Cost-effectiveness of varenicline, bupropion and nicotine replacement therapy for smoking cessation

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
No 10–2010
Health economic evaluation

kunnskapssenteret
Norwegian Knowledge Centre for the Health Services

Background: Smoking is an important risk factor for several diseases, including different cancers, lung diseases and cardiovascular diseases. About 21% of the Norwegian population are daily smokers. In Norway, two prescription drugs are available for use in smoking cessation; varenicline (Champix ® or Chantix ®) and bupropion (Zyban ®). In addition, several options for nicotine replacement therapy (NRT) are available, such as nicotine-gum, patches and lozenges. • We were commissioned to evaluate the cost-effectiveness of drugs for smoking cessation in a Norwegian setting. The economic evaluation will inform a revised treatment guideline for smoking cessation in primary care. **Method:** We preformed a model based economic evaluation of nicotine replacement therapy (NRT), bupropion and varenicline for smoking cessation. The drugs were compared to placebo and to each other. **Results:** When NRT, bupropion and varenicline are each compared to placebo, they will respectively yield 0.02, 0.09 and 0.14 additional life years, at an additional cost of respectively NOK 4 141, NOK 5 729 and NOK 9 672. The net health benefit (NHB) of nicotine replacement therapy *(continued)*

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Report: ISBN 978-82-8121-341-8 ISSN 1890-1298

no 10–2010

kunnskapssenteret

(continued from page one) (NRT), bupropion and varenicline compared to placebo then becomes respectively 0.012, 0.079 and 0.121. Compared to bupropion, varenicline gives 0.05 additional life years at an additional cost of 3 944. The incremental cost-effectiveness ratio of varenicline compared to bupropion is NOK 78 880 per life year gained, giving a net health benefit of 0.042 life years. • In the scenario analysis on alternative cost input, all treatments are more effective and cost saving (dominant) compared to placebo. Varenicline yields the highest health gains and the largest savings. • The sensitivity analyses indicate that the conclusions are robust. **Conclusion:** Nicotine replacement therapy (NRT), bupropion and varenicline can all be considered cost-effective compared to placebo. When the drugs are evaluated relative to each other, varenicline is the most cost-effective alternative.

Title	Cost-effectiveness of varenicline, bupropion and nicotine replacement therapy for smoking cessation.
Norwegian title	Kostnadseffektiviteten av vareniklin, bupropion og nikotinerstatningspreparater for røykelsutt.
Institution	Norwegian Knowledge Centre for the Health Services (Nasjonalt kunnskapssenter for helsetjenesten) John-Arne Røttingen, *Director*
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ISBN	978-82-8121-341-8
ISSN	1890-1298
Report nr	10 - 2010
Project number	535
Type of report	Health economic evaluation
No. of pages	48
Client	Directorate of Health (Helsedirektoratet)
Keywords	Cost-effectiveness, economic evaluation, smoking cessation, varenicline, bupropion, nicotine repacement therapy, NRT, Champix, Chantix, Zyban, nicotine gum, nicotine patch, økonomisk evaluering, røykeslutt, røyking, røyk, vareniklin, bupropion, nikotinerstatninspreparater, nikotintyggegummi, nikotinplaster, kostnadseffektivitet.
Citation	Hagen G, Wisløff T, Klemp M. Cost-effectiveness of varenicline, bupropion and nicotine replacement therapy for smoking cessation. Report nr 10-2010. Oslo: Norwegian Knowledge Centre for the Health Services, 2010.

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Norwegian Knowledge Centre for the Health Services assumes final responsibility for the content of this report.

Norwegian Knowledge Centre for the Health Services
Oslo, May 2010

Key messages

Background

Smoking is an important risk factor for several diseases, including different cancers, lung diseases and cardiovascular diseases. About 21% of the Norwegian population are daily smokers.

Interventions for smoking cessation are normally divided into counselling and drug treatment support. In Norway, two prescription drugs are available for use in smoking cessation; varenicline (Champix ® or Chantix ®) and bupropion (Zyban ®). In addition, several options for nicotine replacement therapy are available, such as nicotine-gum, patches and lozenges.

Commission

We were commissioned to evaluate the cost-effectiveness of drugs for smoking cessation in a Norwegian setting. The economic evaluation will inform the revised treatment guideline for smoking cessation in primary care.

Main findings

- Compared to no treatment, nicotine replacement therapy, bupropion and varenicline can all be considered cost-effective.

- When the drugs are evaluated relative to each other, varenicline is the most cost-effective alternative.

Executive summary

BACKGROUND

Smoking is an important risk factor for several diseases, including different cancers, lung diseases and cardiovascular diseases. About 21% of the Norwegian population are daily smokers. Interventions for smoking cessation are normally divided into counselling and drug treatment support. In Norway, two prescription drugs are available for use in smoking cessation; varenicline (Champix ® or Chantix ®) and bupropion (Zyban ®). In addition, several options for nicotine replacement therapy (NRT) are available, such as nicotine-gum, patches and lozenges. These do not require a prescription from a doctor.

We were commissioned to evaluate the cost-effectiveness of drugs for smoking cessation in a Norwegian setting. The economic evaluation will inform a revised treatment guideline for smoking cessation in primary care.

METHOD

We preformed a model based economic evaluation of nicotine replacement therapy (NRT), bupropion and varenicline for smoking cessation. The drugs were compared to placebo and to each other.

We constructed a Markov model with the health states “smoker”, “smoke free more than five years (ex smoker)”, “smoke free less than five years (quitter)”, “resumed smoking less than five years ago” and “dead”. A Markov model follows a hypothetical cohort of patients over time, in our model we followed the individuals from a variable age at treatment initiation and until they all were dead or 100 years old. In the first year of the model, the individuals received treatment with NRT, bupropion or varenicline or they received no treatment. The efficacies of the treatments were collected from our systematic review of the literature. The model calculated the life years gained and the costs associated with pharmacological treatments for smoking cessation.

