ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/vhri

Economic Evaluation

Cost-Effectiveness Analysis of Varenicline Versus Currently Funded Smoking Cessation Strategies in Brazil

Ricardo Ribeiro Alves Fernandes, BPharm, MSc, PhD, Brayan Viegas Seixas, BPharm, MSc, André Salem Szklo, PhD, Renata Leborato Guerra, MD, PhD, Laura Augusta Barufaldi, PhD, Rita de Cássia Ribeiro de Albuquerque, PhD, Cid Manso de Mello Vianna, PhD

ABSTRACT

Objectives: To assess the cost-effectiveness of varenicline in comparison to currently funded smoking cessation strategies in Brazil.

Methods: We modeled the lifetime direct costs and health-related quality of life of a hypothetical cohort of smokers with a single attempt to quit smoking using one of the following: (1) cognitive behavioral therapy (CBT) without any pharmacological intervention, (2) varenicline, (3) bupropion, (4) nicotine replacement therapy (NRT) with transdermal patch, (5) bupropion in combination with NRT transdermal patch, and (6) combined NRT (oral plus transdermal). All drug alternatives were considered with concomitant CBT. The analysis relied on a Markov model based on the Benefits of Smoking Cessation and Outcomes study and used different age and sex categories in the consideration of relative risks and incidence rates of the diseases included in the model. The analysis was conducted from the healthcare system perspective, and a 3% discounting rate for costs and outcomes was applied. Model parameter values were sourced from published literature. Probabilistic and deterministic sensitivity analyses assessed robustness.

Results: Among the smoking cessation alternatives available in Brazil, varenicline and combined NRT were estimated to have higher effectiveness; varenicline, however, was dominated due to its higher average cost. In the base-case analysis, combined NRT had an incremental gain of 0.25 quality-adjusted life-years (QALYs) in comparison to the second-best option (bupropion in combination with NRT transdermal patch) and an incremental cost-effectiveness ratio of R$2173.47/QALY ($595.45/QALY).

Conclusions: Combination of oral and transdermal NRT (coupled with CBT) was the most effective smoking cessation option and was 100% cost-effective within a conservative willingness-to-pay threshold.

Keywords: bupropion, cost-effectiveness, economic evaluation, nicotine replacement therapy, smoking cessation, varenicline.

VALUE HEALTH REG ISSUES. 2022; 27:25–31

Introduction

Smoking is a leading preventable risk factor of mortality and morbidity in the world. It has been demonstrated to increase the incidence risk of cardiovascular diseases,[1] several types of cancer,[2] pulmonary diseases,[3] and to have an impact on a variety of other health conditions, such as diabetes,[4] dementia,[5] and eye disorders.[6] According to estimates by the US Centers for Disease Control and Prevention, smoking was the cause of 20.4 million deaths worldwide between 1965 and 2014.[7]

In Brazil, prevalence of smoking is estimated at 9.8% in Brazilian state capitals and has wide intergroup variability. For instance, smoking is more prevalent among men (12.3%) than women (7.7%) and affects those with low levels of educational attainment more—13.8% in adults with less than 8 years of education and 6.7% in those with 12 or more years of education.[8]

Nationally established clinical guidelines in Brazil recommend that smokers should receive cognitive behavioral therapy (CBT) as first-line treatment. For those with high levels of nicotine addiction, however, pharmacological treatment is considered. Thus, the use of drugs is seen as an additional therapeutic tool when psychotherapeutic resources are not sufficient.[9]

To date, 2 pharmacological options have been covered by the Brazilian public healthcare system: nicotine replacement therapy (NRT) (either through gum or patch, or both concomitantly) and bupropion. While the former offers relief for some of the withdrawal symptoms directly related to nicotine dependence, the latter helps patients more indirectly because it releases additional dopamine in the brain. After discussing the pros and cons of available alternatives, a treatment plan is chosen through a decision-making process that is shared between patient and provider.[9]

Another pharmacotherapy for smoking cessation with proven efficacy is varenicline,[10] which is currently not funded by the public healthcare system in Brazil. Acting as a selective partial agonist of the nicotinic acetylcholine receptor $\alpha 4\beta 2$, it reduces the urge to smoke and can induce dopamine release, helping with anxiety and compulsion in the patient experiencing abstinence.

