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Editor's Choice

Systematic review of the cost-effectiveness of varenicline vs. bupropion for smoking cessation

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SUMMARY

The purpose of this systematic review was to review the cost-effectiveness of first-line non-nicotine therapies (varenicline and bupropion SR) for smoking cessation, identify differences in the models used and their conclusions of cost-effectiveness, and to determine which variables, if any, impact conclusions of cost-effectiveness. A systematic literature search was conducted in MEDLINE, PsychINFO, the National Health Service Economic Evaluation Database, the Health Technology Database and the Tufts Cost-effectiveness Analysis Registry from the earliest possible date through May 2011. To be included, studies had to compare cost-effectiveness of varenicline to bupropion using either a Markov model or discrete event simulation and be published as a full text manuscript in English or Spanish. Study selection and data extraction were done in duplicate with disagreement resolved through discussion. Data regarding the model characteristics, results and conclusions were extracted as were details to assess the quality of the study. Model characteristics and cost-effectiveness results were compared across studies and summarised qualitatively. Ten unique studies were included, all of which were Markov models. Eight studies used the Benefits of Smoking Cessation on Outcomes (BENESCO) model and all found varenicline to dominate bupropion. The two non-BENESCO models found varenicline to be cost-effective. Conclusions regarding the cost-effectives were changed upon sensitivity analysis with the following variables: time horizon, cost of bupropion, efficacy of either drug, age and the incidence of smoking related disease. Varenicline dominated bupropion in most cost-effectiveness models. However, applicability of models to clinical practice and variables which changed conclusion of cost-effectiveness should be considered in the interpretation of results.

Review Criteria

We used a systematic review process to identify, evaluate and to synthesise data for this review. Starting with an explicit question, we comprehensively searched for data using multiple databases including those specific to economic data. Selection of the studies and data extraction were done in a systematic way using explicit criteria, in duplicate. Data were analysed and synthesised qualitatively and the clinical applicability was highlighted.

Message for the Clinic

Although current Markov models suggest that varenicline is a dominant strategy compared with bupropion for smoking cessation, several limitations in the models reduce the clinical applicability of the conclusions. Recent safety data regarding the association of varenicline and serious cardiovascular events are not considered in these models and may change conclusions of cost-effectiveness.

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Introduction

Cigarette smoking remains the leading risk factor for chronic diseases worldwide and thus imposes a tremendous health and economic burden on society (1,2). Among the most common lethal health conditions attributed to smoking are lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (3,4) along with additional conditions such as other malignancies, pregnancy complications and osteoporosis (5). In the United States (US) alone, an estimated 443,000 people die prematurely each year of smoking related diseases, amounting to 5.1 million years of potential life lost annually (6). US data from 2001 to 2004 showed the economic burden of smoking to be $193 billion per year, of which $97 billion can be explained by productivity losses, whereas smoking-related healthcare expenditures amount to $96 billion per year (6).

Given the burden of cigarette smoking, strategies to support smoking cessation bear tremendous health as well as economic benefits. Two non-nicotine therapies are among those recommended as first-line agents to aid in smoking cessation in patients without contraindications, including varenicline (Chantix®) and bupropion SR (Zyban®) (7). Compared with placebo, either agent significantly increases a patient's odds of quitting (7). However, both randomised trials and a pooled analysis have found varenicline to be more effective than bupropion in maintaining continuous abstinence at 52 weeks (8–10). Clinicians are encouraged by guidelines to choose from first-line agents based on patient specific characteristics and consideration of safety profiles for each agent (7). Against this background,

reliable projections of the economic impact of these interventions are of primary interest to public health policy as well as healthcare providers, payers and patients (11).

The aim of this systematic review is to evaluate studies that compare the cost-effectiveness of first-line non-nicotine therapies (varenicline and bupropion SR) for smoking cessation, focusing on differences in the methodology of the economic models. Our goal is to determine differences in the methodology between models used, the variables which changed conclusions of cost-effectiveness, and the applicability of models to current clinical practice.

Methods

A systematic literature search was conducted using the computerised databases MEDLINE (1948 through May 2011), PsychINFO (1806 through May 2011), the National Health Service Economic Evaluation Database (earliest possible date through second quarter of 2011), the Health Technology Assessment Database (earliest possible date through second quarter of 2011) and the Tufts Cost-Effectiveness Analysis Registry (earliest possible date through May 2011). The search strategy used can be found in Appendix A. A manual search for references from systematic reviews was performed to identify additional relevant literature. Two independent investigators reviewed each citation for inclusion using the following *a priori* defined criteria: (i) available as full text publication in English or Spanish and (ii) compared cost-effectiveness of varenicline to bupropion using a Markov model or discrete event simulation. Decision tree analyses were excluded since they do not adequately represent chronic conditions with recurrent events over long periods of time (12).

