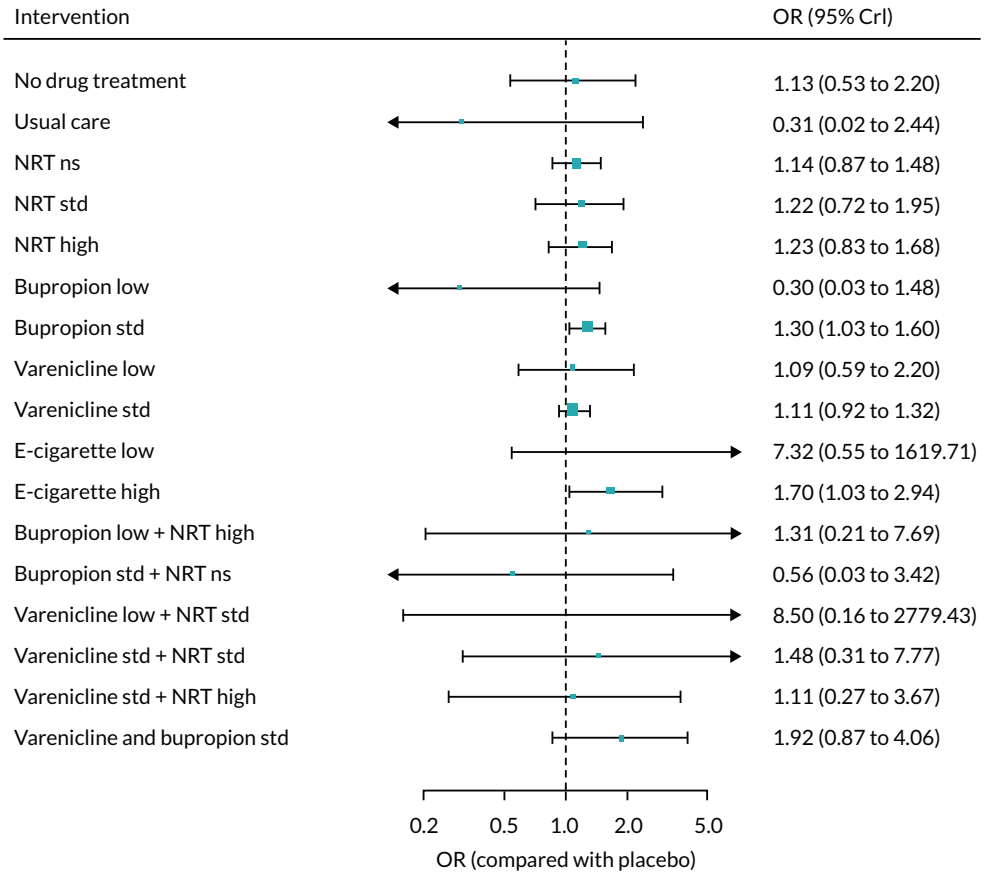

FIGURE 70 Forest plot with fixed-class NMA model results for SAEs adjusted for sponsorship. Ns, not specified; std, standard.

Placebo type as covariate

This analysis was based on 84 studies. There was inconclusive evidence of effect modification based on type of placebo (B = −0.23, −195.1 to 196.5). The estimate of the SD between class effects was 0.12 (0.01, 0.33).

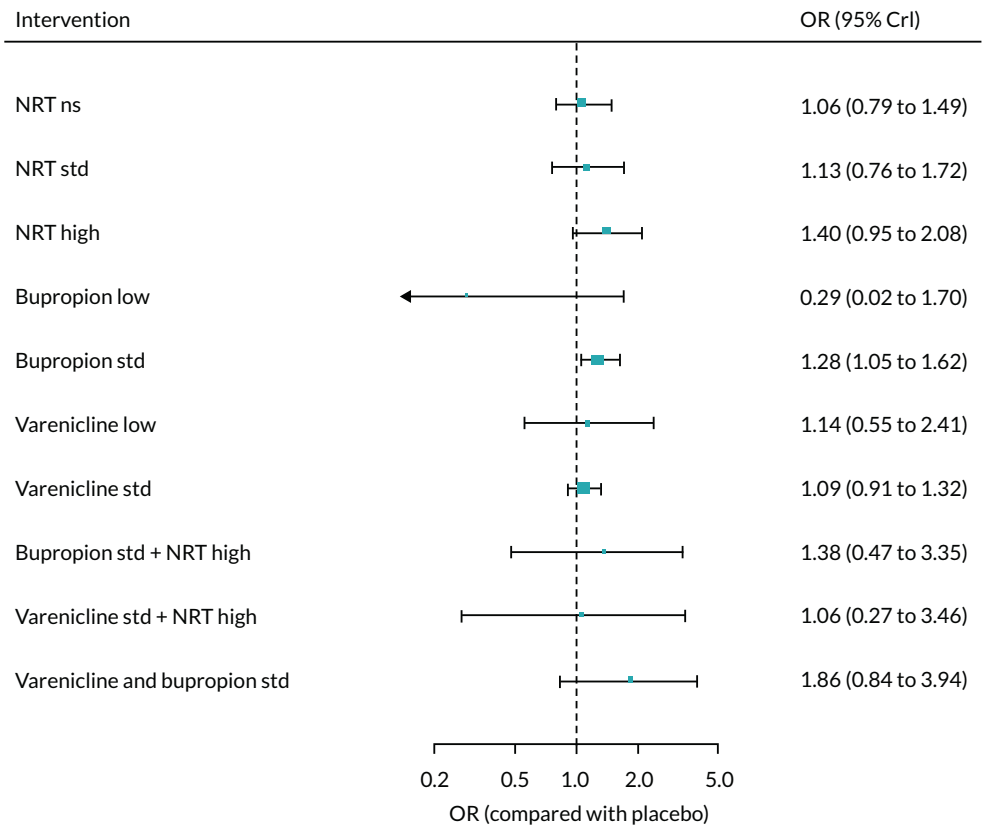

FIGURE 71 Forest plot with fixed-class NMA model results for SAEs adjusted for type of placebo. Ns, not specified; std, standard.

Treatment duration as covariate

This analysis was based on 98 studies. There was inconclusive evidence of effect modification as a function of treatment duration (B = 0.03, –0.04 to 0.10). The estimate of the SD between class effects was 0.16 (0.01, 0.58).

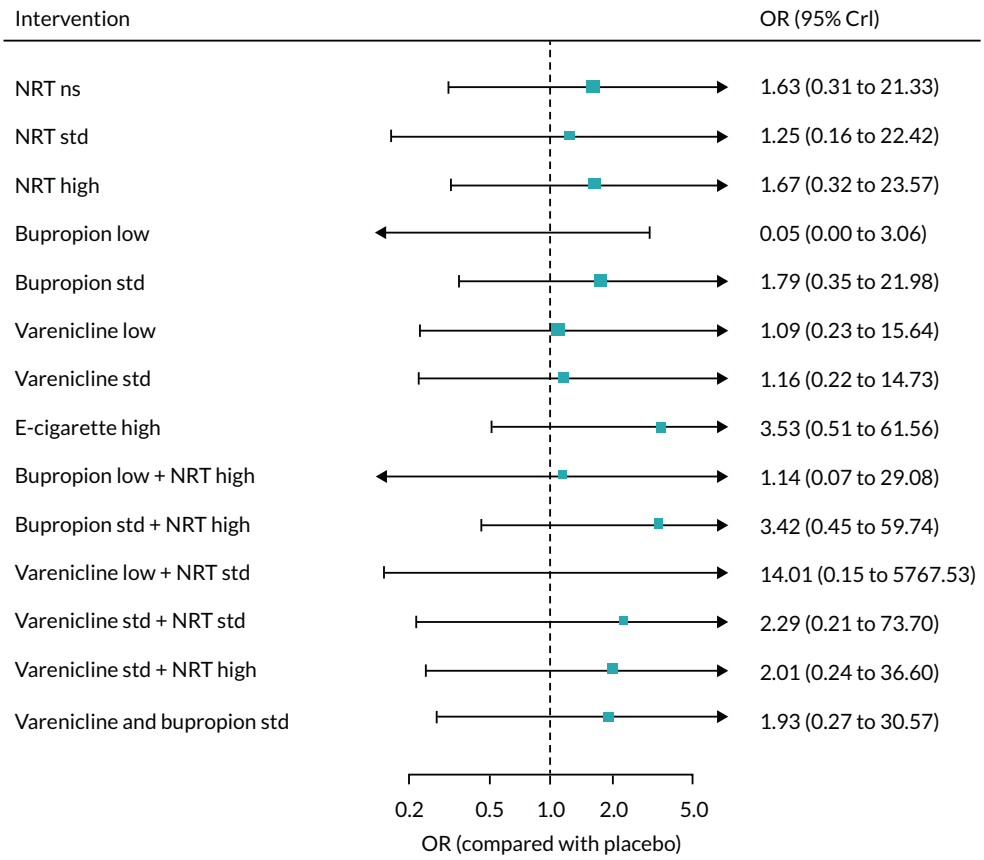

FIGURE 72 Forest plot with fixed-class NMA model results for SAEs adjusted for treatment duration. Ns, not specified; std, standard.

Counselling as covariate

This analysis was based on 101 studies. There was inconclusive evidence of effect modification as a function of counselling (B = –0.26, –2.29 to 1.75). The estimate of the SD between class effects was 0.11 (0, 0.28).

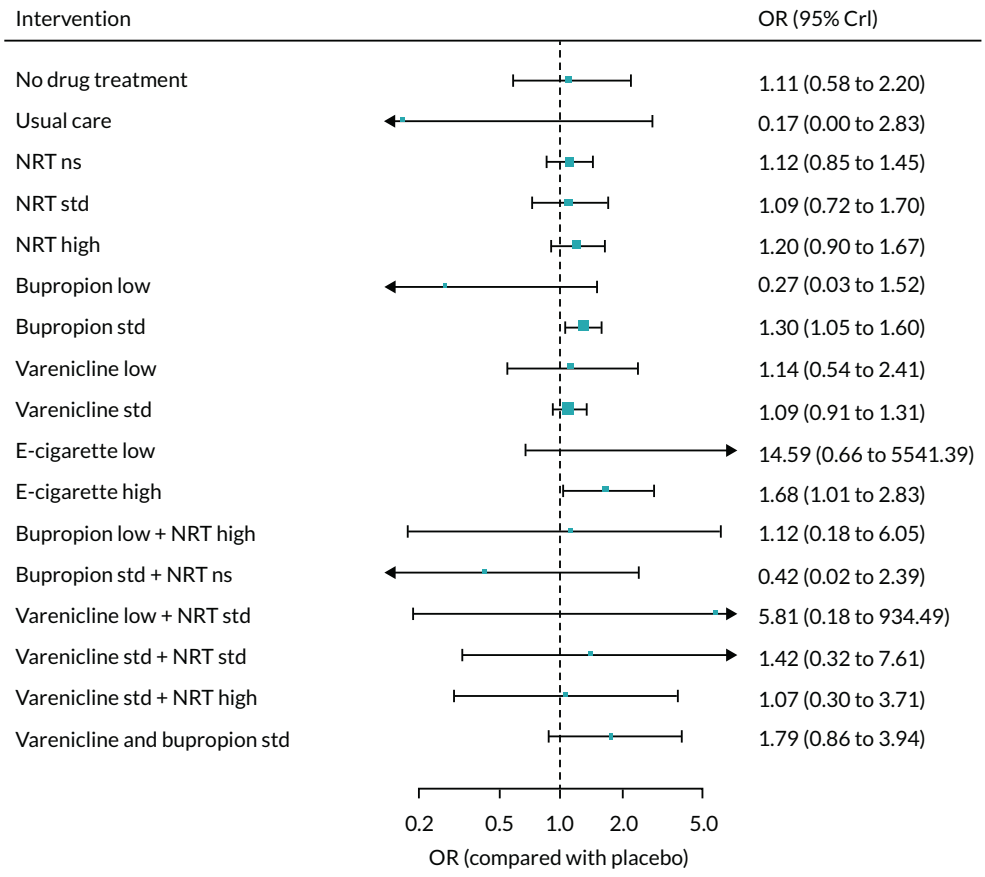

FIGURE 73 Forest plot with fixed-class NMA model results for SAEs adjusted for counselling. Ns, not specified; std, standard.

Dependence as covariate

This analysis was based on 70 studies. There was inconclusive evidence of effect modification as a function of dependence (B = 0.12, −0.28 to 0.47). The estimate of the SD between class effects was 0.09 (0.01, 0.31).