Although several studies have appraised the cost-effectiveness of varenicline in comparison to other existing treatments for smoking cessation,[11–14] no economic evaluation has been performed within the context of the public healthcare system in Brazil. Thus, the aim of this study was to investigate the cost-effectiveness of varenicline for smoking cessation in Brazil from the payer's perspective (the Unified Health System—*Sistema Único de Saúde* [SUS]).

Methods

This work compared the following treatment options: (1) CBT without any pharmacological intervention, (2) varenicline, (3) bupropion, (4) NRT with transdermal patches, (5) bupropion in combination with NRT patches, and (6) combined NRT (gum plus patch). All drug alternatives were considered with concomitant CBT. For NRT, alone or in combination with bupropion, the transdermal patch was considered as the default technology. According to information provided by the Department of Pharmaceutical Care (Ministry of Health), 98.6% of all patients receiving NRT in 2017 relied on the transdermal patch. The therapeutic regimes recommended by the clinical guidelines of the Brazilian Ministry of Health are shown in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005.[15]

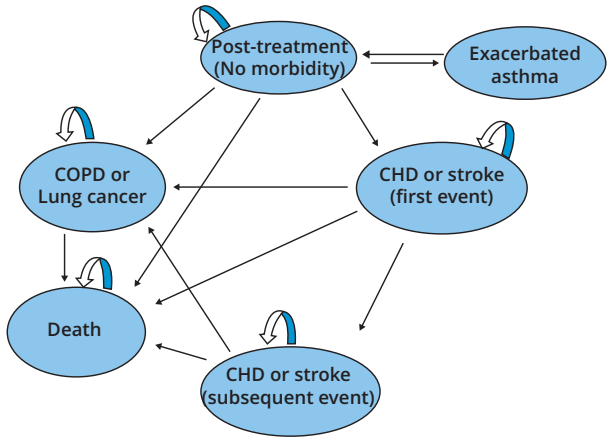
Model Design and Inputs

Using a Markov microsimulation model based on the Benefits of Smoking Cessation and Outcomes (BENESCO) study,[16] we modeled the impact of several treatment options in a hypothetical cohort of 300 000 smoking adults (older than 18 years) who have made a single quitting attempt in the first year of follow-up. This number represents the overall estimated number of individuals who try any smoking cessation program within the Brazilian healthcare system every year and was calculated based on age-stratified percentages of demonstrated desire to stop smoking that were obtained from a nationally representative survey.[17] No other quitting attempt was considered during the study time horizon. In addition, we also considered a relapse rate that decays over the follow-up period, meaning that the probability of returning to smoking decreases with time. We assumed a relapse rate of 6.3% in the first 5 years, 2% from year 6 to year 10, and 1% from year 11 onward.[16,18,19]

As shown in Figure 1, the considered Markov states represent morbidities that are chronic (lung cancer and chronic obstructive pulmonary disease [COPD]), episodic (exacerbated asthma), and acute with subsequent consequences (stroke and cardiovascular disease). There is an assumed hierarchy in the transition between states so that an individual cannot transition from a state of chronic disease to an acute or episodic condition. Except for exacerbated asthma, it is assumed that individuals cannot return to the state without any morbidity. In the particular case of COPD, it has been shown[20] that patients in Brazil have, on average, between 1.9 and 2.1 acute exacerbations per year and 3.4% of these episodes end up in hospitalization. This probability was also included in the model.

The model is based on annual cycles of transition spanning the individuals' lifetime. This large time horizon is necessary to take into account the cumulative and late consequences of smoking on human health. The model considers individuals as current smokers, recent quitters, or long-term quitters. The latter category refers to those who have been abstinent for at least 15 years and who are assumed to have relative risks for coronary heart disease (CHD), asthma, and stroke similar to those who have never smoked but not for lung cancer and COPD due to the cumulative lung damage of smoking.[3,21]

Figure 1. Scheme of event transitions adapted from the BENESCO model.[16]



BENESCO indicates the Benefits of Smoking Cessation and Outcomes; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.

Outcomes

The impact of the interventions on health was considered in terms of quality-adjusted life-years (QALYs). Utilities associated with CHD, COPD, and stroke were obtained from a study conducted across the country among users of the Brazilian public healthcare system (SUS).[22] Because of the lack of available data on the Brazilian population regarding utility associated with lung cancer, exacerbated asthma, and recurrent event stroke, we used data from international studies for these particular outcomes.[13,14,16] Utility values that were used in this study are shown in Table 1.