Data extraction

Two investigators used a standardised data extraction tool to independently extract data. The following information was sought from each study: the country and year in which the study was conducted, starting state smoking status, proportion of participants attempting to quit smoking, modelled health states, modelled pharmacological interventions and regimens, study perspective, discount rate, time horizon, cycle length, source of drug efficacy data, details on sensitivity analyses conducted, characteristics for which risk was adjusted, relapse rate, incremental cost-effectiveness ratio (ICER) and the author's conclusion. Only data relevant to the comparison of varenciline to bupropion were extracted from each study, although additional comparisons may have been studied. The ICER and willingness to pay (WTP) threshold reported by each study for the base-case analysis was converted to 2010 US dollars using the Consumer Price Index for medical care (13).

Quality assessment of included studies

A critical appraisal of the methodology of the included studies was conducted using a checklist developed by Drummond et. al (14). The Drummond rating scale is based on 10 widely accepted dimensions of quality for an economic study.

Results

The literature search yielded a total of 583 initial citations (Figure 1). After excluding 458 citations during abstract review, 92 citations were reviewed at the full text level. A total of 16 citations met our inclusion criteria, which represented 10 unique studies (Table 1) (15–25). The earliest study was published in 2008 while the most recent was published in 2010. The majority of studies were conducted in Europe ($n = 6$) followed by the United States ($n = 3$) and Asia ($n = 1$). All identified studies used Markov modelling to evaluate cost-effectiveness; no discrete event simulations were identified. Eight of the 10 studies used the Benefits of Smoking Cessation on Outcomes (BENESCO) model (15–23) while the remaining two studies used unique Markov models (24,25) (from this point referred to as non-BENESCO models). The 10 studies did not vary substantially in their quality when assessed using Drummond's rating scale (Table 2).

Model characteristics

Eight of the included studies utilised the BENESCO model, a Markov model characterised by a set of mutually exclusive health states (COPD, lung cancer, CHD, stroke, severe asthma exacerbations and death) and transition probabilities that define a subject's movement between health states (15–23). The BENESCO model simulates the consequences of smoking and the benefits of quitting in a hypothetical cohort of current smokers, followed over their lifetime, making a single attempt to quit smoking in the first cycle (20). Individuals are classified as a smoker, recent quitter (abstinent 1–5 years after a successful quit attempt), or long-term quitter (abstinent greater than 5 years after a successful quit attempt). During the first year, transition probabilities between smoking states depend on cessation rates of the interventions. After 1 year, transition probabilities depend on annual relapse rates, which in turn depend on time since quitting.

The BENESCO model assumes that the disease events are mutually exclusive within a cycle, and that

a restricted hierarchy exists. The chronic progressive conditions are given hierarchical prominence over conditions with acute recurrent events, implying that subjects with CHD or stroke can transition to COPD or lung cancer, whereas subjects with COPD or lung cancer reside until they transition to death. Furthermore, distinctions are made between first and subsequent events for CHD and stroke. No smoking-related events occur prior to the age of 35 with the exception of asthma (26).

The studies which used the BENESCO model varied with regard to the incorporated health states, but seven of the eight included the standard health states for the model (15,17–22). One model also included additional country specific malignancies (16). The two non-BENSCO models accounted for death only (24,25).

The studies using the BENESCO model defined the starting state as adults (≥ 18 years), stratified by age (18–34 years, 35–64 years, and 65 years and older) with the chance of making a single quit attempt with one treatment course (15–23). The non-BENESCO model by Hagan et al. defined the starting state as 50-year old male patients with the chance of making one quit attempt in the first year whereas the model by Heitjan et al. defined the starting state as adults aged 20–60 years with the chance of quitting annually. The per cent of subjects allowed to make a quit attempt was 25% in four BENESCO models (17,19–21), although it ranged from 1.8% to 62.5% or unreported in other BENSCO models. One non-BENESCO model reported a quit rate of 50% while the others did not report a quit rate. The model perspective was not explicitly stated in all studies. Of the BENESCO models the perspective was reported in six and was the healthcare payer in two (15,19), healthcare system in two (18,20), and society in two models (17,22) (although one (22) excluded productivity costs). The perspective was not reported in either non-BENESCO model, although based on a lack of indirect costs included in the models, a true societal perspective can be ruled out (24,25). The perspective was likely the Norwegian healthcare system for one model (24); the second model did not provide enough description of the methodology to judge the perspective (25).