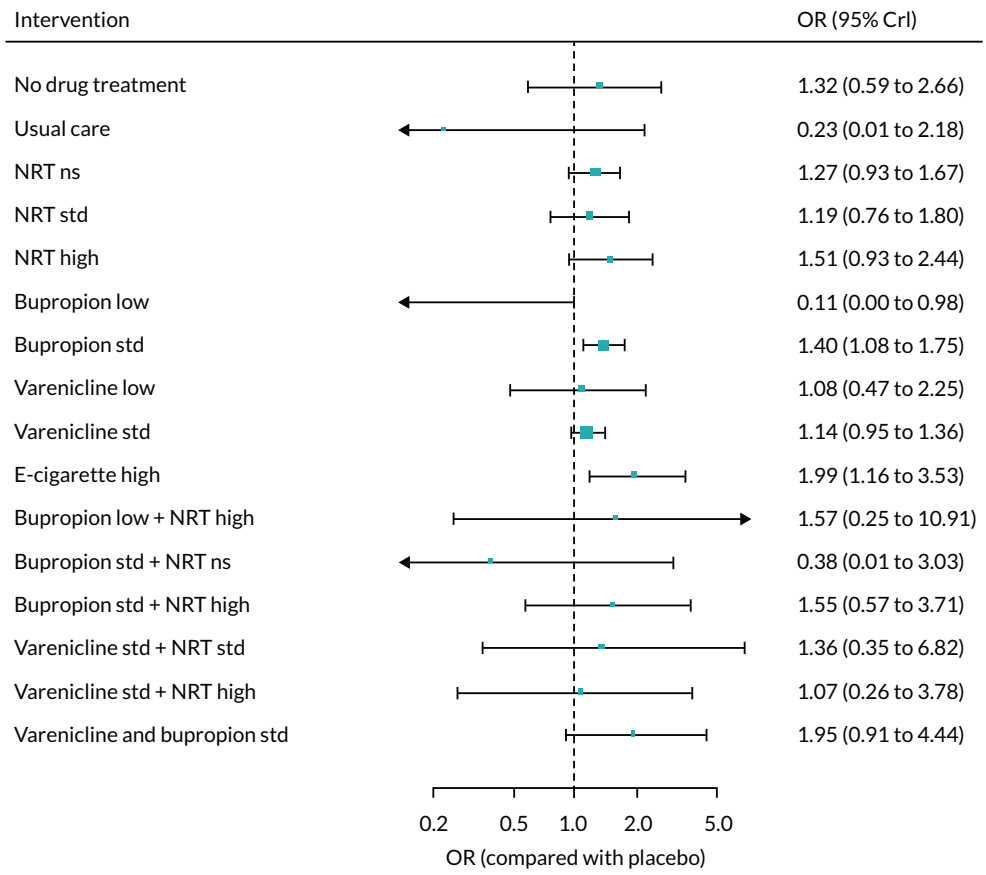

FIGURE 74 Forest plot with fixed-class NMA model results for SAEs adjusted for dependence. Ns, not specified; std, standard.

Comorbidities as covariate

This analysis was based on 101 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = –0.24, –196.8 to 195.1). The estimate of the SD between class effects was 0.09 (0.01, 0.28).

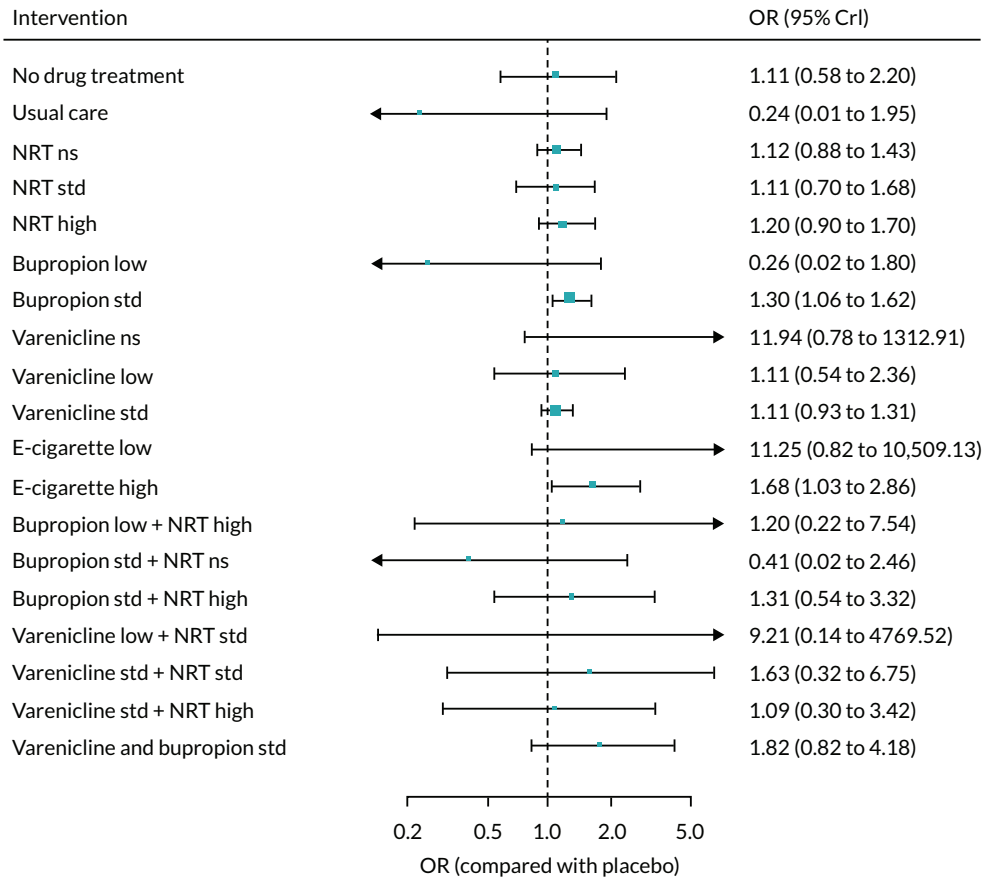

FIGURE 75 Forest plot with fixed-class NMA model results for SAEs adjusted for comorbidities. Ns, not specified; std, standard.

Psychiatric comorbidities as covariate

This analysis was based on 101 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = −0.24, −196.8 to 195.1). The estimate of the SD between class effects was 0.09 (0.01, 0.28).

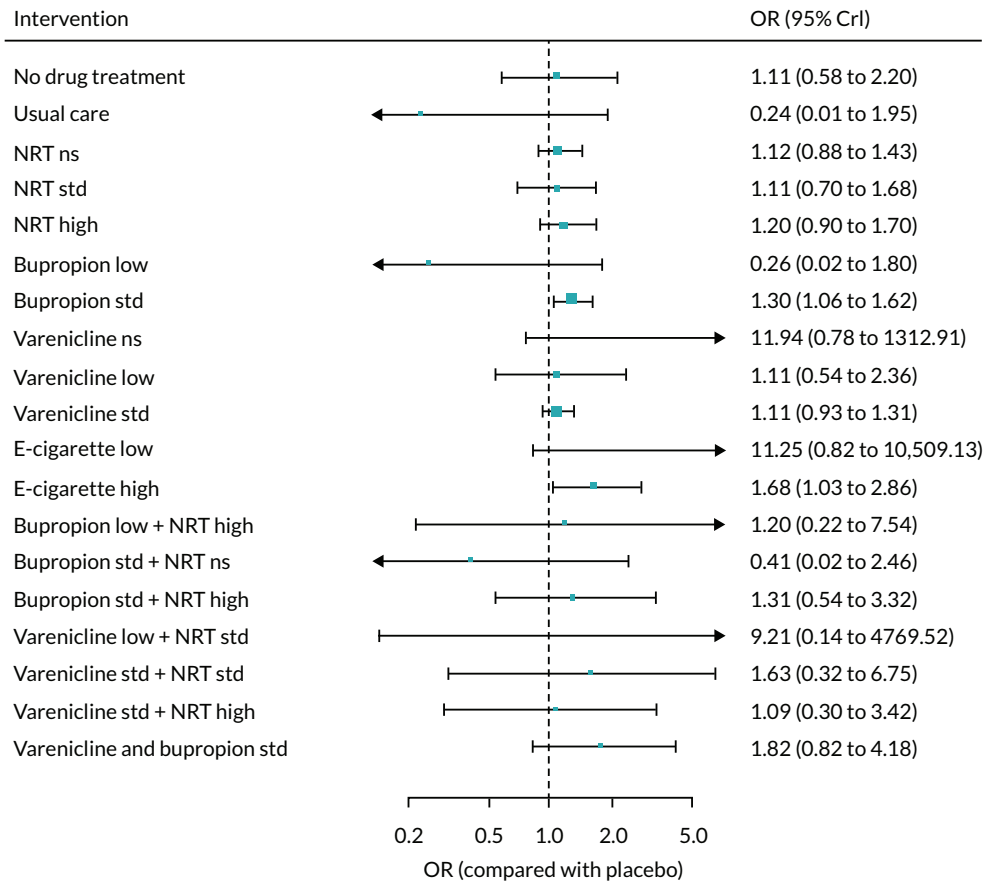

FIGURE 76 Forest plot with fixed-class NMA model results for SAEs adjusted for psychiatric comorbidities. Ns, not specified; std, standard.

Willingness to quit as covariate

This analysis was based on 101 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = –0.24, –196.8 to 195.1). The estimate of the SD between class effects was 0.09 (0.01, 0.28).

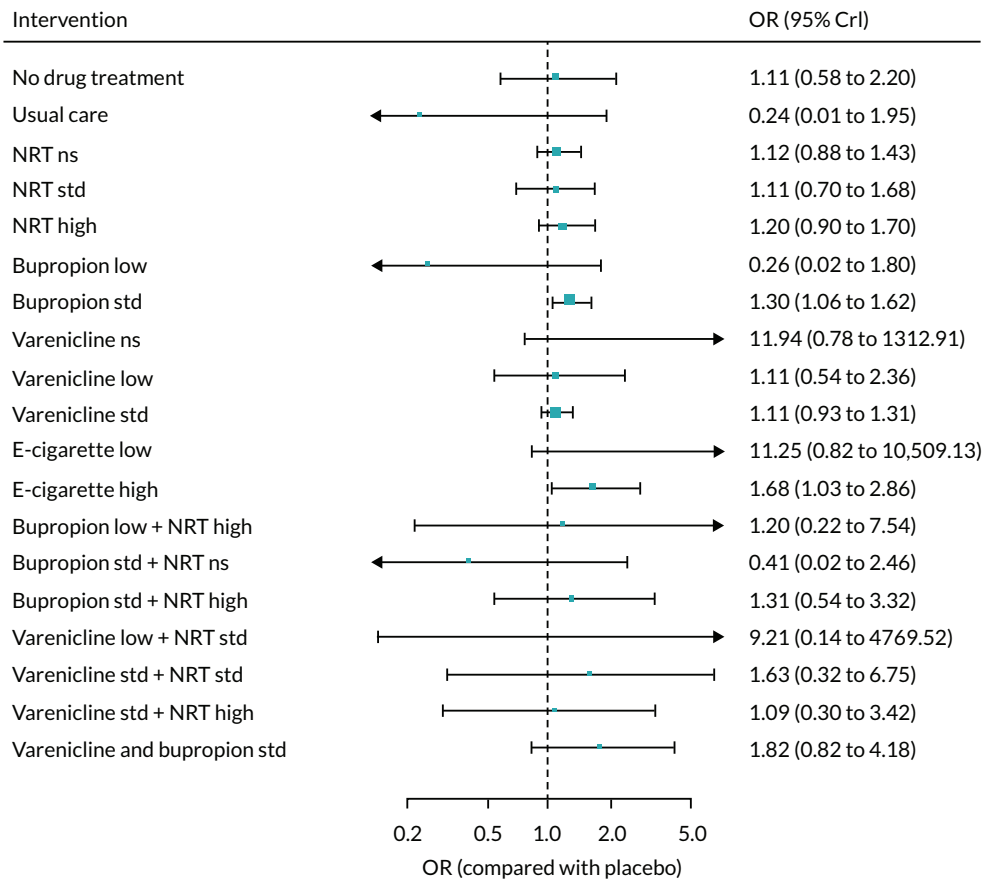

FIGURE 77 Forest plot with fixed-class NMA model results for SAEs adjusted for willingness to quit. Ns, not specified; std, standard.

Smokeless tobacco as covariate

This analysis was based on 101 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = −0.24, −196.8 to 195.1). The estimate of the SD between class effects was 0.09 (0.01, 0.28).