RESULTS

The baseline results presented in this part are for a 50 years old male. Sensitivity analyses indicate that smoking cessation is slightly more cost-effective for men than for women and for younger compared to older people, but the differences are so small that conclusions will not be affected.

When NRT, bupropion and varenicline are each compared to placebo, they will respectively yield 0.02, 0.09 and 0.14 additional life years, at an additional cost of respectively NOK 4 141, NOK 5 729 and NOK 9 672. The net health benefit (NHB) of nicotine replacement therapy (NRT), bupropion and varenicline compared to placebo then becomes respectively 0.012, 0.079 and 0.121.

All treatments have a positive net health benefit and can be considered cost-effective compared to placebo assuming a Norwegian threshold value of NOK 500 000 per life year gained. NRT is however extendedly dominated by bupropion, as the incremental cost-effectiveness ratio (ICER) for NRT is higher than the ICER for bupropion, the second most effective alternative. The implication of this is that if the NRT alternative were to be chosen, effectiveness would be bought at a higher marginal cost than necessary.

When several treatment options are available and they are mutually exclusive, treatments should be compared to the next more effective option. We therefore ordered the treatments according to increasing effectiveness and recalculated the incremental costs and effects. Since NRT was excluded based on extended dominance, bupropion was compared to no treatment and varenicline to bupropion. Compared to bupropion, varenicline gives 0.05 additional life years at an additional cost of 3 944. The incremental cost-effectiveness ratio of varenicline compared to bupropion is NOK 78 880 per life year gained, giving a net health benefit of 0.042 life years. When the drugs are evaluated relative to each other, varenicline is the most cost-effective option.

The one-way sensitivity analyses indicate that the base case results are most sensitive to changes in age at treatment initiation, the price of varenicline, average health care expenses per person per year and choice of discount rate. None of the changes in the parameters will bring the ICER above the assumed willingness to pay per life year of NOK 500 000.

In the probabilistic sensitivity analysis, varenicline was the optimal choice in terms of cost-effectiveness as long as the willingness to pay per life year gained was above NOK 116 000. If the willingness to pay was between NOK 100 000 and NOK 116 000, bupropion was optimal. If the willingness to pay was less than NOK 100 000 per life year gained, none of the treatments could be considered cost-effective.

In the base case we assumed that smokers and ex-smokers had the same annual health care costs and that health care costs were constant across age. This may not be a valid assumption. We therefore constructed a scenario analysis based on Danish data where smokers had higher annual health care costs than the ex-smokers and where annual health care costs varied with age. In the scenario analysis all treatment options were dominant, *i.e.* more effective and less expensive than no treatment. Treatment with varenicline gave the highest health gains in terms of life years and also the largest savings.

The analysis on perfect information on parameters indicated that perfect information on the input parameters would not reduce the uncertainty in the decision, given the assumed willingness to pay of NOK 500 000 per life year gained.

DISCUSSION

All models are simplifications of reality; hence, there is uncertainty associated with the results. Some of the uncertainty is related to the model input, *i.e.* the parameter estimates used. Our model input has been gathered from a range of sources and they may not on their own represent true values for a Norwegian population in a real-life setting. We have however conducted a range of sensitivity analyses on these parameters and the conclusions appear robust to realistic changes in these values.

Another aspect of uncertainty is connected to the model structure. This model was structured to capture the life years gained from smoking cessation. The model therefore only contains the health states necessary to capture costs and health effects of being either dead or alive. In reality however, smoking will increase the risk of a variety of diseases, most notably different cancers, lung diseases and cardiovascular diseases. These diseases can lead to large reductions in health related quality of life. It is therefore possible that we are underestimating the cost-effectiveness of these drugs.

The published economic evaluations we have identified come to the same conclusion as we have. Some of the studies do, however, find that varenicline is dominant (higher health gains and lower costs) compared to bupropion. In our base case analyses, varenicline have higher health gains, but do not have lower costs than bupropion. In our scenario analysis where smokers are more expensive than ex-smokers, we do however find that varenicline is dominant compared to bupropion.

CONCLUSION

Nicotine replacement therapy (NRT), bupropion and varenicline can be considered cost-effective compared to placebo. When the drugs are evaluated relative to each other, varenicline is the most cost-effective alternative.

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Hovedfunn

Bakgrunn

Røyking er en sterk risikofaktor for en rekke sykdommer, blant annet ulike typer kreft, lungesykdommer og hjerte- og karsykdommer. I Norge er det ca 21 % av befolkningen som røyker daglig. Tiltak for røykeslutt deles vanligvis inn i veiledning og medikamentell støttebehandling. I Norge finnes det to reseptpliktige legemidler til bruk ved røykeslutt, vareniklin (Champix® eller Chantix®) og bupropion (Zyban®). I tillegg finnes det flere nikotinerstatningspreparater, som tyggegummi, plaster og sugetabletter.

Oppdrag

Helsedirektoratet har bedt oss om å vurdere kostnadseffektiviteten av legemidler til røykeslutt under norske forhold. Den økonomiske evalueringen er tenkt brukt som en del av dokumentasjonsgrunnlaget for nye nasjonale faglige retningslinjer for røykeavvenning i primærhelsetjenesten.

Hovedfunn

- Sammenlignet med ingen behandling kan både nikotinerstatningspreparater, bupropion og vareniklin ansees som kostnadseffektive.

- Når legemidlene sammenlignes med hverandre, kommer vareniklin ut som det mest kostnadseffektive alternativet.

Sammendrag

BAKGRUNN

Røyking er en risikofaktor for en rekke sykdommer, blant annet kreft, lungesykdommer og hjerte- og karsykdommer. I Norge røyker ca 21 % av befolkningen daglig. Tiltak for røykeslutt deles vanligvis inn i veiledning og medikamentell støttebehandling. I Norge finnes det to reseptpliktige legemidler til bruk ved røykeslutt, vareniklin (Champix® eller Chantix®) og bupropion (Zyban®). I tillegg finnes det en rekke nikotinerstatningspreparater (NEP) i form av tyggegummi, sugetabletter, sublingvaltabletter, plaster og inhalator som ikke er reseptbelagt.