Most of the BENESCO models based drug efficacy on two head-to-head randomized controlled trials (RCTs) comparing varenicline to bupropion therapy for 12 weeks (8,9). Four BENESCO models did so by pooled data from these two RCTs (15,17,18,20), although only Howard et al. explicitly stated the methodology for pooling and used a previously conducted meta-analysis (27). Although Linden et al. also based efficacy on these two RCTs, it was unclear

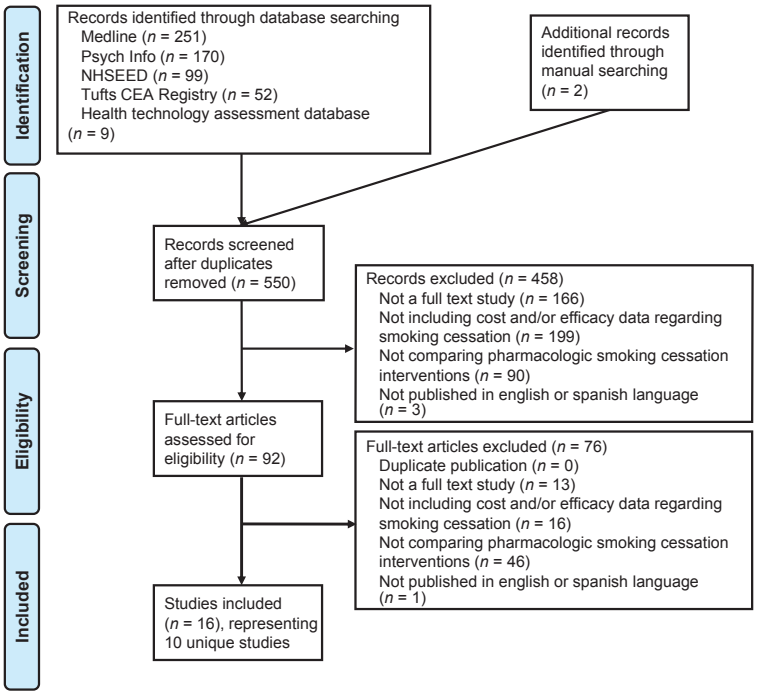

Figure 1 PRISMA diagram. NHSEED, National Health Service Economic Evaluation Database; Tufts CEA Registry, Tufts Cost-Effectiveness Analysis Registry

as to how or if the data were pooled. Overall, the abstinence rates for both varenicline and bupropion did not vary considerably across these models, ranging from 22.4% to 22.5% for varenicline and from 15.4% to 15.7% for bupropion. The two BENESCO models which used differing sources had slightly different efficacy rates (16,19). Bae et al. pooled data through meta-analysis, but included one additional head-to-head RCT (28) and two placebo controlled trials (29,30) resulting in abstinence rates of 25.5% for varenicline and 17.8% for bupropion 17.8%. Lastly, Hoogendorn et al. based vareniciline efficacy on the same two head-to-head RCTs as most models (varenicline abstinence 22.4%) but then calculated bupropion efficacy relative to the placebo from the same trials (bupropion abstinence 17.0%). The exact drug regimens evaluated in these RCTs used for efficacy were modelled by five BENESCO models whereas two BENESCO models shortened the duration of bupropion treatment to 7 weeks and did not provide justification for doing so (17,22).

Only one model, also a BENESCO model, sought to compare extended duration vareniciline (24 weeks) to standard duration varenicline (12 weeks) or bupropion (21). Efficacy data were based on a mixed-treat-

Table 1 Design and model characteristics of included studies

Author, Year Country	Starting state Quit attempt %	Health states	Interventions of interest modelled	Perspective Discounting	Time horizon cycle Length (years)	Major efficacy data source	Sensitivity analysis	Adjusted risk Relapse allowed
Knight, 2010 US	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt at start of model with one course of therapy 25% Quit attempt	Lung cancer, COPD, CHD, stroke, asthma exacerbation, death	Varenicline 1 mg BID × 24 weeks* or 12 weeks or bupropion 150 mg QD × 3 days then BID × 12 weeks	NR Costs and benefits at 3%	Lifetime or 100 year old 1	Conducted MTC using original mode (20) efficacy data adding in RCT of varenicline 12 weeks vs. 24 weeks (31)	P‡	Age, gender, time since quit (recent vs. long-term quitters) Relapse allowed and rate diminished over time
Linden, 2010 Finland	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt within the first year with one course of therapy 28.1–62.5% Quit attempt based on age and gender	Lung cancer, COPD, CHD, stroke, severe asthma exacerbation requiring a physician visit, death	Varenicline 1 mg BID × 12 weeks or bupropion 150 mg QD × 3 days then BID × 7 weeks	Societal Costs and benefits at 5%	Lifetime or 100 year old 1	Based on the two HTH RCTs (8,9); Methodology unclear	D and P‡	Age, gender, time since quit (recent vs. long-term quitters) Relapse allowed and rates adjusted by time since quit
Hagan, 2010 Norway	50 year old male smoker attempting to make one quit attempt within the first year Quit attempt % NR	Death	Varenicline or bupropion	NR Costs and benefits 4%	Lifetime or 100 year 1	Relative effect estimates based on internal systematic review	D and P‡	Age, gender, ex-smoker status Relapse allowed and set at constant annual rate
Annemans, 2009 Belgium	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt with one course of therapy Quit attempt % NR	Lung cancer, COPD, CHD, stroke, asthma exacerbation requiring hospital visits in an emergency, death	Varenicline 1 mg BID × 12 weeks or bupropion 150 mg QD × 3 days then BID × 12 weeks	Healthcare payer Costs 3% and benefits 1.5%	Lifetime or 100 year 1	Obtained by pooling HTH RCTs (8,9)	D and P‡	Age, gender, time since quit (recent vs. long-term quitters) Relapse allowed and rates adjusted by time since quit
Bae, 2009 South Korea	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt with one course of therapy 1.8–19.5% Quit attempt based on age and gender	Lung, stomach, and liver cancer; IHD, stroke, COPD, death	Varenicline 1 mg BID or bupropion 150 mg BID × 12 weeks**	NR Costs and benefits 5%	Lifetime or 100 year 1	Conducted meta-analysis of HTH RCTs (8,28)and two placebo controlled trials (29,30)	D and P‡	Age, gender, time since quit (recent vs. long-term quitters) Relapse allowed and rates adjusted by time since quit
De Bobadila, 2008 Spain	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt Quit attempt NR	Lung cancer, COPD, CHD, stroke, severe asthma exacerbation, death	Varenicline 1 mg BID or bupropion 150 mg BID × 12 weeks**	National health system Costs and benefits at 3.5%	Lifetime 1	Taken from meta-analysis of HTH RCTs (8,9)	D and P	Age, gender, time since quit (recent vs. long-term quitters) Relapse was allowed and rate diminished over time