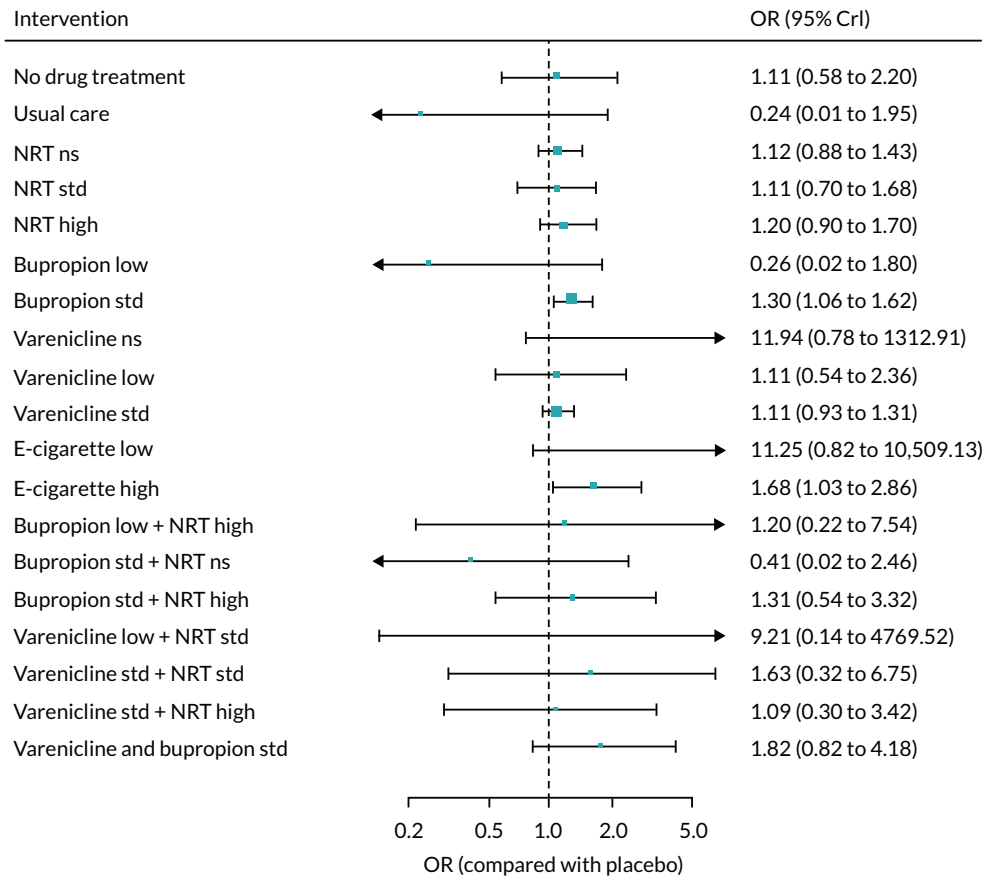

FIGURE 78 Forest plot with fixed-class NMA model results for SAEs adjusted for smokeless tobacco. Ns, not specified; std, standard.

Smoking level as covariate

This analysis was based on 78 studies. There was inconclusive evidence of effect modification as a function of the covariate (B = 0.01, –0.53 to 0.48). The estimate of the SD between class effects was 0.09 (0, 0.30).

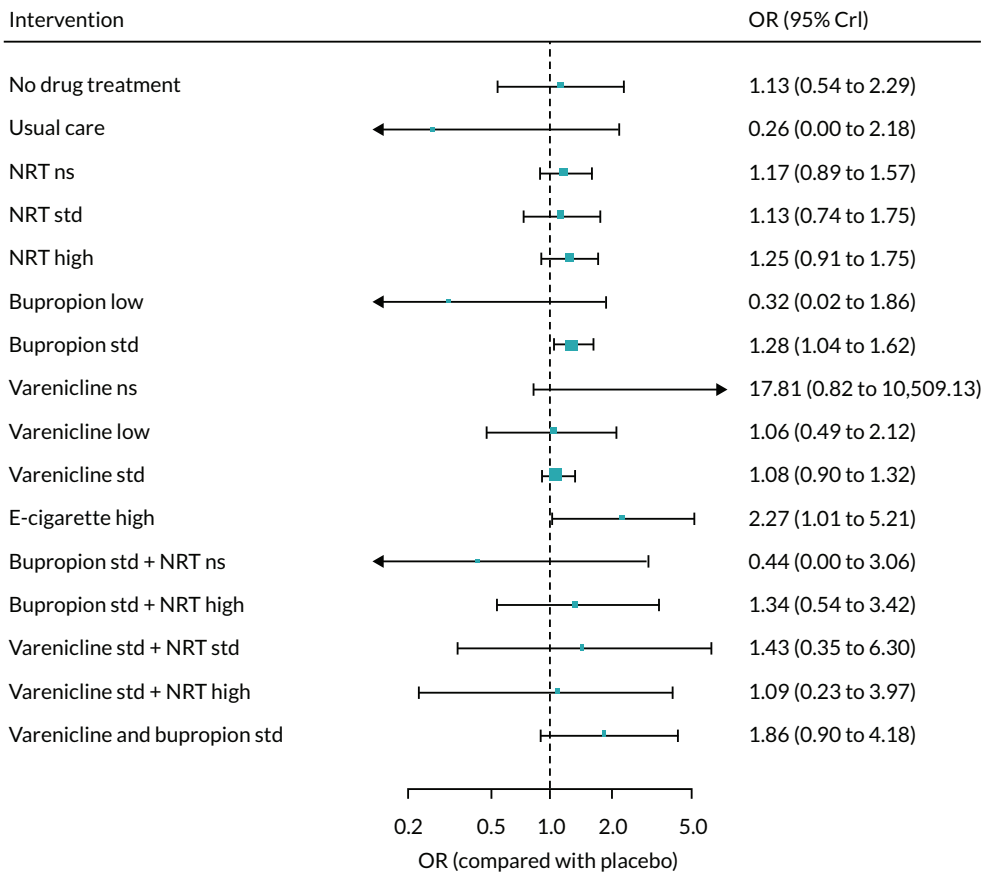

FIGURE 79 Forest plot with fixed-class NMA model results for SAEs adjusted for smoking level. Ns, not specified; std, standard.

Publication year as covariate

This analysis was based on 96 studies. There was inconclusive evidence of effect modification based on publication year (B = 0.14, −196.2 to 194.9). The estimate of the SD between class effects was 0.41 (0.01, 0.29).

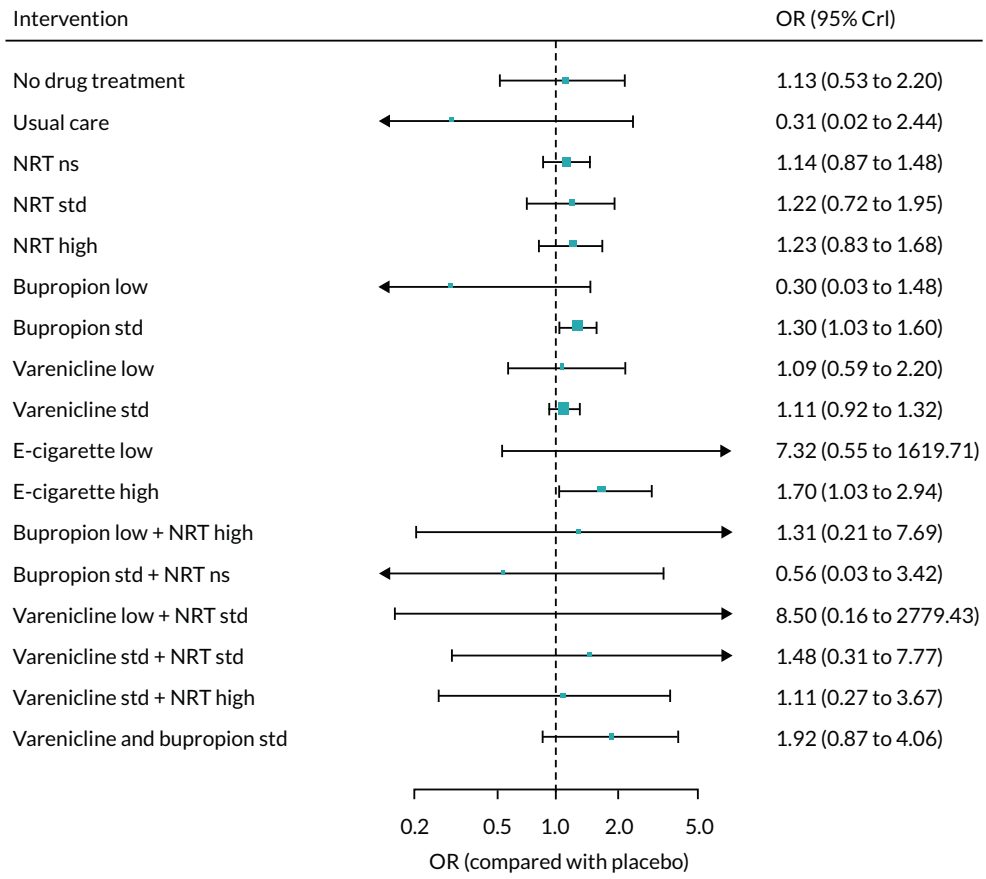

FIGURE 80 Forest plot with fixed-class NMA model results for SAEs adjusted for publication year. Ns, not specified; std, standard.

Major adverse cardiovascular events

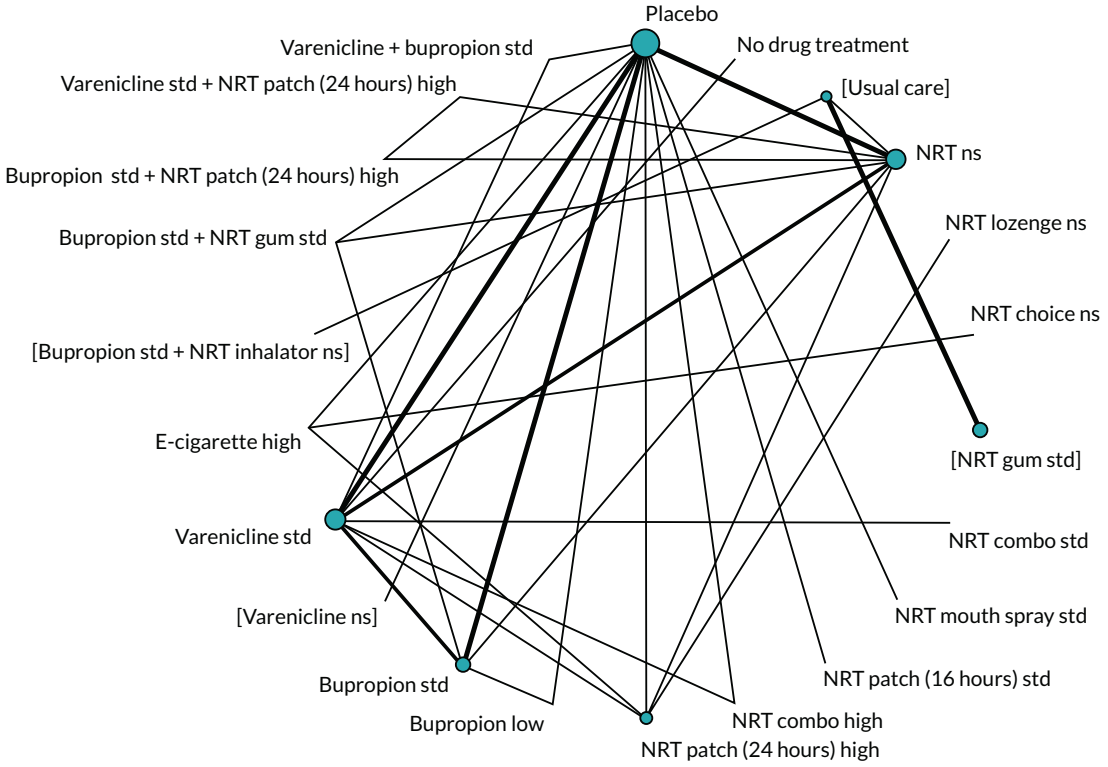

FIGURE 81 Network plot for major adverse cardiovascular events at treatment level. Square brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard.

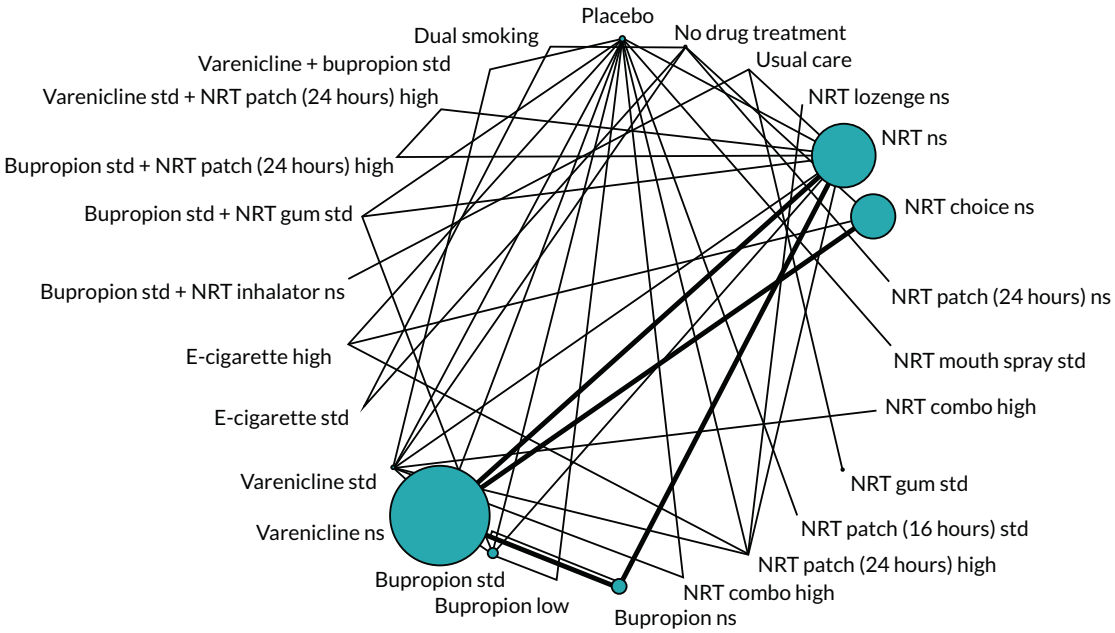

FIGURE 82 Network plot for major adverse cardiovascular events (including randomised and non-randomised studies) at treatment level. Ns, not specified; std, standard.

