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Original

Cost-effectiveness of Varenicline versus existing alternatives for smoking cessation using the BENESCO model in the costarican adult population

(Costo-efectividad del uso de la Vareniclina versus las alternativas existentes para la cesación del fumado usando el modelo BENESCO en la población adulta costarricense)

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Abstract

Aim: Tobacco use is one of the most serious health problems worldwide and it´s a preventable addiction; this is why the availability of treatments to quit smoking represents a great benefit to each individual's health as to institutional systems. Given the use of new treatments, particularly Varenicline, the available choices in Costa Rica must be comparatively evaluated because it is not clear which therapeutic option is the best and which generates the best cost-effectiveness ratio. The aim of this study was to model the cost-effectiveness of the therapeutic options for smoking cessation available in Costa Rica using the BENESCO model.

Methods: The BENESCO model was used to simulate the morbidity and mortality of the smoking population of Costa Rica, for both genders, between 18 and 99 years old. In this model, each smoker makes only one attempt to quit smoking at the beginning of the simulation. The strategies compared were: Varenicline, Bupropion, Nicotine replacement therapy, self determination (without intervention) and motivational group-speeches. The smoking-related diseases taken into account were: acute myocardial infarction, chronic obstructive pulmonary disease, stroke and lung cancer. The prevalence, incidence and mortality were obtained and calculated from the Costarican Social Security´s (CCSS) data base and the Institute of Alcoholism and Pharmacodependence of Costa Rica (IAFA). The costs of the diseases were calculated and updated to September, 2008.Deterministic, probabilistic and sensitivity analyses were carried out.

Results: Of all the strategies for smoking cessation, Varenicline was the therapeutic alternative with the less mortality and morbidity in the studied years. Regarding costs, Varenicline was also the less expensive option after the fifth year. After 2 years, motivational speeches were ¢3.443.167 cheaper than Varenicline. The intervention with the largest number of quality-adjusted life years and gained life years was Varenicline. Varenicline was the most effective option in the cost-incremental analysis, this means, it was clinically the most

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Abbreviations: TC, Tobacco Consumption; CCSS, Caja Costarricense del Seguro Social; CVD, Cardiovascular Disease; ICD, Ischemic Coronary Disease; COPD, Chronic Obstructive Pulmonary Disease; IAFA, Instituto sobre Alcoholismo y Farmacodepencia; AMI, Acute Myocardial Infarction; INEC, Instituto Nacional de Estadística y Censo; IMS, Intercontinental Marketing Services; QALY, life quality-adjusted life years; GLY, gained life years; NRT, Nicotine Replacement Therapy

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Conclusion: The results obtained suggest that Varenicline is the best cost-effective intervention for smoking cessation in comparison with Bupropion, NRT, self determination and motivational speeches. It was proven that Varenicline represents important economic savings for health systems and health institutes using it, since it reduces morbidity and the costs related to tobacco-associated diseases.

Keywords: Pharmacoeconomics, cost-effectiveness, Varenicline, BENESCO simulation model, smoking cessation, life prevalence.

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Conflicts of interest

We the authors do note that we work for Pfizer S.A. (Inc.) and that we have no commercial associations that might pose a direct conflict of interest with this article, except the aforementioned.

Tobacco consumption (TC) is one of the most serious health issues worldwide, killing one person every 6 seconds. Nowadays, tobacco causes 1 out of 10 adult deaths worldwide, ie, more than 5 million people each year. [1]

Usually, tobacco-related problems are chronic diseases, resulting in a huge economic impact on health systems. Between the most important diseases we could mention lung cancer, Chronic Obstructive Pulmonary Disease (COPD), coronary artery disease and stroke. [2]

In Costa Rica, data from the IAFA´s 2000-2001 National Survey showed a TC prevalence of 29,9% in the population between12 and 70 years old. In men, a 41,1% prevalence was found, while an 18,8% prevalence was found in the female population. [3]

When comparing data from the 2000 survey with data from 1995, the average daily cigarette consumption increased to 12,6 units. Men consumed 13,6 cigarettes a day and women 10 cigarettes daily. [3]

In Costa Rica, since 1970, mortality from cardiovascular disease (CVD) has constituted the main cause of death for both men and women. 48% of CVD deaths are because of ischemic coronary disease (ICD), and two thirds of ICD deaths are because of acute myocardial infarction (AMI), the leading individual cause of death for both sexes in Costa Rica; with the majority of cases occurring in men. [4]