På oppdrag fra Helsedirektoratet har vi vurdert kostnadseffektiviteten av legemidler til røykeslutt. Rapporten er tenkt brukt som en del av dokumentasjonsgrunnlaget for nye faglige retningslinjer for røykeavvenning i primærhelsetjenesten.

METODE

Vi utførte en modellbasert økonomisk evaluering av legemidler til røykeslutt. Legemidlene som ble evaluert var vareniklin, bupropion og nikotinerstatningspreparater (NEP). Legemidlene ble sammenlignet med ingen behandling og med hverandre.

Vi utviklet en Markov-modell med helsetilstandene ”røyker”, ”røykfri i mer enn fem år (eksrøyker)”, ”røykfri mindre enn fem år”, ”begynt å røyke igjen for mindre enn fem år siden” og ”død”. En Markov-modell følger en tenkt kohort over tid, i vår modell fulgte vi individene fra en tenkt startalder og til alle personene var enten døde eller hundre år gamle. I første år av modellen mottok individene behandling med vareniklin, bupropion, nikotinerstatningspreparater eller ingen behandling. Effekter av behandlingene som gikk inn i modellen ble hentet fra vår systematiske kunnskapsoppsummering (1).

Modellen beregner leveårsgevinsten og kostnadene ved å gi medikamentell støtte til røykeslutt.

RESULTATER

Resultatene presentert under er for en mann på 50 år. Sensitivitetsanalysene indikerer at røykeslutt er noe mer kostnadseffektivt for menn enn for kvinner og for yngre sammenlignet med eldre, men forskjellene er så små at konklusjonene ikke påvirkes.

Sammenlignet med ingen behandling gir nikotinerstatningspreparater, bupropion og vareniklin henholdsvis 0,02, 0,09 og 0,14 ekstra leveår per person til en merkostnad på henholdsvis kr 4 141, 5 729 og 9 672. Netto helsenytte av henholdsvis nikotinerstatningspreparater, bupropion og vareniklin blir da 0,012, 0,079 og 0,121.

Sammenlignet med ingen behandling, kan alle intervensjonene ansees som kostnadseffektive ettersom de gir en positiv netto helsenytte, gitt at vi antar at samfunnets betalingsvilje per leveår er kr 500 000. Nikotinerstatningspreparatene blir imidlertid eksternt dominert av bupropion, hvilket vil si at man ved å velge nikotinerstatning vil kjøpe ekstra leveår til en høyere merkostnad enn nødvendig, nikotinerstatningspreparater bør derfor ekskluderes fra videre analyse av kostnadseffektivitet.

Når flere alternativer er tilgjengelige og de er gjensidig utelukkende, bør legemidlene sammenlignes med hverandre og ikke med ingen behandling. Vi rangerte derfor legemidlene etter økende effekt og rekalkulerte mereffektene og merkostnadene. Siden nikotinerstatningspreparatene ble ekskludert, ble bupropion sammenlignet med ingen behandling og vareniklin sammenlignet med bupropion. Sammenlignet med bupropion vil vareniklin gi 0,05 ekstra leveår til en merkostnad på kr 3 944, dette gir en inkrementell kostnad-effekt brøk på 78 880 kr per leveår og en netto helsenytte på 0,042 leveår. Vareniklin ble det mest kostnadseffektive alternativet når legemidlene ble sammenlignet med hverandre.

En-veis sensitivitetsanalysene indikerte at base case resultatene var mest følsomme for endringer i intervensjonsalder, prisen av vareniklin, gjennomsnittlig årlig helsekostnad per innbygger og valg av diskonteringsrate. Å endre disse parametrene en og en, ga ikke tilstrekkelig utslag på kostnad-effektbrøken til at denne kom over den antatte grensen på NOK 500 000 per leveår.

I den probabilistiske (stokastiske) sensitivitetsanalysen, ble vareniklin det optimale i form av kostnadseffektivitet så lenge betalingsviljen per leveår var høyere enn kr 116 000. For en betalingsvilje mellom kr 100 000 og kr 116 000 var bupropion det optimale valget. Dersom betalingsviljen per leveår var mindre enn kr 100 000, var ingen av legemidlene kostnadseffektive sammenlignet med ingen behandling.

I hovedanalysen antok vi at røykerne og eksrøykerne hadde like store årlige helsekostnader. Dette er sannsynligvis ikke en realistisk forutsetning. Vi utførte derfor en senarioanalyse basert på danske data, hvor røykerne hadde høyere årlige helsekost-

nader enn eks-røykerne og hvor de årlige helsekostnadene varierte med alder. I dette scenarioet ble alle behandlingene mer effektive og kostnadsbesparende sammenlignet med ingen behandling. Behandling med vareniklin ga størst gevinst i form av leveår og førte også til de største besparelsene.

Analysen på verdien av videre forskning indikerte at perfekt informasjon på parametrene i modellen ikke ville minke usikkerheten i beslutningen hvis vi antar en betalingsvilje per leveår på kr 500 000.

Sensitivitetsanalysene indikerer at konklusjonene er robuste.

DISKUSJON

Alle modeller er forenklinger av virkeligheten og det er derfor usikkerhet knyttet til resultatene. Usikkerheten er delvis knyttet til modellstrukturen og delvis til verdien av de ulike modellparametrene. De ulike parameterverdiene brukt i denne analysen kommer fra en rekke kilder og er ikke nødvendigvis representative for norsk praksis.

Vi har imidlertid utført en rekke sensitivitetsanalyser for å kvantifisere effekten av usikkerheten i modellparametrene og konklusjonene synes robuste.

Et annet aspekt av usikkerhet er forbundet med modellstrukturen. Denne modellen ble bygd for å fange opp leveårsgevinsten ved røykeslutt. Modellen inneholder derfor kun de helsetilstandene som er nødvendige for å fange opp kostnader og helseeffekter av å være levende eller død. I virkeligheten vil røyking øke risikoen for en rekke sykdommer, først og fremst ulike krefttyper, lungesykdommer og kardiovaskulære sykdommer. Disse sykdommene kan føre til store tap i helserelatert livskvalitet. Det er derfor mulig at vi i hovedanalysen har underestimert kostnadseffektiviteten av disse legemidlene.