Table 1 *Continued*

Author, Year Country	Starting state Quit attempt %	Health states	Interventions of interest modelled	Perspective Discounting	Time horizon cycle Length (years)	Major efficacy data source	Sensitivity analysis	Adjusted risk Relapse allowed
Heitjan, 2008 US	Cohort of adult (20–60 years) smokers 50% Probability of making a quit attempt annually	Death	Varenicline 1 mg BID × 12 weeks or bupropion 150 mg BID × 10 weeks (2 weeks prior and 8 weeks after target quit date)	NR Costs and benefits at 3%	Lifetime or 100 year old 1	Bupropion pharmaco-genetic studies (32), two HTH RCTs (8,9), and a meta-analysis (33)	D	Age and time since quit used to adjust mortality rates Relapse allowed and set as constant rate for temporary quitters
Howard, 2008 US	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt in the first 1-year cycle of the model 25% Quit attempt	Lung cancer, COPD, CHD, stroke, asthma exacerbation, death	Varenicline 1 mg BID × 12 weeks or bupropion 150 mg QD × 3 days then BID × 12 weeks	US healthcare system Costs and benefits at 3%	Lifetime or 100 year old 1	Previosuly conducted pooled analysis (27)	D and P	Age, gender, time since quit (recent vs. long-term quitters) Relapse was allowed and rate diminished over time
Hoogen-doorn, 2008 and Vemer, 2008† the Netherlands	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt at the beginning of the simulation 25% Quit attempt	Lung cancer, COPD, CHD, stroke, severe asthma exacerbation, death	Varenicline 1 mg BID** or bupropion 150 mg BID × 12 weeks**	Dutch healthcare payer Costs at 4% and benefits at 1.5%	Lifetime or 100 year old 1	Varenicline efficacy estimated from HTH RCTs (8,9) and bupropion efficacy calculated relative to placebo data from those trials	D and P	Age, gender, time since quit (recent vs. long-term quitters) Relapse was allowed and rate diminished over time
Bolin, 2008 Sweden	Cohort of adult (≥ 18 years) smokers attempting to make one quit attempt at the outset of the simulation 25% Quit attempt	Lung cancer, COPD, CHD, stroke, death	Varenicline 1 mg BID** × 12 weeks or bupropion 150 mg BID** × 7 weeks	Society Costs and benefits at 3%	20 and 50 years 1***	Based on pooled clinical trial data from HTH RCTs (8,9)	D and P	Age, gender, time since quit (recent vs. long-term quitters) Relapse was allowed and rate diminished over time

*Varenicline was continued for 24 weeks only in patients who were successful at quitting at 12 weeks. **Regimen based on the RCTs from which the efficacy data was derived for this model. ***Based on the assumptions of the BENSCO model (25). †The original base analysis by Hoogendorn is reflected in this table. Vemer et al. varied the base analysis, inflated to 2006, based on data from five other European countries to observe between country differences that lead to variability in the cost-effectiveness. Three pair-wise comparisons were used in the work by Vemer et al., based on the full base analysis: nicotine replacement vs. unaided, bupropion vs. nicotine replacement and varenicline vs. bupropion. ‡Although this sensitivity analyses was conducted in the model, specific data for the comparison of varenicline vs. bupropion was not reported. BID, twice daily; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; D, deterministic; HTH, head-to-head; IHD, ischaemic heart disease; NR, not reported; P, probabilistic; RCT, randomized controlled trial; US, United States.