Most recent rates from Caja Costarricense del Seguro Social (Costarican Social Security Institution, CCSS) in relation to AMI are from 2001, and show a mortality rate of 39,99 deaths per 100 000 inhabitants, being 46,11 in men and 33,83 in women. [5]

Regarding malignant tumors, in 2003, these tumors represented the second death cause in the costarican population. [6]

Data from CCSS in 2003 show that lung cancer was the third more frequent neoplasia in men, with a 13,1 per 100.000 inhabitants mortality. Mortality in women was determined as 5,7 per 100.000 inhabitants. [7]

In the case of COPD, the mortality rate is 17,86 per 100.000 inhabitants, being 18,25 in men and 17,55 in women. [5]

Regarding stroke, it was found that its mortality rate is 27,72 per 100.000 inhabitants; 25,36 in men and 30,31 in women. [5]

The first requirement for smoking cessation is the will to quit. However, the will, by itself, has a low efficacy, from 1 to 5% in a year, with a relapse rate of 93% after 10 months. [8]

In Costa Rica, the CCSS doesn´t offer any alternative to quit smoking, but all of the following alternatives are available in the local market: Varenicline, Bupropion, Nicotine patches, tablets and chewing gum.

Methods

Table 1 shows each treatment´s characteristics. The studied population was: women and men from Costa Rica between 18 and 99 years old in 2001, taken from the projection made by the National Statistics and Census Institute of Costa Rica (Instituto Nacional de Estadística y Censo, INEC), which was 2.474.028. [9]

For this study, data was used from actual smokers, former smokers and non smokers, obtained from the Institute of Alcoholism and Pharmacodependence of Costa Rica (Instituto sobre Alcoholismo y Farmacodependecia, IAFA; table 2). [10]

BENESCO model was used, which has been used in several studies. [11, 12, 13] The BENESCO model is a programmed worksheet, which must be filled in order to perform a simulation that continues a hypothetical cohort of smokers who made a single attempt to quit at the beginning of the simulation [14] (Figure 1). This simulation predicts morbidity and mortality, with their associated costs. This model´s structure and functionality is based on the same principles from the "Health and Economical Consequences of Smoking" (HECOS) model, which has been prepared for the World Health Organization´s European Project to decrease tobacco dependence. It was revised by the same entity. [12]

The BENESCO model was developed to present payers strong arguments about benefits, costs and relative cost-effectiveness of the interventions to quit smoking (Table 3).

The strategies compared for smoking cessation were: Varenicline, Bupropion, Nicotine replacement, Self-determination (no intervention) and motivational group speeches for smoking cessation (from now on: speeches). All costs, excepting speeches, were obtained from the International Marketing Services (IMS).

Once obtained the data required by the model, we proceeded to compare Varenicline versus Bupropion, Nicotine Replacement Therapy (NRT) and speeches to obtain the results. Deterministic analysis was used in each comparison, and mortality, cumulative incidence, costs, life quality-adjusted life years (QALYs) and gained life years (GLY) were analyzed. For each one of these, results are obtained after 2, 5, 10, 20 years and lifetime from the beginning of each therapy.

Finally, in the probabilistic analysis, we obtained the sensibility analysis and the probability curve.

Regarding Varenicline, the effectiveness taken into account after one year of therapy was 22,5%, [15] despite literature showing an effectiveness of 40% [16]. It

Table 1. Data from available drugs for smoking cessation in Costa Rica

Drug	Treatment duration	Recommended doses	Total treatment cost (USD)	Effectiveness for smoking cessation
Varenicline	12 weeks	0,5 to 2 mg/ day	$ 340,14	22,5**-44†%
Bupropion	12 weeks	300mg/ day	$ 353,76	15,7**-30,5%
Nicotine chew gum	12 weeks	Depends on week of treatment	$ 159,12	15,4***-17,4%
Nicotine patches	12 weeks	Depends on week of treatment	$ 170,32	13,7%