TABLE 52 Comparison of different NMA models for major adverse cardiovascular events (91 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	82.49	341.1	0.26 (0.01 to 0.82)	–
Random-class model, consistency	80.3	366.7	0.26 (0.02 to 0.79)	0.54 (0.02 to 2.75)
Fixed-class model, consistency	79.51	334	0.23 (0.01 to 0.73)	–
Fixed-class model, inconsistency	80.61	338.3	0.22 (0.01 to 0.72)	–

SD_d, standard deviation across treatment effect estimates; SD_D, standard deviation across class effect estimates.

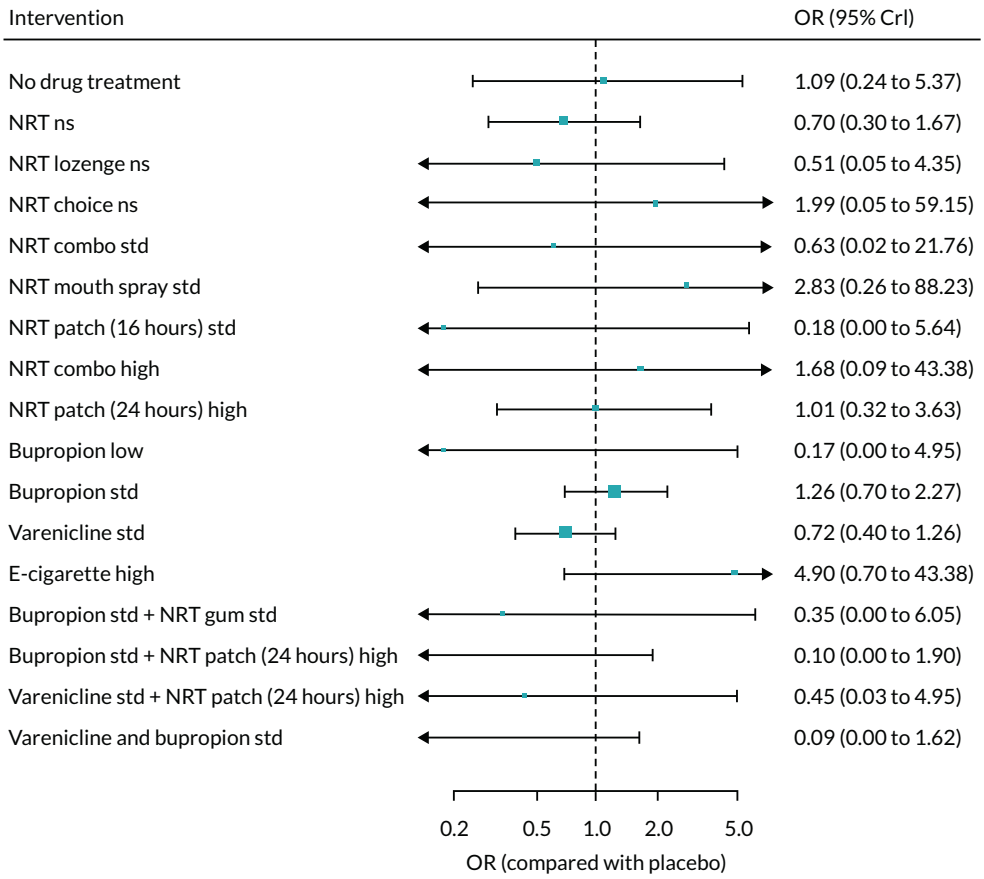

FIGURE 83 Forest plot with full interaction NMA model results for major adverse cardiovascular events. Ns, not specified; std, standard.

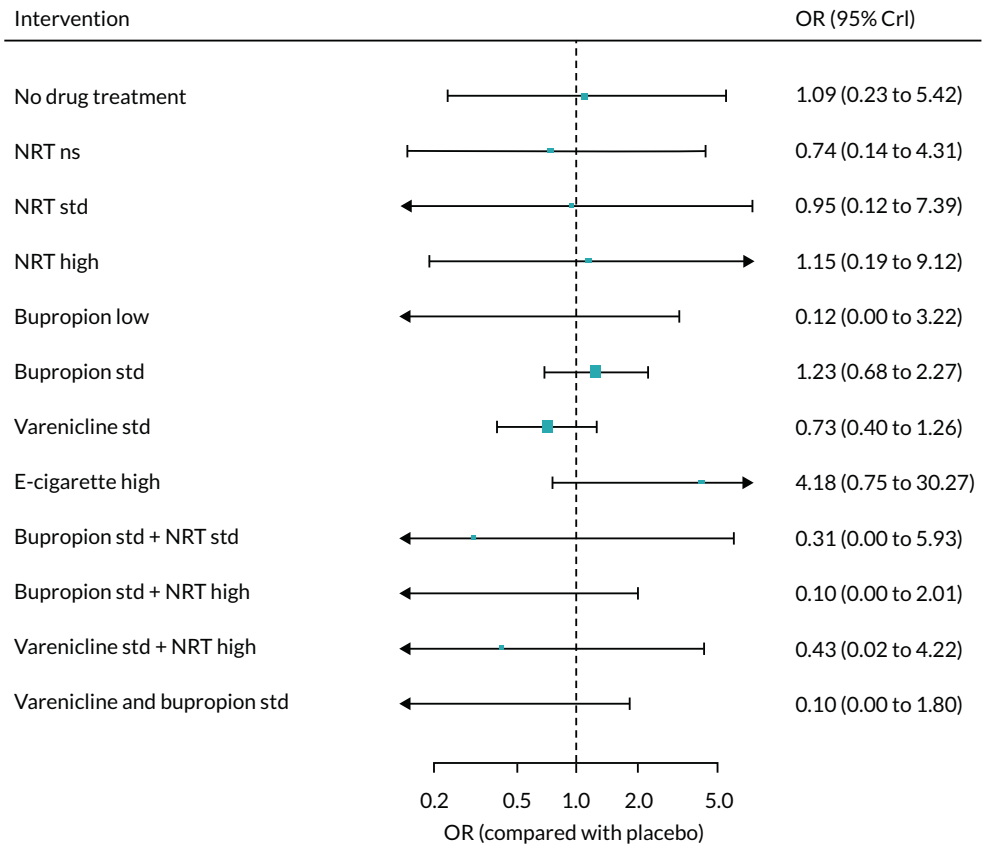

FIGURE 84 Forest plot with random-class NMA model results for major adverse cardiovascular events. Ns, not specified; std, standard.

Meta-regressions

Comorbidities as covariate

This analysis was based on 40 studies. There was inconclusive evidence of effect modification based on comorbidities (B = −1.01, −197.3 to 195). The estimate of the SD between class effects was 0.23 (0.02, 0.76).

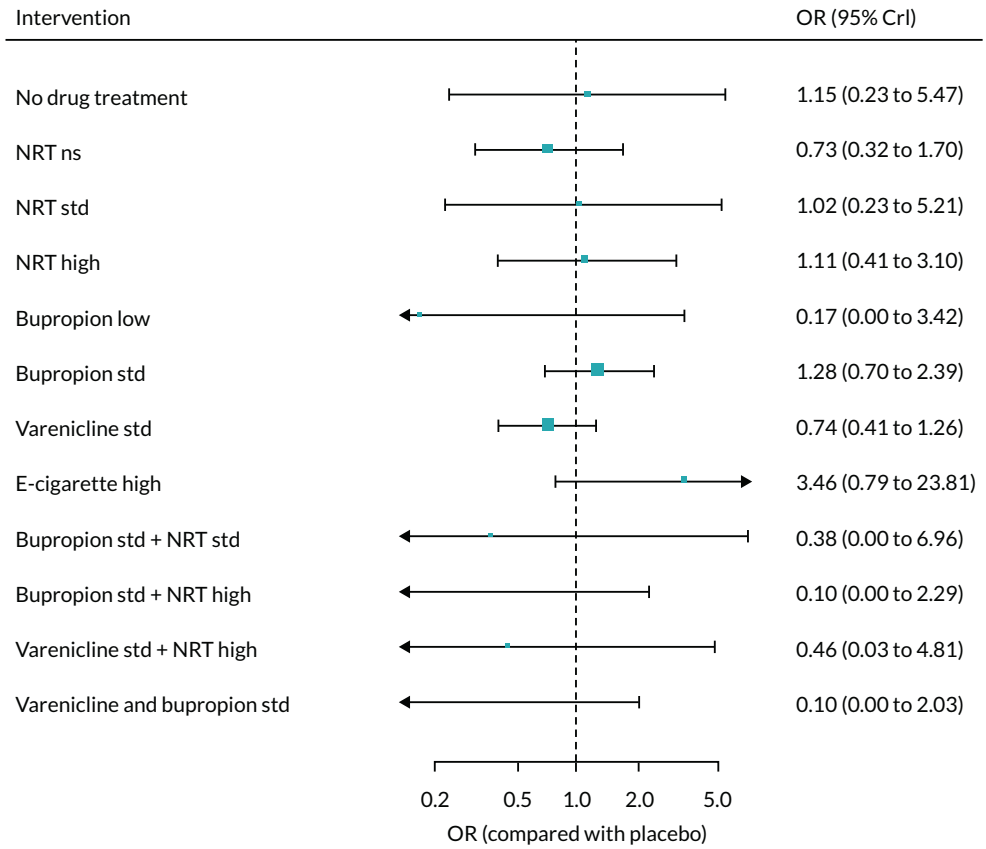

FIGURE 85 Forest plot with fixed-class NMA model results for MACE adjusted for comorbidities. Ns, not specified; std, standard.

Smoking level as covariate

This analysis was based on 33 studies. There was inconclusive evidence of effect modification based on smoking level (B = −0.29, −6.12 to 3). The estimate of the SD between class effects was 0.37 (0.02, 1.06).

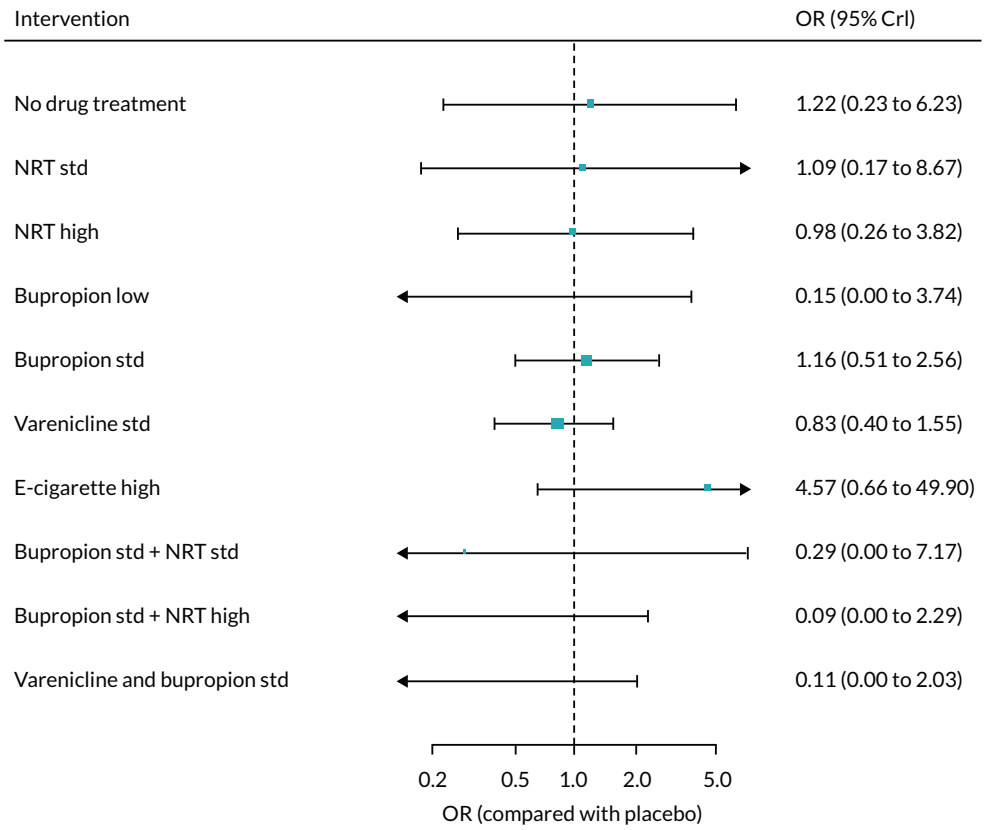

FIGURE 86 Forest plot with fixed-class NMA model results for MACE adjusted for smoking level. Std, standard.