Table 2 Critical appraisal of incuded studies

Item	Knight, 2010	Hagan, 2010	Linden, 2010	Annemans, 2009	Bae, 2009	Bolin, 2008	De Bobadilla, 2008	Heitjan, 2008	Hoogendoorn, 2008 and Vemer, 2008	Howard, 2008	Halpern, 2007
Was a well defined question posed in answerable form?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was a comprehensive description of competing alternative given?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Was the effectiveness of the programme or service established?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were all important and relevant costs and consequences for each alternative identified?	N	N	Y	Y	N	Y	Y	N	Y	Y	Y
Were all costs and consequences measured accurately in appropriate physical units?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Were the costs and consequences valued credibly?	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y
Were costs and consequences adjusted for differential timing?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was an incremental analysis of costs and consequences of alternative performed?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was allowance made for uncertainty in the estimates of costs and consequences?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Did the presentation and discussion of study results include all issues of concern to users?	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y

N, no; Y, yes.

ment comparison using data from the original model by Howard et al. as well as a RCT that directly compared varenicline 12 weeks vs. 24 weeks (31).

The non-BENSCO models used varying sources for efficacy data (24,25). Hagan et al. calculated relative effects based on a systematic literature search conducted by the authors, resulting in a relative risk of abstinence for varenciline vs. bupropion of 1.46 with 95% confidence interval of 1.18–1.81. Heitjan et al. based bupropion abstinence rates on two pharmacogenetics studies (32) (17–27% based on genetic polymorphism present) while the varenicline rate (35%) was based on two head-to-head RCTs (8,9) and a previously conducted meta-analysis (33). Authors were unclear as to the methodology used to derive this rate from these three sources. Hagan et al. did not specify the drug regimens modelled and Heitjan et al. modelled regimens according to the trials used for efficacy data. None of the BENESCO or non-BENESCO models explicitly stated the formulation of bupropion modelled although efficacy data were derived from RCTs studying the SR formulation.

The BENESCO models commonly assume that the risk of acquiring the given health states is elevated for a 'recent quitter', but once considered a 'long-term quitter', the risk becomes equal to a 'never smoker'. Smoking-related disease risk is also adjusted for age and gender. One BENESCO model differed in that the risk of lung cancer remained elevated regardless of time since the successful quit (15). In the non-BENESCO models, the risk of death was adjusted for age and diminished over time, with one study decreasing the risk annually after quitting (25)

Table 3 Results and conclusions of included studies

Author, Year	ICER (2010 US$/QALY)	ICER (2010 US$/unit*)	Subgroup and sensitive analysis considerations	Author's conclusion
Knight, 2010	Varenicline × 12 weeks or 24 weeks dominated bupropion	NA	NR	Compared with other pharmacologic strategies, 12 weeks of varenicline followed by an additional 12 weeks of therapy in successful quitters is cost-effective
Linden, 2010	Varenicline dominates	LYG: varenicline dominates	Varenicline remained dominant regardless of relapse rate, annual treatment costs of smoking related disease, HRQoL utilities, and discount rates applied. Varenicline was no longer dominant but still cost-effective (WTP €33,200) when changes in cost of bupropion, incidence of smoking-related disease, and efficacy of both drugs were made. When the time horizon was shortened to 20 y, varenicline was cost-effective and when efficacy of varenciline was also decreased to 18% or bupropion had no cost, varenicline was no longer cost effective	In a lifetime situation, varenicline dominated bupropion in Finnish smokers while during a shorter time horizon of 20 years varenciline was cost-effective
Hagan, 2010	NA	$14729/LYG	Varenicline remained cost effective regardless of age, price of interventions, healthcare costs, discount rate, unaided quit rate, gender, relapse rate, risk of death based on smoking status, drug efficacy, practitioner visits, cost of death, time till full health effect of cessation, or practitioner visit costs. When costs were adjusted for age and smoking status, based on data from Denmark, varenicline dominated	Varenicline is cost-effective compared with bupropion and when healthcare costs are increased varenicline becomes dominant
Annemans, 2009	Varenicline dominates	LYG: varenicline dominates	Varenicline remained dominant or cost-effective (WTP €30,000) according to authors when evaluating various sensitivity analyses with results most sensitive to the time horizon and when limited to 20 years, varenicline no longer dominated bupropion	Varenicline is cost-effective and cost-saving compared with current alternatives and from the healthcare perspective should be the first choice in Belgium for smoking cessation
Bae, 2009	$951	NA	Varenicline dominated bupropion regardless of discount rate, varenicline efficacy or costs, utility weights or gender	Varenicline can be considered as a cost-effective therapy
De Bobadila, 2008	Varenicline dominates	Varenicline dominates	In the lifetime horizon, varenicline was cost effective vs. bupropron in 95% of simulations (WTP €30,000). The model was sensitive to time horizon and at 2 years, 5 years and 10 years varenicline was no longer cost effective. Authors report that varenicline remained dominant when age and utility values were adjusted in the lifetime horizon and was cost-effective in the 20 year time horizon	In the lifetime horizon, varenicline is a dominant treatment option compared with bupropion. At 20 years, varenicline is cost-effective compared with bupropion
Heitjan, 2008	NA	$3303/LYG	Varenicline remained cost-effective regardless of discount rate, probability of permanent quit, hazard ratio of death and in scenarios least and most favourable to genetic testing and tailoring of bupropion therapy	Treatment with untailored bupropion or varenicline is cost-effective