*Prices source: IMS. *Schnoll, Robert A, Lerman Caryn. Current and emerging pharmacotherapies for treating tobacco dependence. Expert Opinion Emerging Drugs. 2006 Sep;11(3):429-44 **Reus VI, Obach RS, Coe JW, Faessel H, Rollema H, Watsky E, Reeves K. Vareniclina: new treatment with efficacy in smoking cessation. Drugs Today. 2007; 43: 65-75 ***Predetermined data in the BENESCO model † Gonzales D,Rennard SI, Nides M et al: Vareniclina, an ά4ß2 nicotinic acetylcoline receptor partial agonist, versus sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA(2006) 296:47-55*

Table 2. Smoking prevalence in Costa Rica, distributed by gender, age, actual smokers, former smokers, non smokers. IAFA, 2006					
Gender	Age	Current smokers	Former smokers	Non smokers	Total
Male	18 to 34 yo	43, 26%	29,11%	27,63%	100%
	35 to 64 yo	47,97%	28,89%	23,15%	100%
	>65 yo	54,05%	28,55%	17,39%	100%
Female	18 to 34 yo	24,05%	9,90%	66,06%	100%
	35 to 64 yo	20,59%	1,51%	77,90%	100%
	>65 yo	17,86%	1,00%	81,14%	100%

was decided to use the lower percentage to reduce result bias. After one year, the included effectiveness for Bupropion was 15,7%. [15] Despite other effectiveness are known, this percentage was used because it comes from the same study that obtained the aforementioned effectiveness for Varenicline. Both data are from the year 2006. For NRT, effectiveness after one year was 13,7%. 16 In the case of self-determination (no intervention), effectiveness was maintained in 5,9%, as default in the BENESCO model. [14] The speeches alternative was included, an option currently offered at CCSS. Given that there aren´t available costs data for speeches, it was assumed that these lasted one hour. Having the costs for an outpatient medical consultation (¢ 19.704, for 2007), [17] it was projected to September 2008 as ¢ 22.035. Indirect costs weren´t included. At CCSS, 4 outpatients