Andre publiserte økonomiske evalueringer vi har identifisert har den samme konklusjon som vi finner i vår analyse. Noen av studiene finner imidlertid at vareniklin er dominant (gir større helsegevinster og lavere kostnader) sammenlignet med bupropion. Dette er resultatet vi også kommer til i scenarioanalysen når vi lar røykerne pådra seg større kostnader i sine leveår enn eks-røykerne.

KONKLUSJON

Både nikotinerstatningspreparater, bupropion og vareniklin ansees som kostnadseffektive sammenlignet med ingen behandling. Når legemidlene sammenlignes med hverandre, kommer vareniklin ut som det mest kostnadseffektive alternativet.

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Glossary

Term	Explanation
One-way sensitivity analysis	A change in one model parameter from a lower to an upper value and the effect of the change on the ICER (*i.e.* estimated upper and lower ICER based on the upper and lower parameter value).
ICER	The incremental cost-effectiveness ratio, *i.e.* the difference in costs between two strategies divided by the difference in health effects (often life years or quality adjusted life years). ICER= ΔC/ ΔE
Willingness to pay (WTP)/threshold value/λ	Societal willingness to pay per unit of effectiveness, for example per life year or quality adjusted life year. Assumed to be maximum NOK 500 000 per life year or quality adjusted life year in Norway.
NHB	Net health benefit. NHB=ΔE-(ΔC/ λ) A treatment is considered cost-effective if it yields a positive net health benefit.
Tornado diagram	Visual representation of a series of one-way sensitivity analyses. Presents a number of bars, each representing the change in the ICER based on the change in one

	parameter. The bars are ordered according the impact the change in the parameter has on the estimated ICER. Indicates which parameters the ICER is most sensitive to changes in. Often presented with a horizontal line which represents either the estimated ICER or the threshold value for the ICER. The tornado diagram is very sensitive to the upper and lower value chosen for each parameter.
Probabilistic sensitivity analysis (PSA)	A stochastic sensitivity analysis. Each parameter is assigned a probability distribution instead of one fixed number. A Monte Carlo simulation with n-number of draws (often 10 000) is performed based on the input distributions and the ICER recalculated n-number of times. Often presented in the form of an ICE scatter plot.
Incremental cost-effectiveness scatter plot	A graphical representation of different simulated ICERs (from a Monte Carlo simulation) on the cost-effectiveness plane.

Preface

The Norwegian Knowledge Centre for the Health Services was commissioned by the Directorate of Health to evaluate the cost-effectiveness of drugs for smoking cessation in the Norwegian setting. The drugs were to be compared to placebo and to each other. The economic evaluation will inform the revision of the current treatment guideline for smoking cessation in primary care.

The project team has consisted of:

- Gunhild Hagen (project manager), Kunnskapssenteret
- Torbjørn Wisløff, , Kunnskapssenteret

We would like to thank our external peer reviewers Ivar Sønbø Kristiansen and Bjarne Robberstad and our internal peer reviewer Espen Movik.

The aim of this report is to make decisions in health care more well-informed and to contribute to improved quality of services. The evidence should be considered together with other relevant factors, such as clinical experience and patient preferences.

Gro Jamtvedt	Marianne Klemp	Gunhild Hagen
Excecutive Director	*Research Director*	Health Economist
		Project Manager

Objective

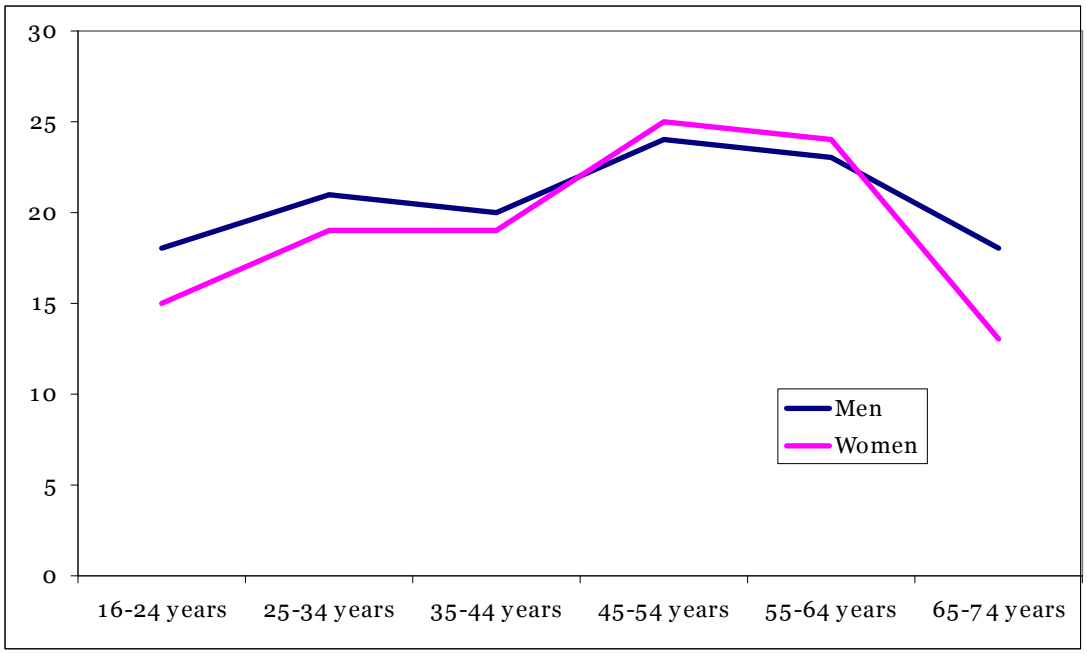
The objective of this report was to evaluate the cost-effectiveness of varenicline, bupropion and nicotine replacement therapy for smoking cessation in the Norwegian setting.