Table 3 *Continued*

Author, Year	ICER (2010 US$/QALY)	ICER (2010 US$/unit*)	Subgroup and sensitive analysis considerations	Author's conclusion
Howard, 2008	Varenicline dominates	NA	Varenicline remained dominant in 68.8% of iterations vs. bupropion and was cost-effective (WTP $30,000) in 77.3% of iterations vs. bupropion. Varenicline remained dominant regardless of gender and when time horizon was changed to 20 years. At age ≥ 65 years or when there was no cost for bupropion varenicline remained cost-effective but no longer dominated bupropion	Varenicline is cost-effective compared with other pharmacotherapies and should be considered for reimbursement
Hoogen-doorn, 2008 and Vemer, 2008	Varenicline dominates	LYG: varenicline dominates Costs per additional quitter: $2394	The probability of varenicline being cost-effective was 84% compared with bupropion (WTP €5000). Varenicline remained dominant regardless of bupropion efficacy, discount rates, relapse rates, excluding asthma exacerbations, time horizon, or treating relative risk of long-term quitters as former smokers. Vemer et al., found that the incremental net monetary benefit across six European countries was most influenced by discount rates, followed by epidemiology, utility weight, amount of resource used, cost of resource, smoking prevalence, all-cause mortality, costs of smoking related disease, and demography. The rank order of these factors varied when time horizon or WTP values were modified	Varenicline is cost saving compared with bupropion in the Netherlands. The cost-effectiveness of smoking cessation therapies vary across countries and seem to be most influenced by the discount rate and epidemiology data used
Bolin, 2008	20 year horizon: M, $3807; F, $2210 50 year horizon: M, $27298; F, $18578	NA	The probability of varenicline being cost-effective was 80.3% in female patients and 75.6% in male patients compared with bupropion (WTP €20,000).** Varenicline became a dominant strategy when the perspective was changed to healthcare and the indirect costs were removed or when baseline treatment costs were increased, in both genders. Varenicline was no longer cost-effective when in male patients the horizon was shortened to 2 years and in female patients when the time horizon was shortened to 2 years or 5 years. Conclusions did not change with variation in discount rates, QALY weight, varenicline costs or efficacy, and relative risks between current and never smokers***	Varenicline is amongst the most cost-effective life-saving medical treatments for smoking cessation

*Units are defined per study when applicable. **The results of the probabilistic sensitivity analysis were extracted from the figures using Enguage and were reported up to an ICER of €20,000. ***Willingness to pay threshold was not reported. A €33,200 threshold was applied when making this statement. BID, twice daily; F, female patients; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; LYG, life years gained; M, male patients; NA, not applicable; WTP, willingness to pay.

and the other considered the risk of death to decrease after 5 years, also adjusting for gender (24).

The discount rate applied to BENESCO models ranged from 3% to 5%. Non-BENESCO models used a discount rate of 3% and 4%. All models used a lifetime horizon with a 1-year cycle length with one exception. The model by Bolin et al. used a 20-year and 50-year time horizon for the base-case analysis and although no cycle length was reported, the BENESCO model was used which assumes an annual cycle (26). Relapse was allowed in all models, although the rate in which relapse occurred varied. All BENESCO models set the risk of relapse highest in the 2–5 years after a quit with diminishing rates until the 11th year in which the rate was constantly 1%. The two non-BENESCO models set a constant annual relapse rate of 10% and 50%. Although the RCTs which were used for efficacy data included counselling as part of the intervention, only three BENESCO models indicated including counselling costs, as did one non-BENESCO model (15,17,19,25). Lastly, one non-BENESCO model used an annual healthcare cost equal in smokers and former smokers (24).

Model conclusions

Six studies, all of which were BENESCO models, found varenicline to dominate bupropion in the studies' defined base-case analysis (Table 3) (15,18–22). Incremental-cost-effectiveness ratios (ICERs) were measured using quality-adjusted life years (QALYs). The remaining two BENESCO models concluded that vareniciline was cost-effective in the studies' defined base-case analyses (16,17). Bolin et al. evaluated male patients and female patients separately using two time horizons, as the base-case analysis. Varenicline was found to be cost-effective with ICERs in male patients at 20 years and 50 years of $3807 and $21,298/QALY and ICERs in female patients at 20 years and 50 years of $2210 and $18,578/QALY. Bae et al. found varenicline to be cost-effective at $951/QALY. The two non-BENESCO models measured ICERs using life years gained (LYG) and found varenicline to be cost effective with ICERs of $14729 and $3303/LYG (24,25).