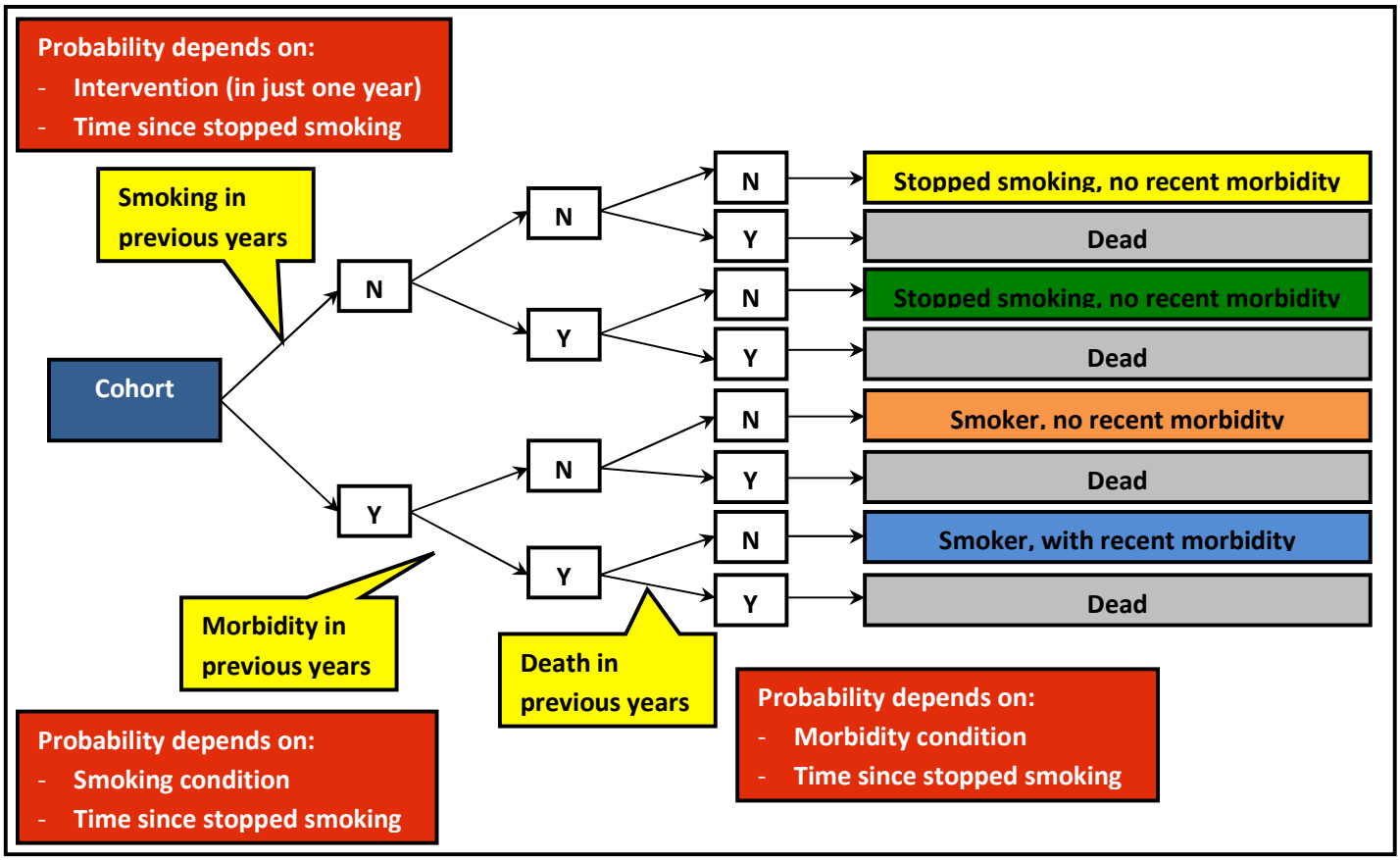

Figure 1. Schematic view of the probabilities in the BENESCO simulation model. These probabilities arise from three factors: the used intervention´s cessation rate (effectiveness), time since stopped smoking (recurrence rate) and the relative risk of developing a tobacco-associated disease. Probabilities come from tobacco-related morbidity and mortality.

Table 3. Summary of the BENESCO model´s characteristics

- Simulates the consequences of smoking in a population
- Reflects the achievable economical and health benefits in different time spaces after a single attempt to quit smoking
- Determinate the cost-effectiveness of Varenicline against the other alternatives to quit smoking
- Maintains a high quality level without generalizing
- Seeks to be as simple, friendly and comprehensible as possible
- Seeks for the health authority´s most sophisticated and demanding requirements, which needs the cost-effectiveness evidence for decision making.

are attended per hour. Besides, it was assumed that there could be an average of 20 participants per speech, so it was divided among these to get the total (in colones) for each participant. The effectiveness used in the model, after one year of treatment was of 17,2%. [18]

Currency was turned to dollars, using the exchange rate of April 1st 2008, because in that month the price revision for the mentioned alternatives was performed. According to the Central Bank of Costa Rica, the exchange rate was: 1 dollar= 497,62 colones. [19]

Concerning to the analyzed diseases, the BENESCO model includes: prevalence, events incidence and mortality. These data were obtained from CCSS and the others estimated.

At CCSS there aren´t data about the costs for diseases, therefore a calculation was made for each one. To make such estimates, each disease´s number of outpatient visits and inpatient days were multiplied by their average cost. In the cases without inpatient days, only outpatient visits were taken into account. Data used was as updated as possible. Considering inflations obtained by INEC, its cost was updated to September 2008 (Table 4). Due that data from CCSS just mention its

Table 4. Calculated annual costs for AMI, lung cancer, stroke and COPD, updated to September 2008

Disease	Estimated cost per year
AMI	¢ 2.584.370.676,06
Lung cancer	¢ 637.851.904,95
Stroke	¢ 67.009.761,36
COPD	¢ 101.861.077,57

year, we thought it was more appropriate to assume that these were from each year´s December; for example, if one outpatient visits data is from 2001, inflations were considered from January 2002.

It is important to mention that each disease´s cost is lower than its real cost because of the lack of information. Other costs weren´t taken into account, such as: laboratories, radiological exams, chemotherapy application, radiotherapy, drug use, surgical procedures, hospitalization and intensive care, among others. Table 4 shows the total estimated cost for each disease.

In general, the CCSS data are not divided by age groups or "first event" and "subsequent events", so it was assumed that the predetermined percentages for the BENESCO model for each age group would be the same for the Costarican population. [14]

The used discount rate was of 3% per year because this is the rate used by the BENESCO model. [14]

Results

The results obtained are a product of the simulation performed with the BENESCO model. The model simulates what would happen using each alternative at the second, fifth, tenth and twentieth year, as well as its lifetime use.