Background

PREVALENCE

The prevalence of daily smoking in Norway has been decreasing over the last few years. Data from 2008 indicate that approximately 21% of the Norwegian population report to be daily smokers. An additional, 9-10% report that they smoke occasionally (2). The percentage of reported daily smokers varies with age and gender.

Figure 1: Prevalence of reported daily smokers in Norway in percent according to age and gender in 2009 (3)



Smoking prevalence also varies with level of education: Highly educated individuals are less likely to be smokers than individuals with lower levels of education (4).

HEALTH AND ECONOMIC COSTS OF SMOKING

Smoking is an important risk factor for a variety of diseases, most notably different forms of cancer, lung diseases and cardiovascular diseases (5). The Norwegian Institute of Public Health has estimated that smoking is responsible for 26% of deaths among women between 40 and 70 years of age. The corresponding number for men is 40 % (5). A report from the Swedish institute of Public Health estimates that smoking cost the Swedish society SEK 8 267 million in 2001 (6). This figure comprises costs of health care as well as costs related to loss of production.

PHARMACOLOGICAL TREATMENT OPTIONS

There are two prescription drugs on the Norwegian market approved for smoking cessation; bupropion and varenicline. In addition, several different formulations of nicotine replacement therapy (NRT) are available, among them transdermal nicotine patch, gum, lozenges and vapour inhaler.

Details on the different treatment options can be found in our review of the efficacy and safety of drugs for smoking cessation (1).

INTRODUCTION TO THE METHODS OF ECONOMIC EVALUATION

An economic evaluation is a comparison of the costs and health effects of different treatment options, the results of which are often represented in the form of an incremental cost-effectiveness ratio (ICER). The incremental cost-effectiveness can be regarded as the cost per unit of health, and is calculated as the ratio of the difference in costs between two options over the difference in effectiveness.

$$ICER = \frac{Cost_{\text{intervention}} - Cost_{\text{comparator}}}{Effect_{\text{intervention}} - Effect_{\text{comparator}}} = \frac{\Delta C}{\Delta E}$$

A treatment is considered cost-effective if the ICER is below a threshold value, or in common language, if the cost per unit of health (*e.g.* a life year or quality adjusted life year) is lower than the societal willingness to pay (λ).

$$\frac{\Delta C}{\Delta E} < \lambda$$

Alternatively the ICER and societal willingness to pay can be presented in the form of net health benefits (NHB). A treatment is considered cost-effective if it yields a positive net health benefit.

$$NHB \ : \Delta E - \frac{\Delta C}{\lambda} > 0$$

Economic evaluations are often based on decision models (such as decision trees, Markov models etc) that calculates the results of the analysis from input parameters in the model. There are always uncertainties related to the values of these parameters, making sensitivity analyses an important feature of any economic evaluation that uses decision models as framework. In short, sensitivity analysis illustrates how much the results vary when model parameters are being changed.

Parameters can be changed one at a time, in a one-way sensitivity analysis. The ICER is then recalculated using an upper and lower value for the given parameter. The upper and lower value can be taken from the upper and lower end of a 95% confidence interval or by increasing and decreasing the value by a percentage. A series of one-way sensitivity analyses can be presented in a tornado diagram. A tornado diagram is a graphical representation of a series of one-way sensitivity analyses, presented as a series of bars. The bars are ordered according to the impact the variable change has on the estimated ICER. A tornado diagram can indicate which parameters the ICER is most sensitive to changes in. The result of a tornado diagram is very sensitive to the upper and lower value chosen.

In a probabilistic sensitivity analysis (PSA) the uncertain parameters in the model are represented by distributions and not fixed values. As opposed to one way sensitivity analysis (like the tornado diagram), all parameters are changed at the same time in a PSA. In Monte Carlo simulations, the computer draws values for each parameter and runs the model for each set of parameters. This is typically done 1 000 or 10 000 times, depending on the number of parameters. The results of these Monte Carlo simulations can be used to calculate the probability of which of the interventions that are cost-effective, if a willingness-to-pay (WTP) is given.

For each draw, the ICER can be recalculated and plotted on the cost-effectiveness plane, *c.f.* Figure 2. ICERs in quadrant 1-3 are considered cost-effective. The sum of percentages of ICERs in quadrant 1-3 is the probability that a treatment is cost-effective given the assumed willingness to pay.