Findings from sensitivity analyses

Four studies, all BENESCO models, conducted probabilistic sensitivity analysis using different WTP-thresholds ranging from $7103 to $42,615 (equivalent to €5,000–€30,000) (Table 3) (17–20). Regardless of the WTP-threshold applied, varenicline was cost-effective in at least three quarters of iterations compared with bupropion (17,19,20). One trial reported that varenicline was dominant in 68.8% of iterations (20).

Seven BENESCO models and both non-BENESCO models reported results of deterministic sensitivity analyses for the comparison of interest (Table 3) (15–20,22–25). The results of sensitivity analyses conducted in studies using the BENESCO model indicate several variables that lead to changes in the original cost-effectiveness conclusion. Six BENESCO models originally concluded dominance of varenicline over bupropion with four of these models conducting univariate deterministic sensitivity analyses (15,18–20) and one conducting both univariate and bivariate deterministic sensitivity analyses (22). Varenicline no longer dominated bupropion and was not cost-effective in one model when the time horizon was shortened to 2, 5 or 10 years (18). Varenicline was no longer dominant although remained cost-effective when the time horizon was shortened from lifetime to 20 years (three models) (15,18,22), the cost of bupropion was decreased (two models) (20,22), the incidence of smoking-related disease was decreased, the efficacy of varenicline was decreased, the efficacy of bupropion was increased, the efficacy of both drugs was simultaneously decreased (22), when participants were ≥ 65 years of age (20) (one model each). Although time horizon seemed to impact conclusions most, one model found that when no discount rate was applied or the treatment costs were increased by 100%, varenicline once again was dominant even with a 20-year time horizon (22).

Two BENESCO models concluded that varenicline was cost-effective compared with bupropion (16,17). In one model variation in the discount rate, varenicline cost or efficacy, utility weight and gender led to dominance of vareniciline over bupropion (16). In the second model, varenicline became dominant when indirect costs were excluded or when baseline treatment costs increased, in both genders and at both time horizons used as the base analysis (20 years and 50 years) (17). In this same model varenciline was no longer cost-effective when in men the time horizon was shortened to 2 years and in women when it was shortened to 2 years or 5 years, regardless if indirect costs were included.

Although the non-BENESCO models conducted univariate deterministic sensitivity analyses on many variables (Table 2) only one changed the original conclusion (24,25). In the model by Hagan et al., when costs were adjusted for age and smoking status, varenicline became a dominant strategy.

Discussion

The majority of studies that compare the cost-effectiveness of varenicline to bupropion use the BENE-

SCO Markov model and have concluded varenicline is a dominant strategy. Variations in methodology between these models did not appear to influence the overall conclusions. The two studies that used non-BENESCO Markov models found varenicline to be cost-effective when applying the ICER in LYG. However, four studies that used the BENESCO models also reported their results using LYG and concluded vareniciline to be a dominant strategy. Therefore, difference between the BENESCO and non-BENESCO models may account for the difference in cost-effectiveness conclusions derived. Through our systematic literature search, no discrete event simulations modelling the cost-effectiveness of varenicline compared with bupropion for smoking cessation were identified. We excluded decision analyses from this systematic review as they do not adequately represent long-term chronic conditions with events that occur repeatedly over a lifetime (12).

In BENESCO models, time horizon affected conclusions most, being the only evaluated variable that led varenicline to be no longer cost-effective when the time horizon was shortened to 2, 5 or 10 years. Varenicline was no longer dominant when the following variables were altered: cost of bupropion, efficacy of either drug, age and incidence of smoking related disease. In one non-BENESCO model, sensitivity analysis determined that cost, when adjusted for age and gender, led varenciline to be a dominant strategy.

The comparison of model strengths and limitations will allow clinicians and decision-makers to select the most applicable model for their individual situation. However, considering all parameters, it appears that BENESCO models are more applicable than the other models identified. In terms of health conditions modelled, the BENESCO models more comprehensively evaluate various conditions compared with non-BENESCO models, which only included death. The BENESCO model by Bae et al. included additional cancers as health states, beyond lung cancer which is the common cancer modelled in other BENESCO models. Although Bae et al. did not include asthma exacerbations in their model, as was the case with Bolin et al., the other BENESCO models did. However, the limitation with BENESCO models is that they equate the risk of morbidity for 'never smokers' to 'long-term quitters'. This might be comprehensible for the health states CHD, stroke, or asthma, but is less satisfactory for irreversible conditions such as COPD or lung cancer. There are also a few cases where only one model is available. First, only one model comprehensively evaluated the societal perspective and therefore if indirect costs are of interest, the BENESCO model by Bolin et al. should be considered. Second, the BENESCO model by Knight et al. was the only model to evaluate the extended duration regimen for varenicline.