When simulating mortality with each therapy, Varenicline was found to prevent the largest amount of deaths in all analyzed years by the model (Table 5). The second alternative preventing the most deaths was Bupropion and speeches, with 3 deaths more than Varenicline at 2 years; while at 20 years, Varenicline

prevented 73 and 94 deaths compared with speeches and Bupropion respectively. The largest quantity of deaths was because of AMI for all alternatives.

The cumulative incidence shows the number of cases that could present when using each therapy. Varenicline was found to be the strategy that avoided the largest number of cases for the analyzed diseases in this study (Table 6). For example, at 2 years, it prevents 21 cases when compared to its closest alternative: speeches. Then, at 20 years, Varenicline prevents 499 cases compared with speeches.

In relation to the obtained costs from the model, Varenicline was also the alternative with the lowest cost after the fifth year of use (Table 7). At two years, speeches were ¢ 3.443.167 more expensive than Varenicline, and at 5 years, this option is ¢ 147.875.774 more expensive. Regarding Bupropion, it was found that the difference compared to Varenicline at 5 years was ¢235.5253.691 and ¢2.817.705.653 at 20 years.

The alternative with the most QALYs was Varenicline, with a difference of 696 years at 20 years compared to the second place, which were speeches (Table 8). At 2 years, the difference was 4 years. Compared to Bupropion and NRT, at 20 years the difference was of 893 year and 1.156 years respectively.

Regarding GLYs, Varenicline was also the alternative with the most years gained (Table 9). A 3 year difference was found compared to Bupropion and NRT, while at 20 years the difference with these alternatives was 599 and 724 years respectively. At 20 years, the difference between Varenicline and speeches was of 436 years.

When analyzing the incremental cost at 20 years, Varenicline was the dominant alternative as it is

Table 5. Number of smoking-related deaths using the BENESCO model (n= 2.474.028)

Treatment	Years				
	2	5	10	20	Life
Varenicline	3.852	12.460	28.494	55.832	209.798
Speeches	3.855	12.475	28.531	55.926	209.798
Self-determination	3.856	12.479	28.542	55.954	209.798
NRT	3.860	12.497	28.585	56.061	209.798
Bupropion	3.855	12.472	28.523	55.905	209.798

Table 6. Cumulative incidence for smoking-related morbidity using the BENESCO model (n= 2.474.028)

Treatment	Years				
	2	5	10	20	Life
Varenicline	2.524	6.628	14.064	31.311	80.128
NRT	2.551	6.727	14.349	31.950	81.302
Speeches	2.559	6.757	14.433	32.138	81.647
Bupropion	2.590	6.871	14.760	32.871	82.993
Self-determination	2.545	6.705	14.286	31.810	81.043

Table 7. Smoking-related costs (colones) using the BENESCO model (n= 2.474.028) (million colones)

Treatment	Years				
	2	5	10	20	Life
Varenicline	12.393	34.362	76.299	179.484	423.305
Bupropion	12.434	34.598	77.184	182.301	430.151
NRT	12.427	34.648	77.425	183.110	432.145
Self-determination	12.455	34.898	78.421	186.323	439.978
Speeches	12.390	34.510	76.953	181.644	428.605

the most effective and less costly strategy for smoking cessation (Table 10). In the rest of the years, Varenicline also resulted to be dominant with one exception: after two years compared with speeches.

Sensitivity analysis and probability curve

The sensitivity analysis results showed that Varenicline is cost-effective, because it increases the number of life quality-adjusted life years and decreases the costs derived from the long term complications. In figure 2 ("a" and "b") results can be seen versus Bupropion and speeches respectively.

Finally, related to the probability percentage, a 100% was obtained when comparing Varenicline versus the remaining alternatives. In figure 3 ("a" and "b") acceptability curves can be seen against Bupropion and speeches respectively.

Discussion

In this study, cost-effectiveness was evaluated for the possible different alternatives for smoking cessation in the male and female Costarican population between 18 and 99 years old. The therapeutic alternatives taken into account were those available in Costa Rica, which were: Varenicline, Bupropion, Nicotine replacement therapy (patches), self-determination (no intervention) and speeches.