Figure 2: The cost-effectiveness plane

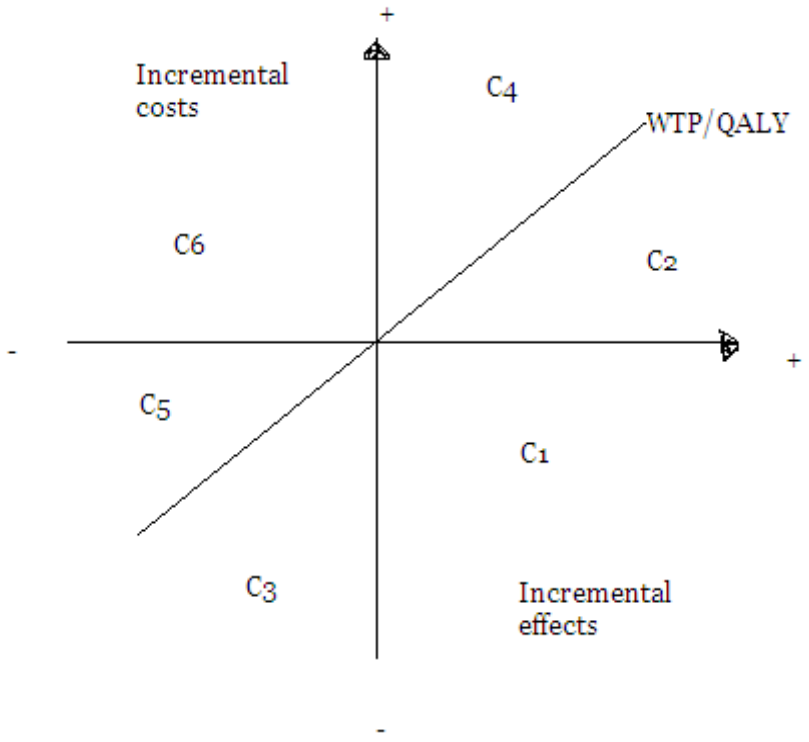


Table 1: Quadrants in the cost-effectiveness plane

Quadrant	Interpretation
C1	The treatment is dominant ('superior'), *i.e.* more effective and less costly than the comparator (positive NHB).
C2	The treatment is more costly and more effective than the comparator and the ICER lies below the WTP (positive NHB).
C3	The treatment is less costly and less effective than the comparator and the ICER lies below the WTP (positive NHB).
C4	The treatment is more costly and more effective than the comparer and the ICER is above the WTP (negative NHB).
C5	The treatment is less costly and less effective, and the ICER lies above the WTP (negative NHB).
C6	The treatment is dominated ('inferior'), *i.e.* less effective and more expensive than the comparator (negative NHB).

ECONOMIC EVALUATION AND PRIORITY SETTING

According to Norwegian policy documents (7-11), a treatment should be prioritised if the following criteria are met:

1. *The disease is severe;* A disease is considered severe to the degree that it causes pain and discomfort, loss of physical, psychological and social function and if it limits the individual in his or her daily activities. Severity is also evaluated according to the risk increase the disease entails in terms of death, disability and discomfort, if treatment is postponed.

2. *The treatment is effective;* the patient should be expected to benefit from treatment in terms of longevity or improved quality of life of certain duration. The treatment effectiveness should also be well documented.

3. *The treatment is cost-effective;* the added costs of the treatment should be reasonable compared to the added benefits.

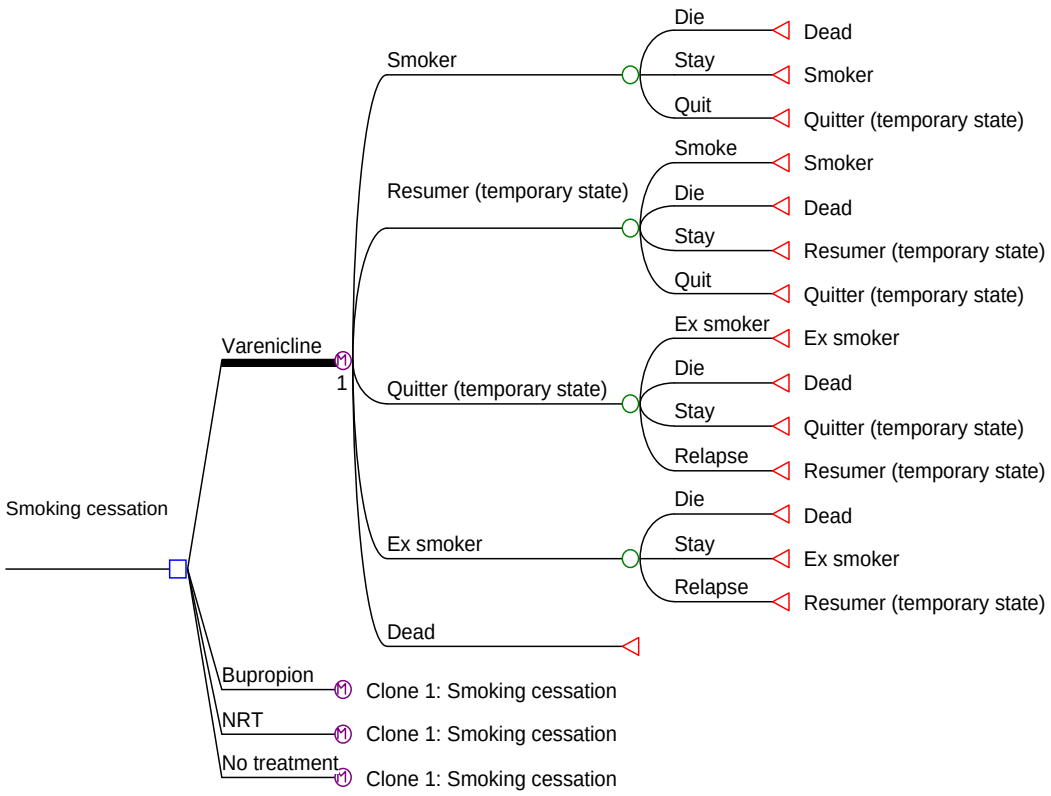
The policy documents mentioned above give no guidance as to what constitutes a"reasonable" relationship between costs and effectiveness. The Directorate of Health however, has recently recommended a preliminary estimate of NOK 500 000 per statistical life year in full health (12;13). However, there exists no academic consensus regarding this threshold value, nor has it been subject to a political process, and it can therefore be regarded as nothing more than a tentative suggestion.

Method

MODEL STRUCTURE

In order to assess the cost-effectiveness of drugs for smoking cessation a Markov model was developed in TreeAge Pro ® 2009. The model structure is illustrated in Figure 3.

Figure 3: Model structure



A Markov model is basically a way of simulating a population cohort over time. The model is structured to capture the costs and life years gained associated with smoking cessation and contains three regular health states;" Smoker", "Ex smoker" (smoke free more than five years) and "Dead" and two temporary health states; "Re-

sumer" (relapsed less than five years ago) and "Quitter" (smoke free less than five years).

We have included temporary states ("tunnel states") in order to be able to differentiate the risk of death for people who have recently stopped smoking ("Quitters") and people who have been smoke free for a longer period of time ("Ex smokers"). We also wanted to be able to differentiate between people who had recently relapsed ("Resumers") and people who could be considered "Smokers" again.

When the model starts, all individuals are smokers. During the first year of the model, individuals receive treatment with either varenicline, bupropion, nicotine replacement therapy (NRT) or they receive no treatment. Some of these individuals will stop smoking during the first year and move to the "Quitter" health state, some will continue to be smokers and some may die either as a consequence of smoking or for other reasons. For individuals who stop there is a possibility of relapse, in which case they return to the resumer status. The cycle length of the model is one year, which means that all transitions between the different health states can happen once a year.

