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

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Scientific summary

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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.

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This report

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