Speeches were added to the model because it is the only alternative currently used at the CCSS, even though, its cost had to be assumed because there isn´t an exact data. Even so, the cost given to this alternative is

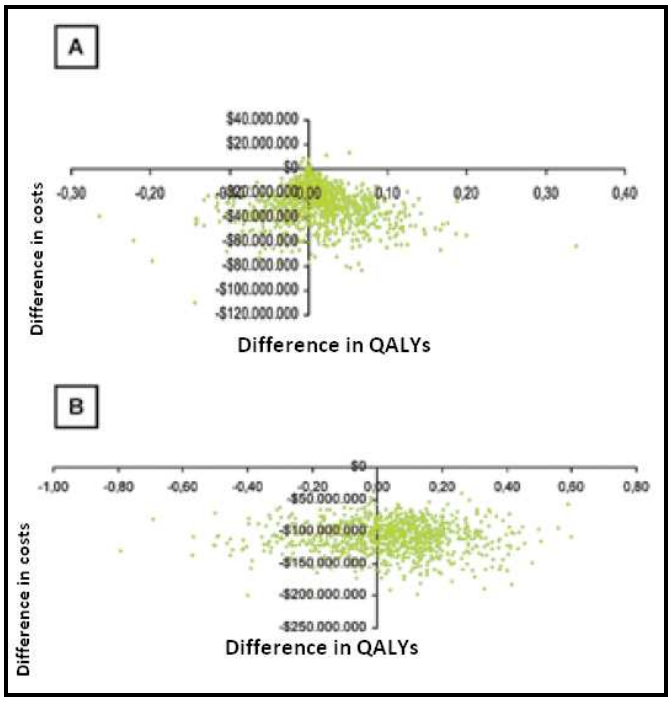

Figure 2. Results for the Sensitivity Analysis Test (SAT) (A) when comparing Varenicline vs Bupropion, which shows the majority of parameters in the right inferior quadrant which signals a lower cost and greater QALYs. The SAT suggests varying key parameters within the model and examining the effect of this variation on the results. The parameters suffer a variation when using a confined random value in the statistical distribution expected for the parameter. During the analysis, parameters in question are varied in this way, and are disclosed in the model results. A complete analysis includes, then, the realization of a large number of exercises to examine the distribution of the produced results. The evaluated parameters are: effectiveness of the alternatives to stop smoking, treatment costs of morbidities and utilities. Results are generated by performing the test 1000 times. (B) SAT when comparing Varenicline vs speeches. It shows most parameters in the inferior right quadrant, signaling a lower cost and more QALY´s.

Table 8. Smoking-related QALYs using the BENESCO model (n= 2.474.028)

Treatment	Years				
	2	5	10	20	Life
Varenicline	350.479	823.837	1.481.881	2.418.036	3.504.164
Speeches	350.475	823.798 1.	481.703	2.417.340	3.501.974

Table 9. Smoking-related GLYs using the BENESCO model (n= 2.474.028)

Treatment	Years				
	2	5	10	20	Life
Varenicline	396.154	930.621	1.672.521	2.730.960	3.972.081
Speeches	396.152	930.596	1.672.409	2.730.524	3.970.628

Table 10. Cost- incremental analysis for Varenicline QALYs compared with the rest of alternatives for smoking cessation at 20 years according to results obtained in the BENESCO simulation model

	Cost	QALYs	CI vs Varenicline	CI vs speeches	CI vs Bupropion	CI vs NRT
Self-Determination	186.323.659.951	2.415.856	Dominated by Varenicline	Dominated by speeches	Dominated by Bupropion	Dominated by NRT
NRT	183.110.998.380	2.416.880	Dominated by Varenicline	Dominated by speeches	Dominated by Bupropion	
Bupropion	182.301.830.653	2.417.143	Dominated by Varenicline	Dominated by speeches		
Speeches	181.644.583.773	2.417.340	Dominated by Varenicline			
Varenicline	179.484.125.000	2.418.036				