We follow the cohort until the individuals are 100 years old or dead. Costs and life years were discounted at a rate of four percent per year.

EFFICACY

Efficacy estimates were taken from our systematic review of the literature (1). We used estimates of efficacy compared to placebo and relative to the other treatments. Before calculating the relative estimates, we ordered the interventions according to increasing efficacy relative to placebo and then compared each treatment with the next most effective option, *i.e.* NRT to placebo, bupropion to NRT and varenicline to bupropion.

Base case and limits for one-way sensitivity analysis

In the base case calculations we used the point estimates for efficacy shown in Table 2 and 3. For the one-way sensitivity analysis, the limits of the 95% confidence interval were used.

Table 2:Efficacy estimates vs. placebo (1)

Treatment	Efficacy vs. placebo in relative risks (RR)	GRADE	Outcome
NRT vs. placebo	1.58 (1.50-1.66)	Moderate	Abstinent at 6-12 months
Bupropion vs. placebo	1.69 (1.53-1.85)	Moderate	Abstinent at 6 + months
Varenicline vs. placebo	2.33 (1.95-2.80)	High	Continuous abstinence at 24 or more weeks

Table 3: Efficacy estimates relative to the next more effective option (1)

Treatment	Efficacy in relative risks (RR)	GRADE	Outcome
NRT vs. placebo	1.58 (1.50-1.66)	Moderate	Abstinent at 6-12 months
Bupropion vs. NRT	1.45 (0.50-4.18)	Very low	Continuous abstinence at 52 weeks
Varenicline vs. bupropion	1.46 (1.18-1.81)	High	Continuous abstinence at 52 weeks

Distributions used in the probabilistic sensitivity analysis

In the probabilistic sensitivity analysis, parameters are represented as distributions, i.e. they can take on a range of different values. We assigned log-normal distributions to the efficacy parameters according to the methodology described by Briggs and co-workers (14). We incorporated the GRADE assessment into the model by assigning probability distributions related to the quality of the evidence, with a wider spread for the lower quality documentation. For example, for estimates with very low quality documentation, we assumed that the 95% confidence interval in reality represented a confidence interval of 70%. The relationship between the GRADE system and the uncertainty in the model is presented in Table 4. The relationship between GRADE and the width of the confidence intervals are based on our assumptions. All distributions used in the model can be found in Appendix 2.

Table 4: Connection between GRADE and efficacy parameter uncertainty

GRADE	Confidence interval
High	95%
Moderate	90%
Low	80%
Very low	70%

In order to calculate the transition probabilities between the different health states epidemiological data is needed.

Unaided quit rate

The efficacy estimates described above are applied to the probability of smoking cessation without intervention (unaided quit rate). Based on a study by Hughes et al. (15), we set this unaided quit rate to five percent per year. This means that five percent will quit during a year, but they are however later exposed to a risk of relapsing, so the five percent will not necessarily stay smoke free.

As the smokers in our model are only treated in the first year of the model, their probability of cessation in years after the intervention year is assumed to be equal to this unaided quit rate, regardless of what treatment they received.

Risk of death

For transitions to the "Dead" health state, we collected age and gender specific mortality tables from Statistics Norway (16). To these tables we multiplied the relative hazard ratios (HR) from a recently published study (17), shown in Table 5. The hazard rates used are adjusted for age, systolic blood pressure, total serum cholesterol, serum triglycerides, physical activity, body mass index, height, and whether or not the patient is on disability pension, sickness leave or has a family history of coronary heart disease.

Table 5: Relative hazards of death (17)

	Relative hazard of dying for Norwegian women	**Relative hazard of dying for Norwegian men**
Non-smokers	1.00	1.00
Smokers	2.49 (2.29-2.71)	2.61 (2.40-2.85)
Resumers	1.40 (1.08-1.81)	1.59 (1.32-1.91)
Quitters	1.64 (1.38-1.95)	1.39 (1.23-1.58)
Ex-smokers	1.06 (0.90-1.26)	1.07 (0.96-1.19)

In our model, quitters will first gain the full effect of smoking cessation after five years, *i.e.* women will have a relative hazard of dying of 1.64 for the first five years after smoking cessation and in later years a hazard ratio of 1.06 if they stay smoke free. Resumers have a hazard ratio of 1.40 (women) for the first five years after continuation and a hazard ratio of 2.49 if they keep on smoking (17).

Relapse rate

As the efficacy estimates are based on intention to treat (ITT), we have not modelled any additional relapse rate in the first year after treatment initiation. Relapse rate at twelve months and onwards was taken from a study by Hughes and co-workers (18) and set to ten percent per year.

COSTS

Treatment costs

Drug costs are based on maximum pharmacy retail prices, costs per treated patient is shown in Table 6. We have assumed that patients treated with varenicline or bupropion will visit their general practitioner (GP) once in order to get a prescription. Visits to a GP were costed using the 2009 GP tariff (19). As nicotine replacement therapy is available in a range of different formulations and over-the-counter/non-prescription prices are not regulated, pricing this intervention is difficult. For treatment with nicotine replacement therapy (NRT) we assumed that the treatment would last for three months, as recommended by the current treatment guideline for smoking cessation in primary care (20). We also used their estimate of the price of NRT per day of NOK 35.

Table 6: Treatment costs

	Treatment costs per patient (NOK)	Assumptions made	Source
Varenicline	2 456	One GP visit Treated for 105 days	(19;21;22)
Bupropion	1 103	One GP visit Treated for 56 days	(19;23;24)
NRT	3 150	Cost of NOK 35 per day. Treated for 90 days.	(20)

Costs associated with health states and events

All individuals followed in the model will incur health care costs as long as they live. This annual cost is assumed to be the average health care expenses per person in Norway, NOK 45 544 (25). We have assumed that the average annual health care cost is the same for smokers and for ex-smokers. This may not be the case; it is possible that smokes have a higher annual health care cost than ex-smokers. We explore this alternative further in the scenario analysis were we take the costs from a Danish study.