Major adverse neuropsychiatric events

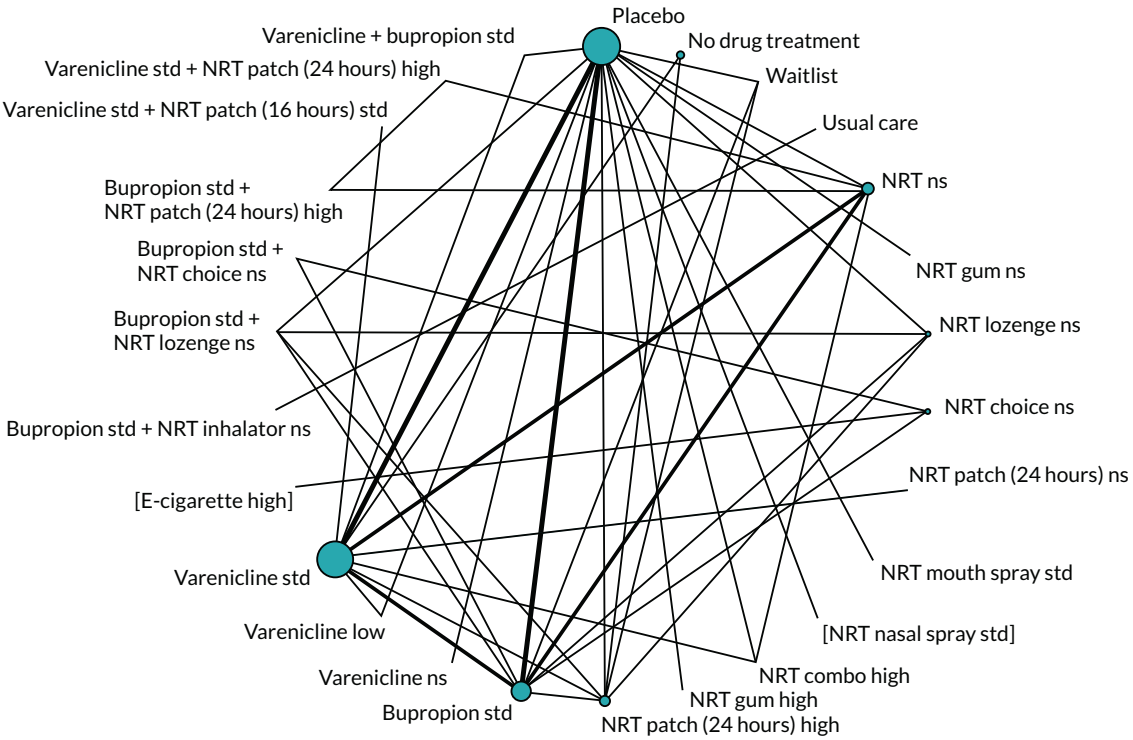

FIGURE 87 Network plot for major adverse neuropsychiatric events at treatment level. Ns, not specified; std, standard.

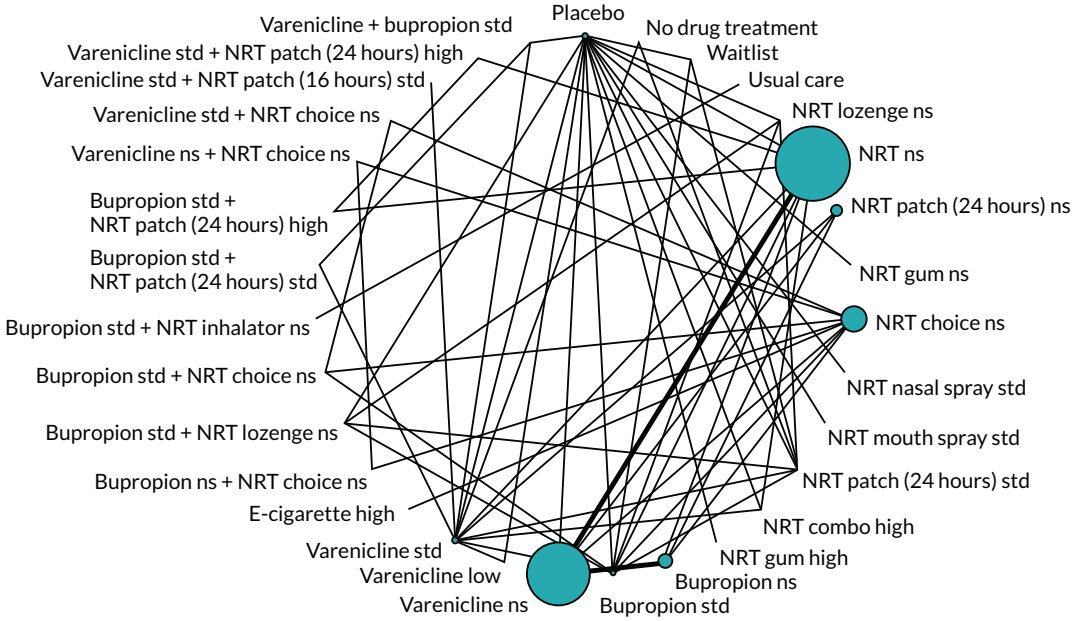

FIGURE 88 Network plot for major adverse neuropsychiatric events (combining randomised and non-randomised evidence) at treatment level. Ns, not specified; std, standard.

TABLE 53 Comparison of different NMA models for major adverse neuropsychiatric events (158 data points)

Model	Residual deviance	DIC	SD_d (95% CrI)	SD_D (95% CrI)
Full interaction model, consistency	154.2	717.5	0.15 (0.01 to 0.44)	–
Random-class model, consistency	153.9	717.1	0.17 (0.01 to 0.45)	0.92 (0.18 to 2.32)
Fixed-class model, consistency	154.4	717.5	0.33 (0.05 to 0.60)	–
Fixed-class model, inconsistency	158.2	722.5	0.18 (0.02 to 0.47)	–

SD_d, standard deviation across treatment effect estimates; SD_D: standard deviation across class effect estimates.

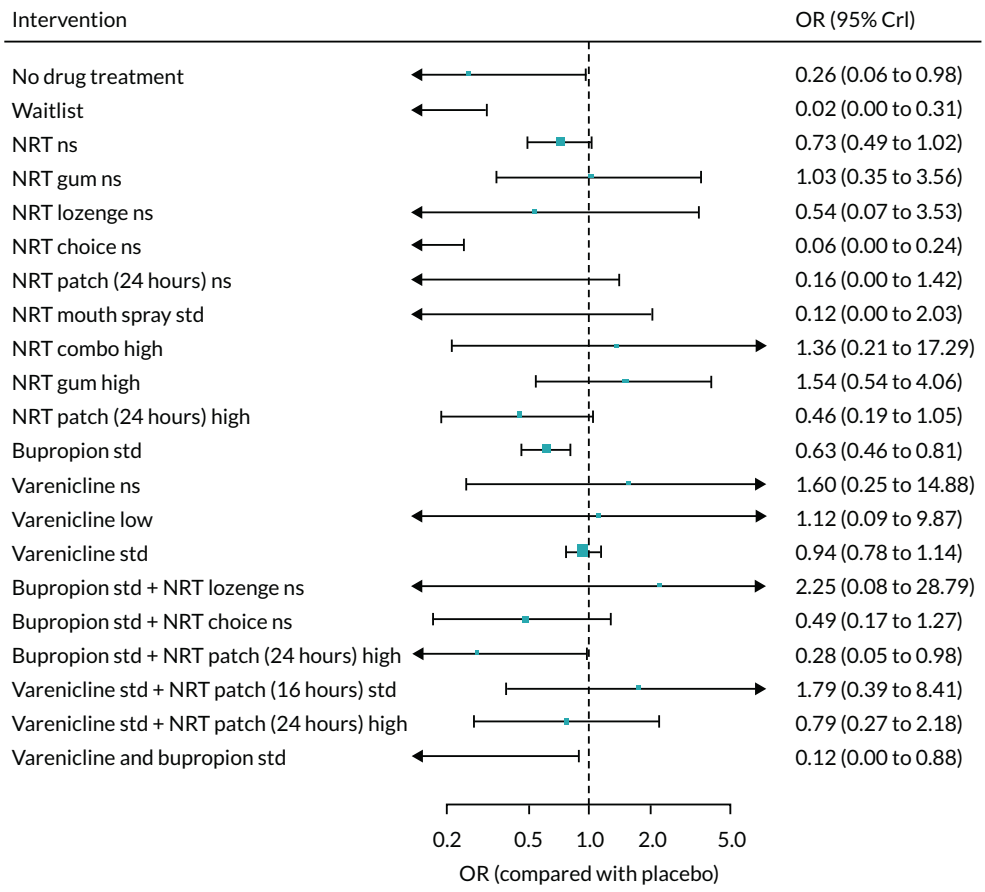

FIGURE 89 Forest plot with full interaction NMA model results for major adverse neuropsychiatric events. Ns, not specified; std, standard.

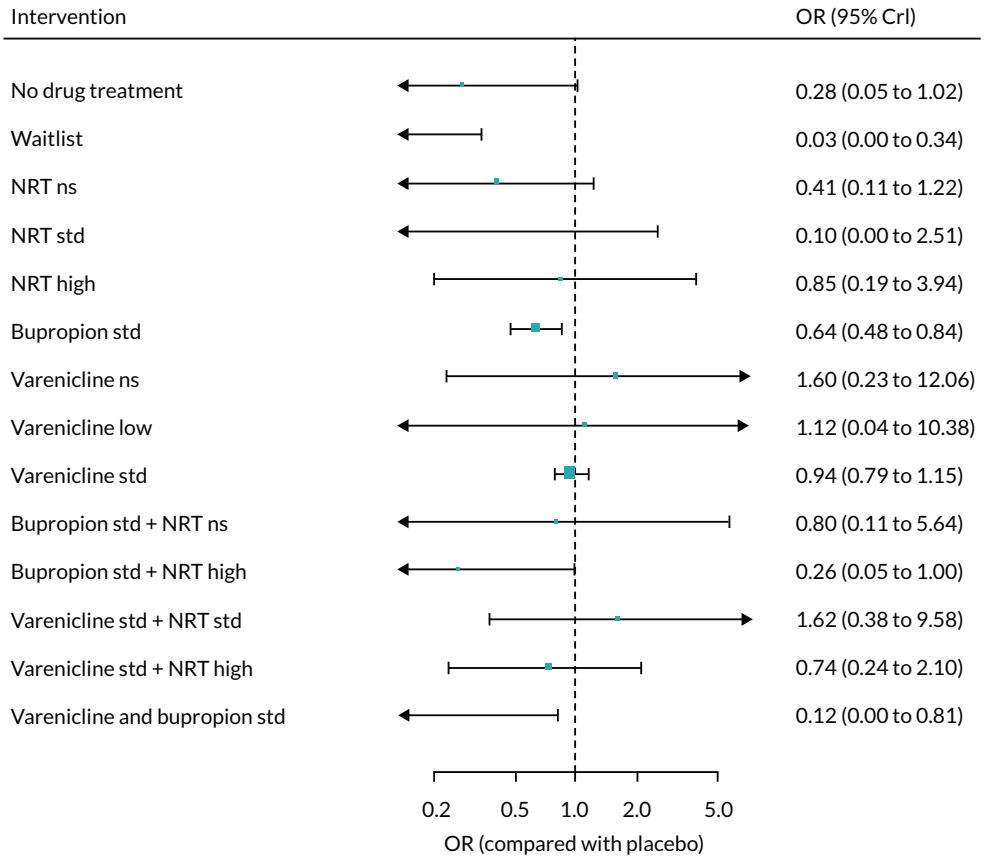

FIGURE 90 Forest plot with random-class NMA model results for major adverse neuropsychiatric events. Ns, not specified; std, standard.

Meta-regressions

Psychiatric comorbidities as covariate

This analysis was based on 71 studies. There was inconclusive evidence of effect modification based on psychiatric comorbidities (B = 0.38, −196 to 195.2). The estimate of the SD between class effects was 0.33 (0.04, 0.61).