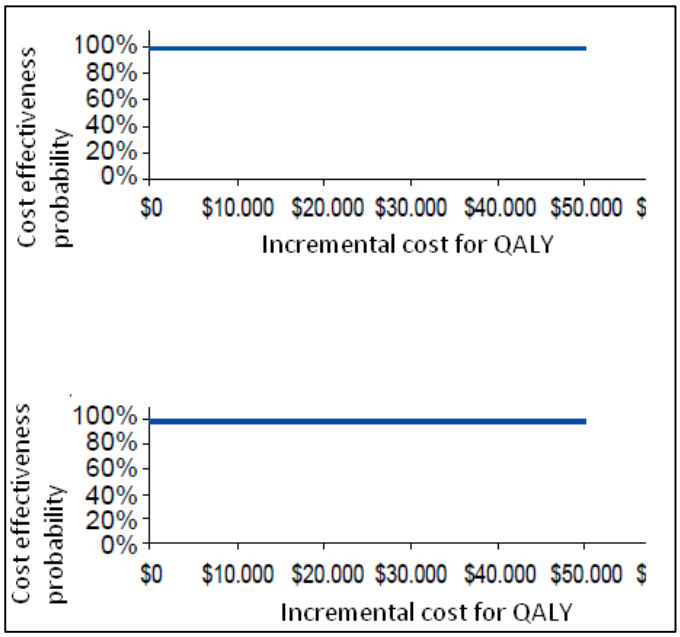

Figure 3. Cost-effectiveness acceptability curve (A) Varenicline vs Bupropion and (B) Varenicline vs Speeches. The acceptability curve results show the probability for the curve being acceptable based on several acceptability thresholds. The obtained results show that the probability for the comparisons to be cost-effective in the $50000/QALY threshold is a 100%.

believed to be lower than its real cost because only one speech with a 20 person crowd was considered and usually there are given more than one speech. Also, it doesn´t take into account other inputs such as physical infrastructure, materials, logistics, among others.

This study shares the statement that the evaluated alternatives give economical benefits, for example, a reduction in the institutional expenses due to a decreased prevalence for tobacco-associated diseases; and in health; finding, also, that Varenicline is the dominant option.

Completing the model was a challenge, because many data aren´t available in our country. A great effort was made to accomplish the model, however, there were some limitations which have to be mentioned.

All data regarding the Costarican population and its morbidity were obtained from government institutions. Even though these have their available data, many data required by the model couldn´t be obtained. In general, almost no data from morbidity and mortality is divided by age, this is why it had to be assumed that the predetermined percentages in the BENESCO model were the same for the Costarican population.

Another limitation was regarding disease costs. CCSS has no data about costs, this is why the calculation had to be as explained in the methods section. We think this calculation is lower than the real one because it only considers outpatient consult and inpatient stay costs, not taking into account important costs such as: laboratories, radiological exams, drugs, attention at the surgery room

and intensive care. These weren´t taken into account because their costs couldn´t be obtained; neither statistics, number nor frequency for each test in each disease could be obtained. We think it would be important to make a study evaluating costs for these diseases, since that would optimize results in this type of study.

Because of the available information, it wasn´t possible to use exactly the same data for each disease, for example, in certain cases we had to use data from the emergency department and in other occasions the hospital discharges to complete the event incidence. For COPD, information was very limited, so it was assumed that prevalence data from Mexico was the same for Costa Rica due to the geographical proximity between both countries.

BENESCO model has the option of whether or not to include asthma according to the investigator´s criteria. In this study, we decided not to include it because most of the information available is about children and not adults. However, it is suggested to include it in future studies and compare the results which we believe would favor even more Varenicline´s cost-effectiveness as the cost savings would be greater by reducing asthma cases, which is known to be a very frequent disease.

The sensitivity analysis showed that Varenicline is a cost-effective option for any health institution who wishes to add it, since it´s been demonstrated that raises QALYs and diminishes costs from tobacco-associated diseases at a short, medium and long term. The obtained probability percentage of 100% reinforces that this drug is the best cost-effective alternative to stop smoking.

Besides the obtained results show an important benefit, both in the economical as in the health fields, our estimations could be considered as conservative, because some relevant institutional expenses aren´t being considered such as diagnostic, evaluation and treatment expenses of the four tobacco-associated diseases analyzed; nor takes into account other diseases such as asthma, as mentioned, or congenital defects caused by cigarette smoke contact.

Similarly, neither consequences nor the statistics, such as prevalence weren´t included for passive smoking.

We share the idea mentioned by other studies [11] that this model is a trustable analysis about the effects on morbidity and mortality of smoking cessation, which makes it useful in decision-making for health institutions.

The used model suggests that Varenicline is the best cost-effective alternative for smoking cessation compared to Bupropion, NRT, self-determination and speeches. It was proven that using Varenicline causes important economical savings for health institutions that use it since reduce morbidity from tobacco-associated diseases. If the current health system decides to add this therapeutic intervention instead of speeches, it could save 4.679.076.178 colones in 20 years. We conclude that Varenicline has to be considered by current smoking cessation programs at health institutions due to its demonstrated health and economical benefits.