Relative risks of mortality for COPD, CHD, stroke, and lung cancer in individuals of the Brazilian population who are current smokers versus those that have never smoked were sourced from published literature.[3,23] The relative risks were stratified by sex and age groups considered in the model, as shown in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005.[3,23] Data on the relative risks of mortality for former smokers versus current smokers were based on the age at which the individual stopped/stops smoking,[3] with the exception of asthma. The relative risks of mortality for having episodes of exacerbated asthma were obtained from the BENESCO study.[16] Incidence rates for these diseases stratified by age and sex (Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005) were extracted from a study in The Netherlands, in the absence of available data on the Brazilian population.[12] A sensitivity analysis was conducted to understand the impact of this methodological choice on model uncertainty. The full description of the relative risks for each disease among the different subpopulations is presented in Appendix Table 2 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005.

Table 1. Main model inputs.

	Mean cost	RR efficacy (95% CI)	Mean utility	Source
Treatment				
Varenicline	R$727.17 ($199.22)	2.24 (2.06-2.43)	-	24
Bupropion	R$29.70 ($8.14)	1.62 (1.49-1.72)	-	24
NRT transdermal patch	R$132.9 ($36.41)	1.55 (1.49-1.61)	-	24
Bupropion + NRT transdermal patch	R$162.6 ($44.55)	1.24 (0.84-1.84)	-	40
CNRT (gum + transdermal patch)	R$501.45* ($137.38)	2.24 (2.06-2.43)	-	24,25
Health conditions				
COPD		-	0.734	20,22
- Acute episode	R$1582.5 ($433.56)			
- Hospital care	R$10 354.15 ($2836.75)			
Exacerbated asthma	R$618.75 ($169.52)	-	0.520	13,14,16,33
Stroke		-	0.583	26–28
- Acute event	R$5353.92 ($1466.80)			
- Year-long treatment	R$1083.19 ($296.76)			
Subsequent stroke	R$5353.92 ($1466.83)	-	0.150	13,14,16
Lung cancer (year-long treatment)	R$8929.82 ($2446.53)	-	0.500	13,14,16,31,32
CHD		-	0.667	22,29,30
- Acute event	R$8010.00 ($2194.52)			
- Year-long treatment	R$5818.55 ($1594.12)			

*R$368,55 for the average gum consumption of 405 units.

Efficacy rates for each considered intervention were sourced from previously published systematic reviews[24,25] and are presented in Table 1.

Costs

All costs related to considered morbidities were obtained from a costing study conducted on patients from the SUS (Brazilian public healthcare system).[20,26–33] Appendix Table 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005 shows detailed costing data and parameters for sensitivity analysis. Whenever multiple studies were available for the same disease, the maximum and minimum values were used to guide the sensitivity analysis and investigate how these estimates affect the result. Values presented here are expressed both in Brazilian real (R$) and in US dollars, based on the average 2018 exchange rate of 3.65.

Treatment costs were calculated based on the therapeutic regimes recommended in the clinical guidelines issued by the Brazilian Ministry of Health (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005).[15] For patients receiving oral NRT, the guideline does not determine a standard dose but advises on the maximum number of tablets that can be ingested. For our model, we considered 50% of that cap as the mean consumption and used a triangular distribution varying from 25% to 100% of the maximum number of tablets suggested by the guideline. Drug costs were obtained from the Platform of Prices in Health (Banco de Preços em Saúde).[34] On the basis of the BENESCO model[16] and in accordance with most published studies on smoking cessation strategies,[11,13,35] we applied a discounting rate of 3% for costs and benefits. A detailed report of the cost parameters used in the model is shown in Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005.

Sensitivity Analysis

A deterministic sensitivity analysis was carried out by varying the values of several relevant model variables, such as the number of NRT oral tablets ingested, incidence rates, and utility values. A tornado diagram was built to visualize the impact of such variation on the incremental cost-effectiveness ratio (ICER).