In their last year of life all persons will incur a higher cost, a cost of dying. In our model, this cost component is taken from a Swedish study (26). Adjusted to 2009 NOK, this cost mounts to 73 306.

Results

The baseline results presented here are for a man 50 years old. Sensitivity analyses show that smoking cessation is slightly more cost-effective for men than for women and for younger compared to older people, but the differences are so small that conclusions will not be affected.

BASE CASE RESULTS

When nicotine replacement therapy, bupropion and varenicline are each compared to placebo, they will respectively yield 0.02, 0.09 and 0.14 additional life years, at an additional cost of respectively NOK 4 141, NOK 5 729 and NOK 9 672. These results are presented in Table 7.

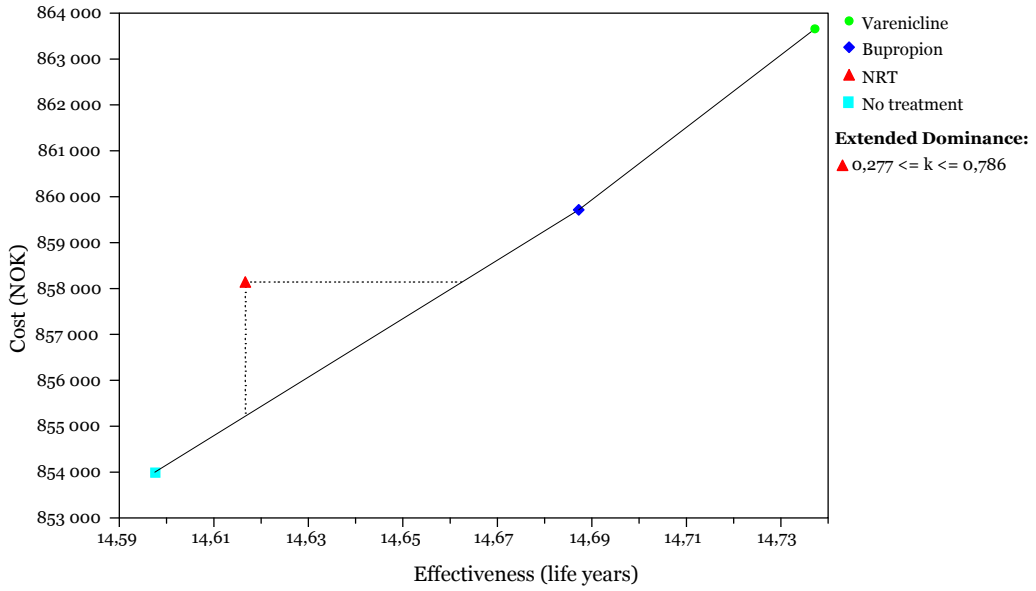
All treatments have positive net health benefits (NHB) assuming a willingness to pay of NOK 500 000 and can therefore be considered cost-effective compared to placebo. Varenicline is the best option in terms of cost-effectiveness, as this treatment yields the highest net health benefit.

Table 7: All treatments compared to placebo

Strategy	*Cost*	*Incremental Cost (NOK)*	*Life years*	*Incremental life years*	ICER *(NOK/life year)*	NHB
No treatment	853 977		14.60			
NRT	858 118	4 141	14.62	0.02	207 050	0.012
Bupropion	859 706	5 729	14.69	0.09	63 656	0.079
Varenicline	863 650	9 672	14.74	0.14	69 086	0.121

Nicotine replacement therapy is, however, extendedly dominated by bupropion, as the incremental cost-effectiveness ratio for nicotine replacement therapy is higher than the incremental cost-effectiveness ratio for bupropion, the next more effective alternative. The implication of this is that if nicotine replacement therapy were to be chosen, effectiveness would be bought at a higher marginal cost than necessary. This is illustrated in Figure 4. Nicotine replacement therapy was therefore excluded from further analysis of cost-effectiveness.

Figure 4:Cost-effectiveness of drugs for smoking cessation, nicotine replacement therapy excluded based on extended dominance



When several treatment options are available and they are mutually exclusive, treatments should be compared to the next more effective option (27). We therefore ordered the treatments according to increasing effectiveness and recalculated the cost-effectiveness ratios. Since nicotine replacement therapy was excluded based on extended dominance, bupropion was compared to no treatment and varenicline to bupropion. Results are shown in Table 8. Compared to bupropion, varenicline gives 0.05 additional life years at an additional cost of 3 944. The incremental cost-effectiveness ratio of varenicline compared to bupropion is NOK 78 880 per life year gained.

Table 8: Treatments compared to the next more effective, when the dominated alternative (NRT) is excluded.

Strategy	***Cost (NOK)***	***Incremental Cost (NOK)***	***Life years***	***Incremental life years***	***ICER (NOK/life year)***	***NHB***
No treatment	853 977		14.60			
Bupropion compared to no treatment	859 706	5 729	14.69	0.09	63 656	0.079
Varenicline compared to bupropion	863 650	3 944	14.74	0.05	78 880	0.042

TORNADO DIAGRAM

A tornado diagram illustrates the impact of a series of one way sensitivity analyses, *i.e.* one parameter is changed at a time. The bars are ordered according to the impact the parameter change has on the ICER. In Figure 5 there's a vertical dotted line representing the assumed willingness to pay per life year of NOK 500 000. Bars that cross the dotted line represent uncertainty that change the decision. The ordering of the parameters is sensitive to the upper and lower values chosen for the different variables.

As illustrated in Figure 5 the results are most sensitive to changes in age at treatment initiation, the price of varenicline, average health care expenses per person per year and choice of discount rate. None of the changes in the parameters will bring the ICER above the assumed willingness to pay per life year of NOK 500 000. A text report from this tornado diagram can be found in Appendix 1.

Figure 5: Tornado diagram of varenicline compared to bupropion