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References

1. WHO Report on the Global Tobacco Epidemia. The MPOWER Package. On: http://www.who.int/tobacco/mpower/en/ Consulted July 18th, 2008.
2. US Department of Health and Human Services. The health consequences of smoking: a report of the surgeon general. Atlanta (GA): US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2004.
3. Bejarano J. Consumo de Drogas en Costa Rica. Resultados de la Encuesta Nacional del 2000-2001.

Instituto sobre Alcoholismo y Farmacodependencia, 2003.
4. Araya R, Guzman M, Padilla S. Mortalidad por infarto agudo de miocardio: distribución geográfica y lugar de ocurrencia. Costa Rica, 1970 - 2002. Rev costarric cardiol 2003; 3: 25-29.
5. Departamento de información estadística de los servicios de salud. Cambios en morbilidad y mortalidad por edad y sexo Costa Rica: 1987, 1992, 1997 y 2002. Caja Costarricense del Seguro Social, 2003.
6. Unidad de Estadística del Ministerio de Salud de Costa Rica. Indicadores de salud. Ministerio de Salud, 2004. On: http://www.ministeriodesalud.go.cr/indicadoressalud/ib04retiro.pdf Consulted October 25th, 2008
7. Departamento de Estadística de Salud. Variaciones cronológicas y geográficas del cáncer de pulmón, piel y otros de menor frecuencia, 1956-57 a 2002-2003. Caja Costarricense del Seguro Social, 2005
8. Valencia A, Heredia I, Ventura C. Costo-efectividad del uso de Vareniclina como alternativa para dejar de fumar en la población derechohabiente al IMSS. Instituto Nacional de Salud Pública, 2007.
9. Población total proyectada por sexo, según años calendarios. Hipótesis recomendada 2000-2050. INEC. Costa Rica. En http://www.inec.go.cr/01EstadPoblacion/04estimacionesYproyec/proyecciones/cuadros/cuadros/C1.%20Población%20total%20proyectada%20por%20sexo,%20según%20años%20calendario.%20%20Hipótesis%20recomendada.%20%202000-2050/Cuadro%201.proy.xls. Consulted October 25th, 2008.
10. Bejarano J, Fonseca S, Sánchez G. Consumo de drogas en Costa Rica. Resultados de la encuesta nacional 2006. San José, C.R.: Instituto sobre Alcoholismo y Farmacodependencia. En http://www.iafa.go.cr/Estadisticas%20y%20Estudios/Estudios%20y%20encuestas/ Consulted January 10th, 2009
11. Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO Simulation model: application to a population of US adult smokers. Pharmacoeconomics 2008; 26:497-511.
12. Bolin K, Mörk AC, Willers S, Lindgren B. Varenicline as compared to bupropion in smoking-cessation therapy. Cost-utility results for Sweden 2003. Respir Med 2008; 102:699-710.
13. Hoogendoorn M, Welsing P, Rutten-van Mölken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Curr Med Res Opin 2008; 24:51-61.
14. Champix BENESCO Long-term Cost Effectiveness Model. Technical Report. Commercial in confidence. January 2007.
15. Reus VI, Obach RS, Coe JW, Faessel H, Rollema H, Watsky E, Reeves K. Varenicline: new treatment with efficacy in smoking cessation. Drugs Today 2007; 43: 65-75.
16. Schnoll, Robert A, Lerman Caryn. Current and emerging pharmacotherapies for treating tobacco dependence. Expert Opinion Emerging Drugs. 2006;11:429-44.
17. Departamento de Estadística de la CCSS. Costo por consulta, 2007. CCSS, Costa Rica. On: http://www.ccss.sa.cr/html/transparencia/estadisticas/actuarial/estadist/anuarios/anuar07AV/ce5207.xls. Consulted October 25th, 2008.
18. I. McDowell K. Mothersill W. Rosser R. Hartman: A Randomized Trial of Three Approaches to Smoking Cessation. Can Fam Physician 1985; 31:845-851.
19. Banco Central de Costa Rica. Exchange rate for US Dollars. On: http://www.bccr.fi.cr/flat/bccr_flat.htm. Consulted: October 25th 2008.

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