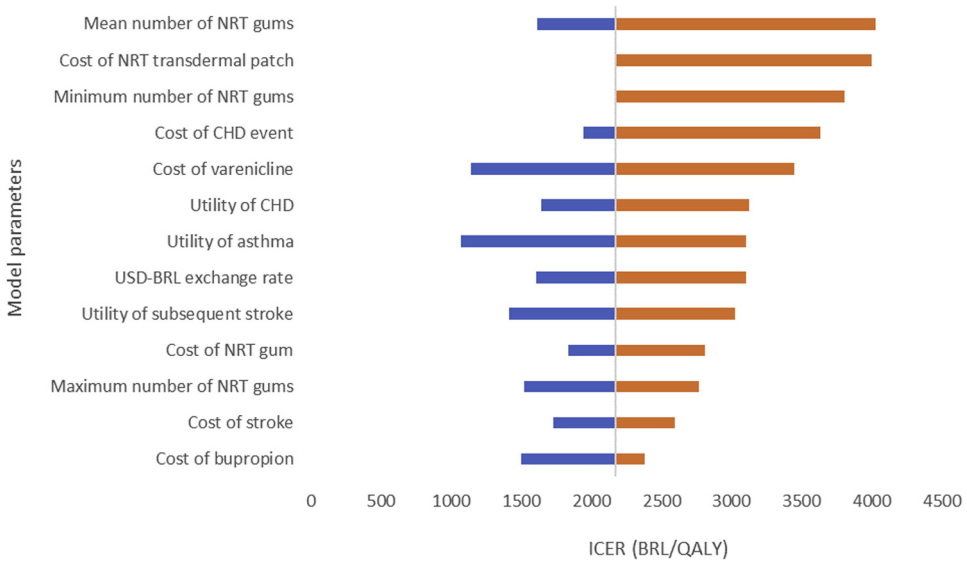
Using Monte Carlo simulation, we conducted a probabilistic sensitivity analysis using 10 000 iterations of cohorts containing 3000 patients. The type of distribution and the parameters used

Table 2. Cost and effectiveness for all smoking cessation alternatives in the base-case analysis.

Intervention	Mean cost	Incremental cost	Mean effectiveness (QALY)	Incremental effectiveness (QALY)	ICER in R$/QALY ($/QALY)
No pharmacological intervention (CBT alone)	R$36 466.28 ($9990.76)	–	14.35	–	–
Transdermal NRT	R$37 442.14 ($10 258.12)	R$975.86 ($267.35)	14.83	0.48	2035.07 (557.55)
Bupropion	R$37 523.46 ($10 280.40)	R$81.32 ($22.27)	14.89	0.06	1257.70 (344.57)
Bupropion + transdermal NRT	R$38 122.23 ($10 444.44)	R$598.76 ($164.04)	15.19	0.29	2037.44 (558.20)
Combined NRT (oral plus transdermal)	R$38 660.62 ($10 581.95)	R$538.939 ($147.50)	15.44	0.25	2173.47 (595.47)
Varenicline	R$38 701.18 ($10 603.06)	R$40.56 ($11.11)	15.44	–	Dominated

All alternatives include cognitive behavioral therapy.

Figure 2. Tornado diagram for the deterministic sensitivity analysis performed in the comparison of bupropion versus combined NRT.



CHD indicates coronary heart disease; ICER, incremental cost-effectiveness ratio; NRT, nicotine replacement therapy; QALY, quality-adjusted life-year.

for each variable can be found in Appendix Tables 2 and 3 in Supplemental Materials found at https://doi.org/10.1016/j.vhri.2021.07.005. Cost-effectiveness planes and acceptability curves were built to understand this analysis.

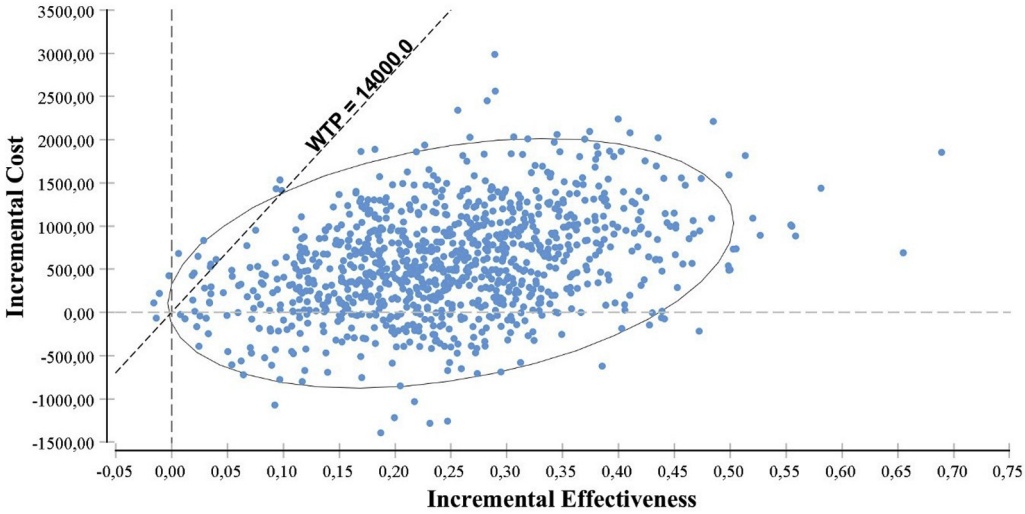
The probability that each technology is cost-effective depends on a given threshold of willingness-to-pay (WTP), which, to date, has not been formally established in Brazil. Our analysis was based on a study that, considering per capita spending in health and life expectancy, estimates that middle-income countries[36] should use a threshold between 0.5 times and 1 times its per capita gross domestic product (GDP; R$14 000/QALY to R$28 000/QALY or $3835.62/QALY to $7671.23/QALY). All analyses were conducted using TreeAge Pro 2018 software.