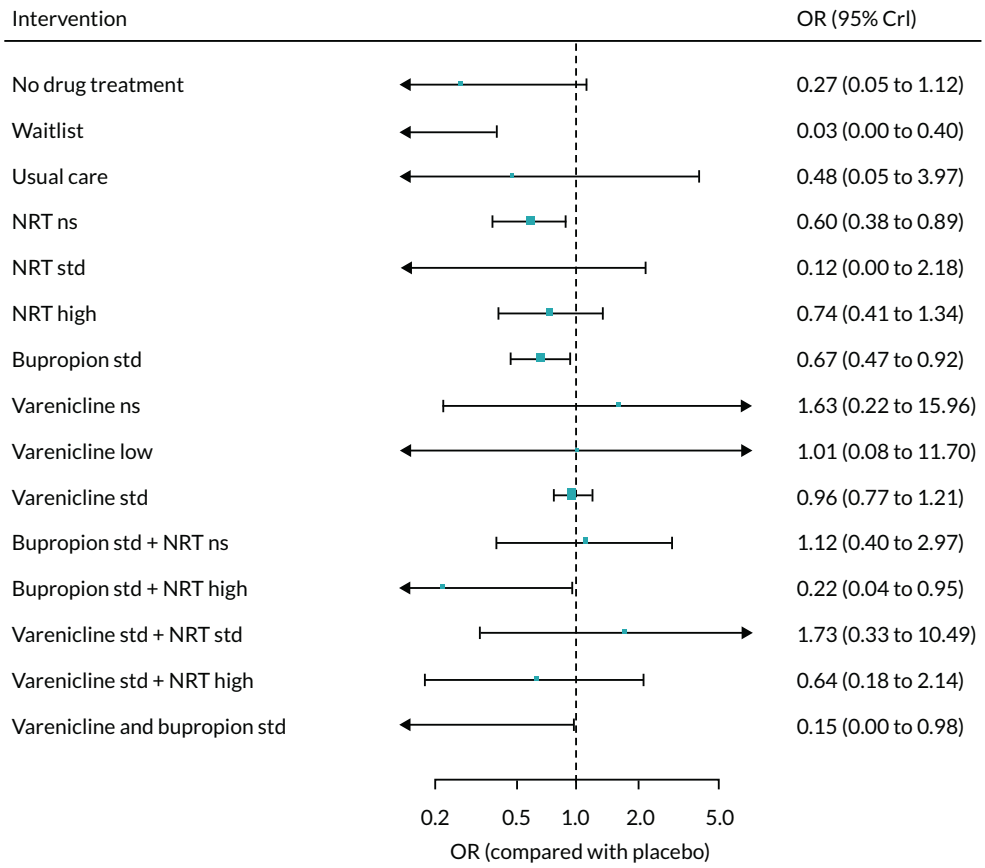

FIGURE 91 Forest plot with fixed-class NMA model results for MANE adjusted for psychiatric comorbidities. Ns, not specified; std, standard.

Appendix 8 Tertiary and other safety outcome analyses

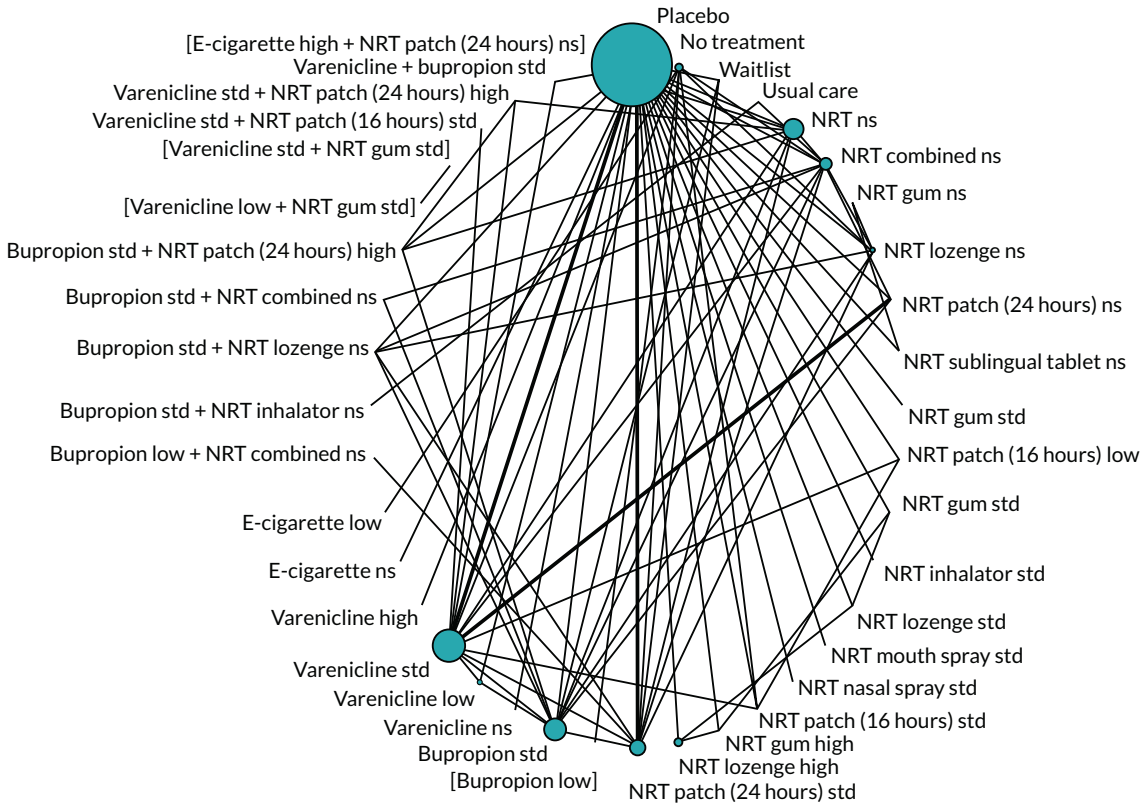

FIGURE 92 Network plot for nausea at treatment level. Square brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard.

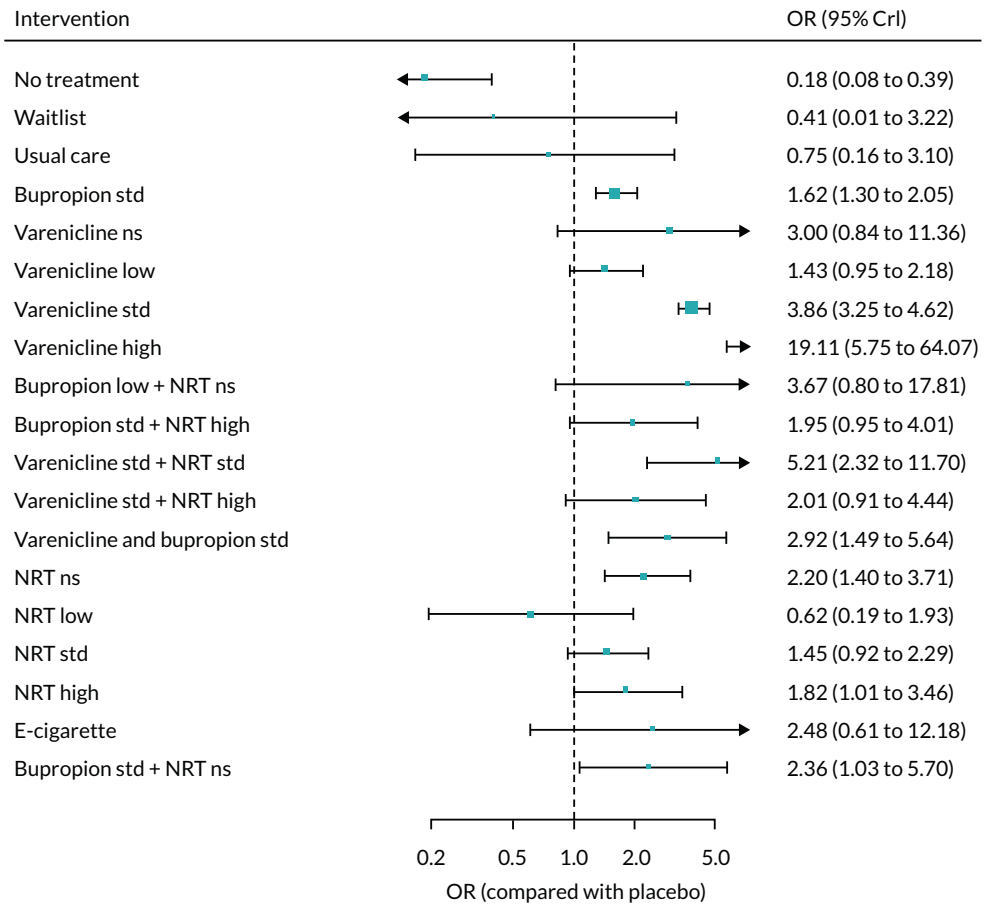

FIGURE 93 Random-class NMA results for nausea. Ns, not specified; std, standard.

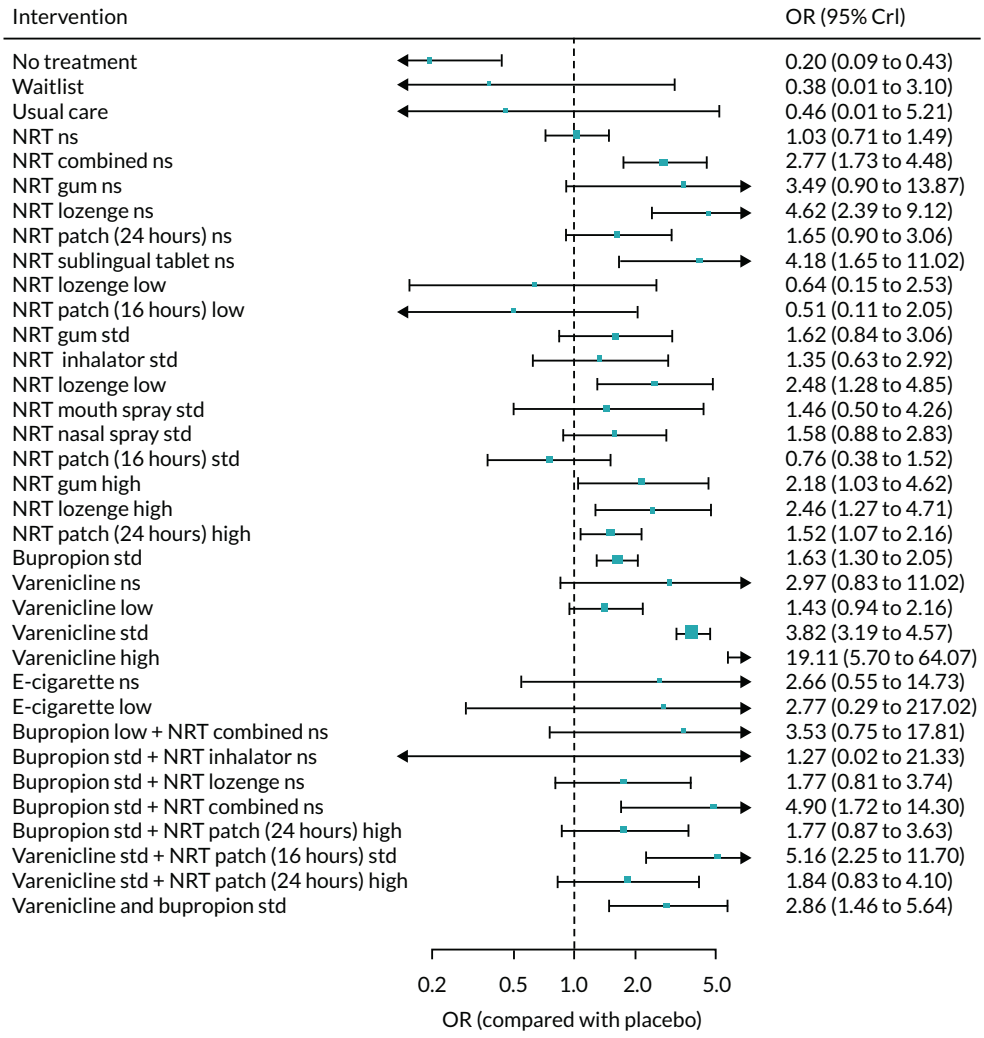

FIGURE 94 Standard NMA results for nausea. Ns, not specified; std, standard.