The only model to allow annual quit attempts was a non-BENESCO model by Heitjan et al. (25), whereas the others permitted one lifetime quit attempt. Taking into consideration that the majority of smokers cycle through periods of abstinence and relapse in their lifetime before successfully quitting (7), this model is the only one which appears to resemble commonly observed smoking cessation patterns. Increasing the number of allowed quit attempts would increase medication costs, and since some models were sensitive to this variable, we suspect that this could lead to changes in the conclusions. However, the model by Heitjan et al. only considered death and the relapse rate of 50% was held constant over time. It is more likely that the risk of relapse diminishes over time (7).

Several limitations have been observed in the applicability of all identified models. Recently, the Food and Drug Administration announced that varenicline, when compared with placebo, may be associated with a small but increased risk of non-fatal myocardial infarction, need for coronary revascularisation, angina pectoris, and new diagnosis of peripheral vascular disease or admission for a procedure for the treatment of peripheral vascular disease in patients with cardiovascular disease (34). This was supported by a recent meta-analysis by Singh et al., that showed the odds of a serious adverse cardiovascular event were significantly increased in patients taking varenicline compared with placebo (Peto's odds ratio 1.72, 95% confidence interval 1.09–2.71) (35). Most of the models in this review included CHD as a health state and two of the models reported that the lifetime accumulated costs in a patient taking varenicline ranged from 20–21%. Therefore, if varenicline itself may increase the risk of heart disease, which is currently unaccounted for within the models, the conclusion of cost-effectiveness may change. In addition, no models account for drug related adverse events, which in clinical practice may lead to non-adherence and subsequent treatment failure. Some of the reviewed studies, however, suggest that the addition of adverse events to the model would in all likelihood not be influential given the short treatment course and relatively low risk of adverse events.

In addition, none of the models define quantity of smoked cigarettes in the starting state. However, all models evaluating vareniciline or bupropion for 12 weeks used efficacy data from trials that included individuals who smoked at least 10 cigarettes a day and on average 21–22.5 cigarettes a day over a 1-

month period (8,9). Hence, the efficacy data are most applicable to individuals who smoke an average of one pack of cigarettes per day. A deterministic sensitivity analysis on the amount of cigarettes smoked per day would be beneficial, and would likely influence the conclusions. Lastly, drug efficacy was identified to change the conclusion in some models and in one model varenciline was no longer cost-effective with decreased efficacy. RCT-based efficacy data used in these models are likely an overestimation for several reasons. To begin with, counselling interventions and patient follow-up are very structured and rigorously implemented in RCTs. Furthermore, data supports that the combination of drug therapy and counselling shows higher efficacy than either intervention alone (7). Therefore, unless rigorous programmes such as those in RCTs are implemented, the cost-effectiveness of interventions may change substantially. In addition, there is little data evaluating cost-effectiveness of extended duration regimens, which may be appropriate in certain clinical situations (7).

Conclusion

The majority of published models that compare the cost-effectiveness of varenicline to bupropion for smoking cessation use the BENESCO Markov model and conclude that varenicline is a dominant strategy. Other non-BENESCO Markov models conclude that varenicline is a cost-effective strategy. The cost-effectiveness of extended duration varenicline is less clear since only one model has evaluated this regimen. Variables which may lead to changes in varenicline's cost-effectiveness vary based on the model type. For the more commonly reported BENESCO model, important variables include time horizon, cost of bupropion, efficacy of either drug, age and incidence of smoking related disease. When applying the results of cost-effectiveness models to clinical practice, clinicians should consider these influential variables as well as the identified limitations in the applicability of the models.

Author contributions

DMS and CIC contributed to the concept, design and drafting of the article. DMS and MM contributed to the data collection, analysis and interpretation and drafting of the article.

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Appendix A. Search strategy

1. Markov Chains/or markov.mp.
2. decision analy*.mp.
3. "Costs and Cost Analysis"/
4. HealthCare Costs/
5. Economics/
6. Models, Economic/
7. 1 or 2 or 3 or 4 or 5 or 6
8. Smoking Cessation/
9. "Tobacco Use Cessation"/
10. smoking cessation.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
11. tobacco cessation.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
12. nicotine replacement therapy.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
13. NRT.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
14. nicotine polacrilex/
15. nicotine gum.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
16. nicotine lozenge.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
17. nicotine inhaler.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
18. nicotine nasal spray.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
19. nicotine patch.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
20. Nicoderm.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
21. Nicorette.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
22. Comitt.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
23. Nicotrol.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
24. Nicotrol NS.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
25. bupropion/
26. bupropion.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
27. Zyban.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
28. varenicline.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
29. varenicline/
30. Chantix.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, an, tc, id, tm, tx]
31. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32. 7 and 31

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