Results

Base-Case Analysis

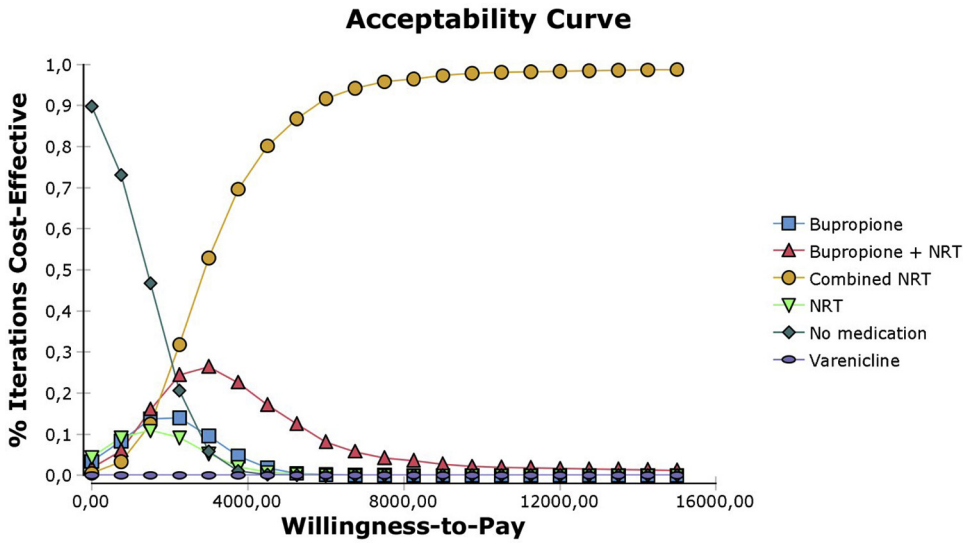
Table 2 presents the results of the base-case analysis in ascending order of effectiveness. The psychotherapeutic option alone had the lowest expected effectiveness (14.35 QALYs) and the lowest expected cost (R$36 466.28 or $9990.76). The transdermal NRT had better effectiveness than CBT alone (0.48 incremental QALYs). Next, we found bupropion to have a higher expected effectiveness than transdermal NRT, although this difference was the smallest difference observed among existing alternatives. In turn, bupropion with transdermal NRT had an even higher expected effectiveness in our model. The highest point estimate of

Figure 3. Cost-effectiveness plane for the comparison between bupropion versus combined NRT.



NRT indicates nicotine replacement therapy; WTP, willingness to pay.

Figure 4. Acceptability curve for all smoking cessation alternatives.



NRT indicates nicotine replacement therapy.

effectiveness was observed for varenicline and combined NRT (15.44 QALYs). The second highest expected effectiveness—bupropion combined with transdermal NRT—showed an incremental effectiveness gain of 0.25 QALYs. Given the average incremental cost of varenicline (R$40.56 or $11.11) relative to combined NRT, varenicline was dominated. The calculated ICER for combined NRT was R$2173.47/QALY ($595.47/QALY). All nondominated alternatives presented ICER much below the WTP threshold.