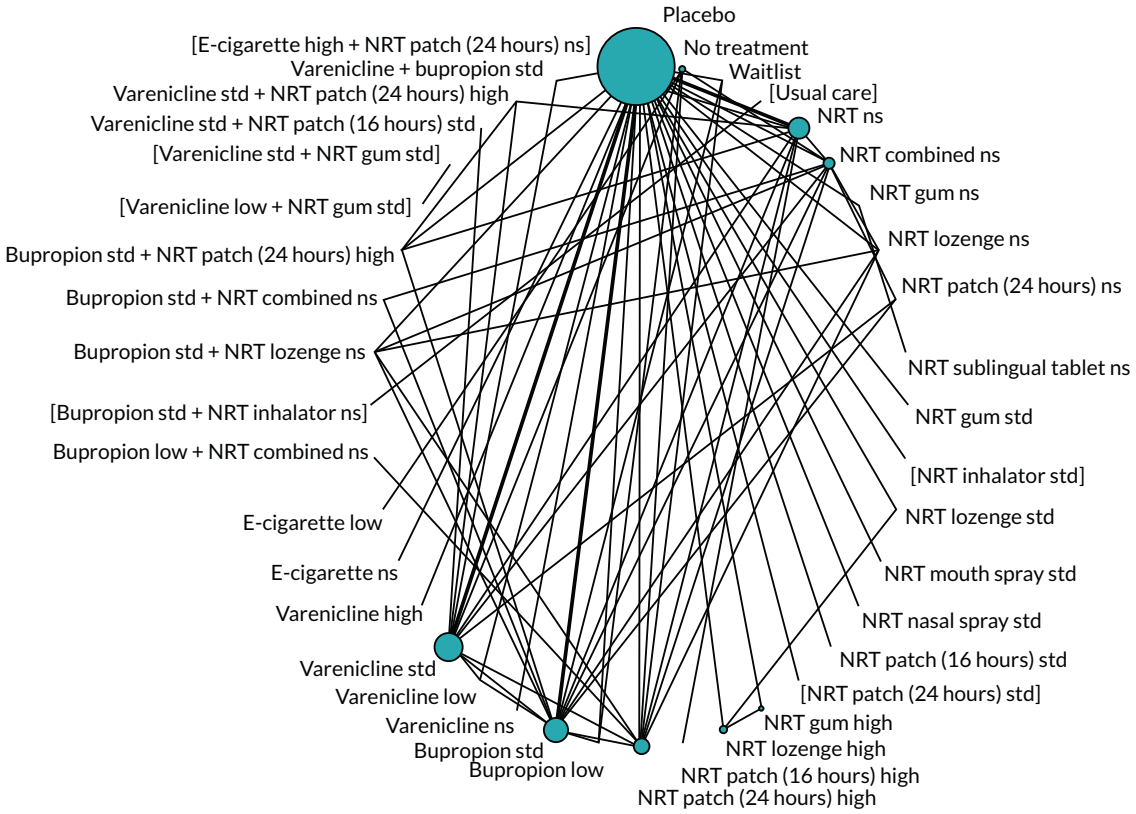

FIGURE 95 Network plot for headache at treatment level. Square brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard.

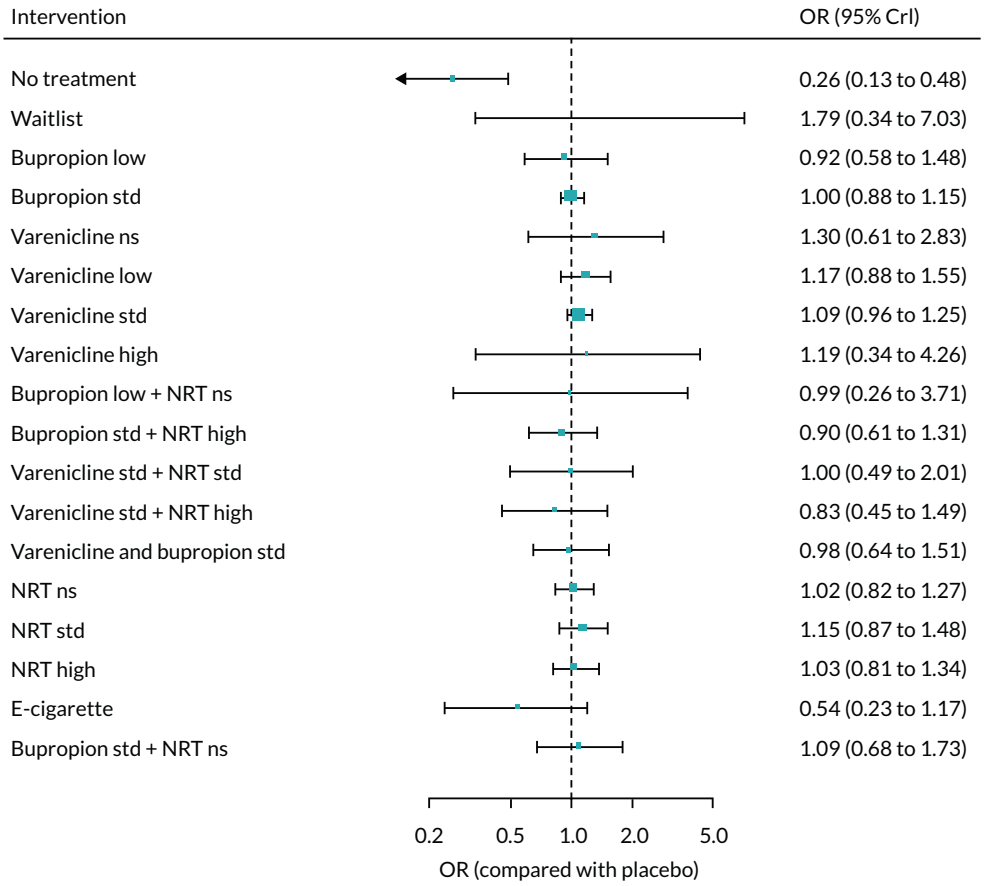

FIGURE 96 Random-class NMA results for headache. Ns, not specified; std, standard.

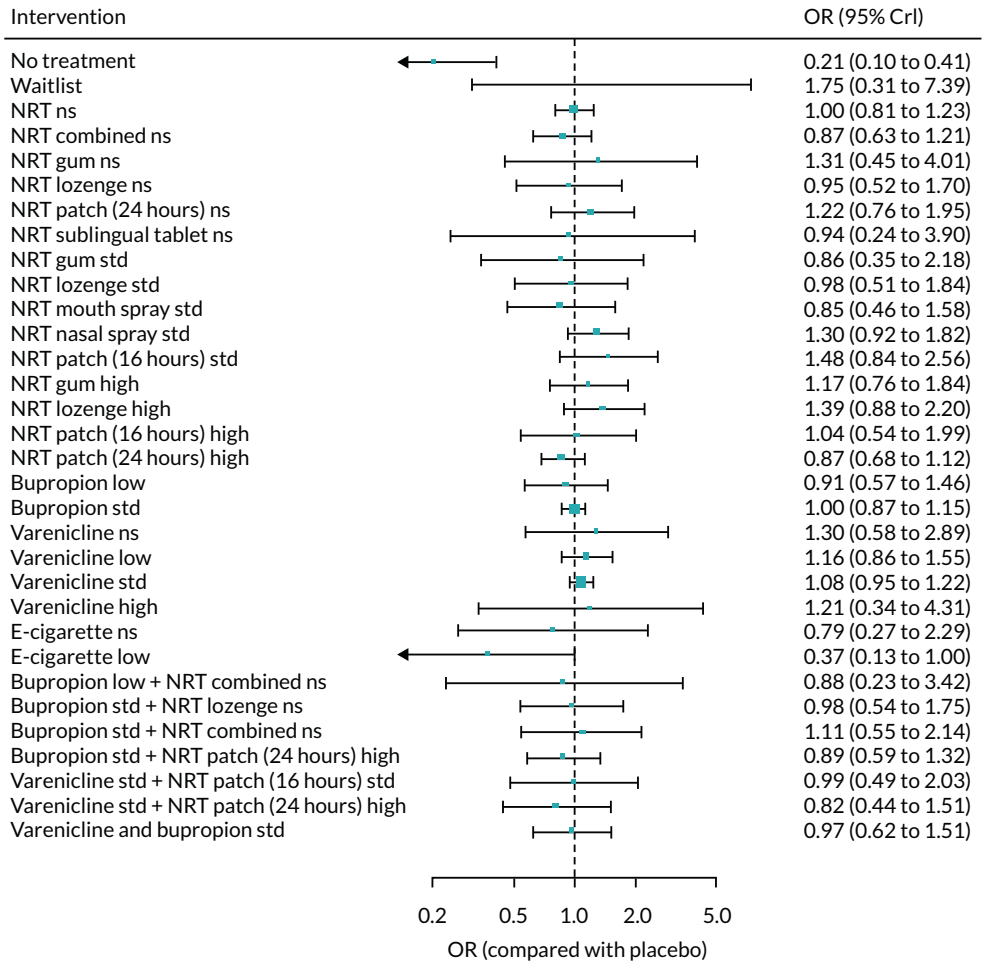

FIGURE 97 Standard NMA results for headache. Ns, not specified; std, standard.

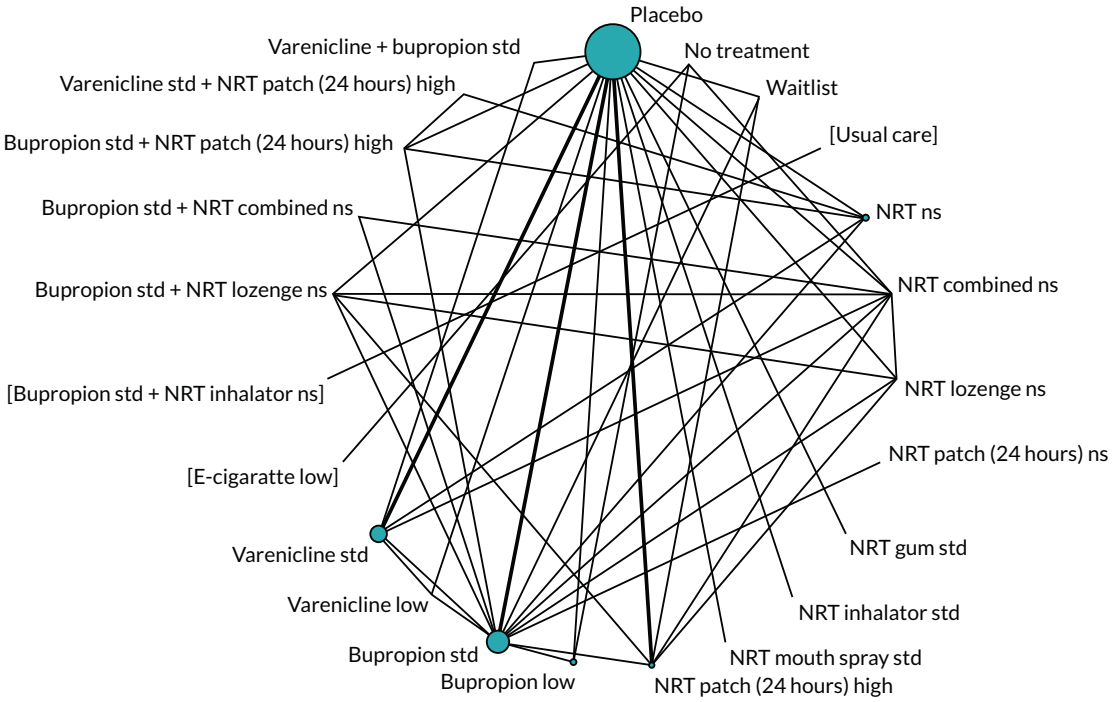

FIGURE 98 Network plot for dry mouth at treatment level. Square brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard.

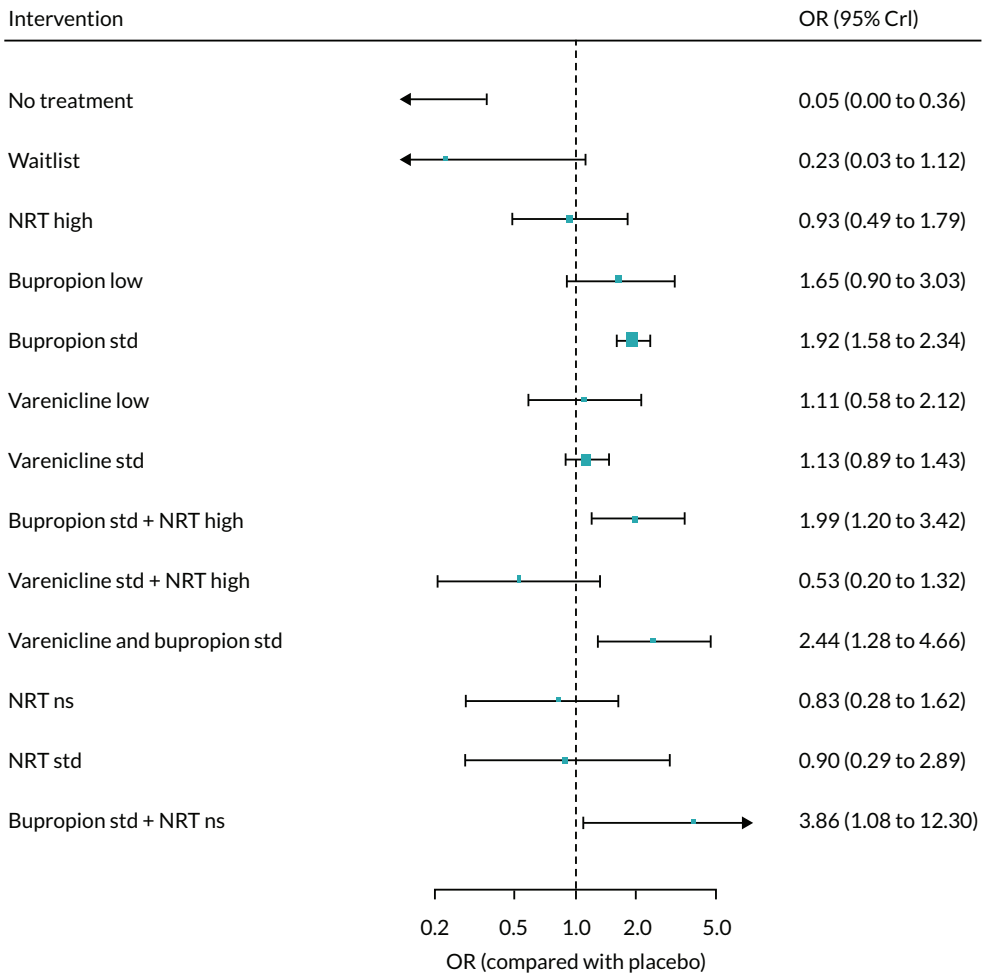

FIGURE 99 Random-class NMA results for dry mouth. Ns, not specified; std, standard.

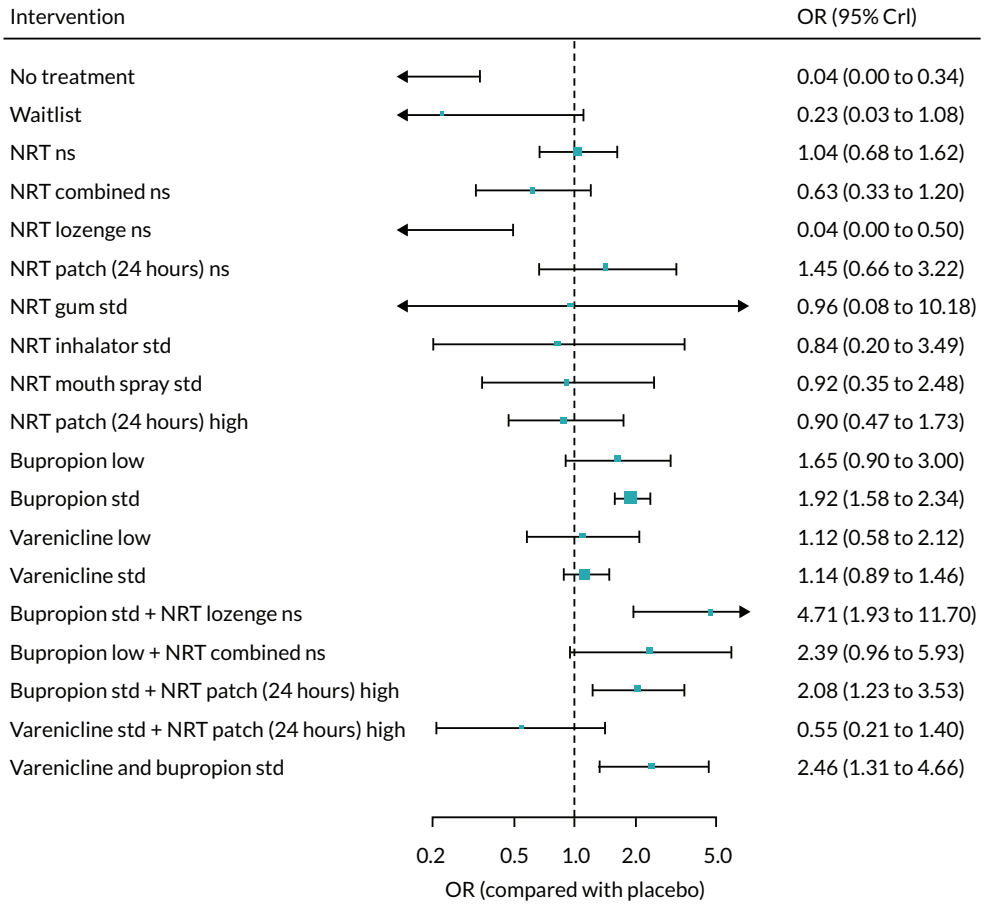

FIGURE 100 Standard NMA results for dry mouth. Ns, not specified; std, standard.

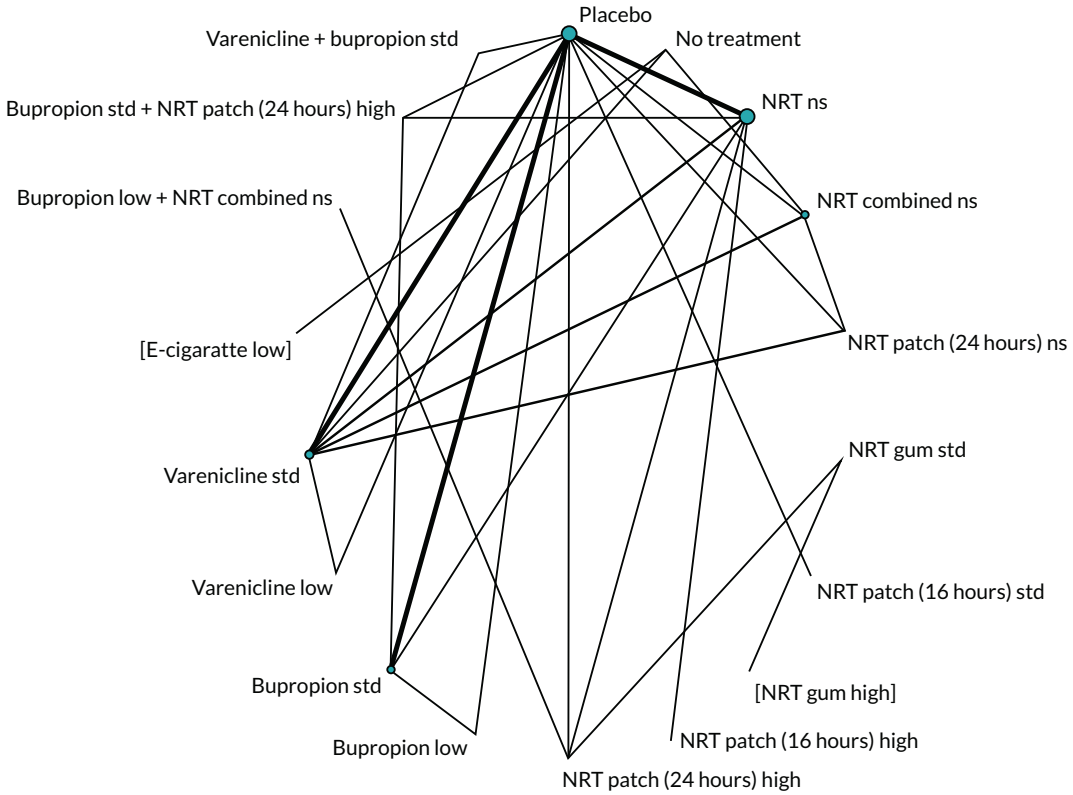

FIGURE 101 Network plot for skin rash at treatment level. Square brackets denote interventions that were not included in the NMA. Ns, not specified; std, standard.

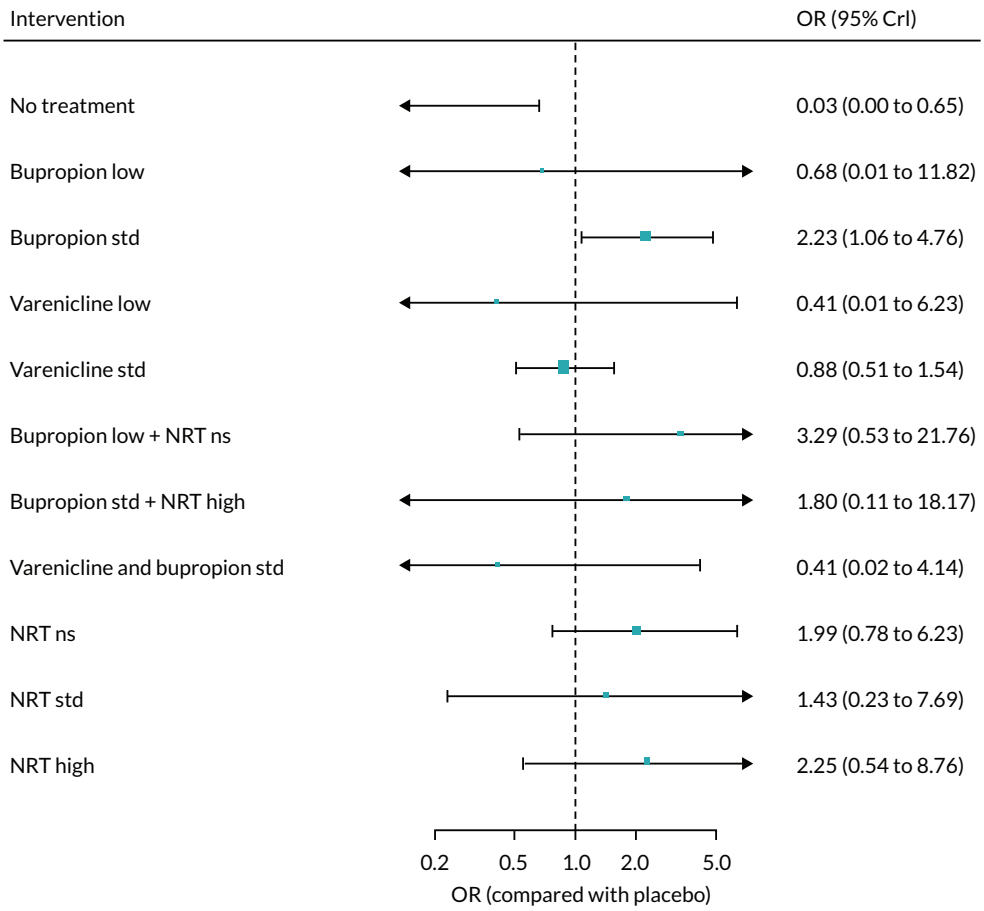

FIGURE 102 Random-class NMA results for skin rash. Ns, not specified; std, standard.

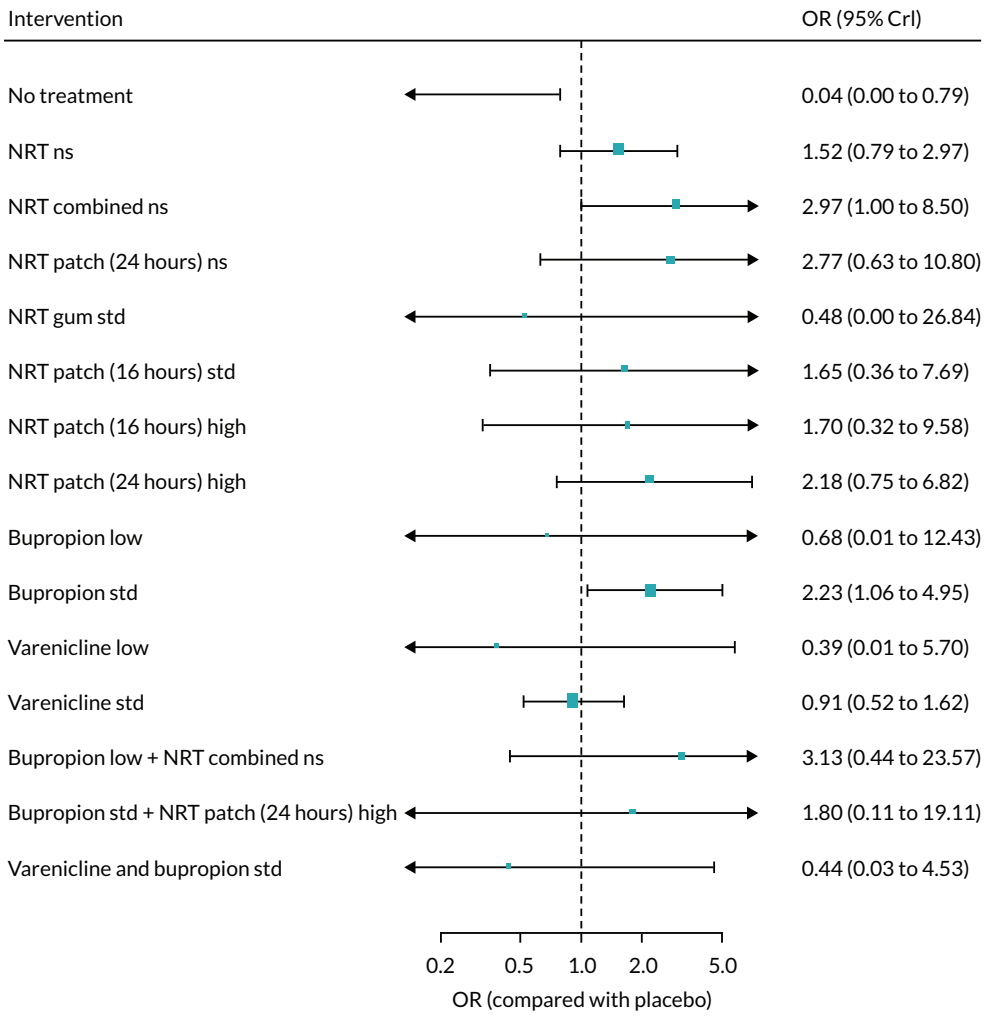

FIGURE 103 Standard NMA results for skin rash. Ns, not specified; std, standard.

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PGfAR
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