Sensitivity Analysis

A deterministic sensitivity analysis investigated how changes in key model input variables would affect the ICER of combined NRT vis-à-vis bupropion with transdermal NRT. The findings for each specific variable are based on 30 000 simulations and the resulting tornado diagram is shown in Figure 2. The 2 variables that had the highest impact on the ICER were the mean number of NRT gums and the cost of the NRT transdermal patch. None of these variations were capable of changing the overall conclusion of the cost-effectiveness of combined NRT when evaluated against the WTP threshold of 0.5 GDP per capita. Yet, these variables could serve to inform decision makers on which parameters could be altered to obtain even more favorable cost-effectiveness ratios.

In the absence of data on the Brazilian population, data on incidence rates from a Dutch study were used in the model; this could raise a concern of biased estimation, especially considering that smoking prevalence in The Netherlands is 1.5-fold higher than in Brazil. To evaluate the impact of this methodological choice, we carried out 300 000 simulations with incidence rates that were 2 and 3 times lower than those used in the base-case analysis. The resulting ICERs for combined NRT vis-à-vis bupropion plus transdermal NRT were R$1504.46/QALY and R$1269.68/QALY, respectively. It decreased the overall magnitude of the cost-effectiveness ratios but did not change the conclusions of the study, keeping the same order of smoking cessation alternatives and keeping all of them below the WTP threshold.

A probabilistic sensitivity analysis was carried out with 10 000 simulations of 3000 patients for comparing the 2 most effective nondominated alternatives (combined NRT vs bupropion plus transdermal NRT), and the results were plotted in a cost-effectiveness plane (Fig. 3). The straight line indicates the conservative WTP threshold at R$14 000/QALY or $3835.62/QALY. Whereas 4.61% of iterations indicate combined NRT in cost-saving scenarios (southeast quadrant), 95.39% showed combined NRT having effectiveness and cost superior to the comparator.

An acceptability curve (Fig. 4) shows the probability of cost-effectiveness under different WTP thresholds for all alternatives. Even when using the conservative WTP threshold of 0.5 GDP per capita, that is R$14 000/QALY ($3835.62/QALY), there is a 100% probability that combined NRT is cost-effective.

Discussion

This study indicated that the 2 most effective smoking cessation alternatives are varenicline and the combination of transdermal and oral NRT (combined NRT), however, of these, varenicline was dominated due to its higher cost. Base-case analysis showed an ICER for combined NRT (R$2173.47/QALY) that was below the lower limit of the recommended WTP threshold for middle-income countries such as Brazil (ie, 0.5 per capita GDP). The sensitivity analysis showed that there is close to a 100% likelihood that combined NRT would be cost-effective at that WTP threshold.

In studies conducted in high-income settings,[11,37–40] there seems to be a consistent pattern in which varenicline dominates other smoking cessation alternatives and is cost-effective at the contextual WTP thresholds. This discrepancy in findings could be attributable to the price of varenicline in Brazil, which may be relatively higher in comparison to the other therapeutic alternatives; it might also be related to the fact that the other studies had not considered combined NRT as an alternative. A study conducted in Vietnam[35] found that varenicline dominates bupropion and transdermal NRT but that these alternatives were not deemed cost-effective under the relevant WTP threshold. The authors argued that their findings were influenced by the excessively high price of pharmaceuticals in Vietnam. More such studies in low- and middle-income countries would shed light on these observed trends.

Our study has several strengths that deserve mentioning. To our knowledge, this is the first economic evaluation of smoking cessation alternatives in Latin America. This is particularly important given that low- and middle-income countries present different scenarios of access to domestic and foreign production of medicines than those of other countries where similar studies are available. Access to medicines affects drug prices, which may explain the dominated scenario of varenicline. Second, this study evaluated all existing alternatives for smoking cessation in Brazil, including psychotherapy without pharmacological treatments. Third, our extensive sensitivity analysis, deterministic and probabilistic, offers robust evidence of the cost-effectiveness of smoking alternatives in Brazil.

Nonetheless, there are a few limitations in this study. First, the disease-specific relative risks of mortality (current smokers vs never smokers, or former smokers vs current smokers) that are available in the literature are estimates based on US cohort analyses; Brazilian smokers, however, might start smoking later in life and might smoke fewer cigarettes than US smokers, which may lower relative risks and therefore increase the corresponding number of QALYs across interventions. Nevertheless, the main conclusions will likely remain unaltered. Second, our model assumes a single quitting attempt throughout the individual's lifetime and this might have biased the ICER estimates. In terms of face validity, however, our work is in accordance with studies conducted in other countries. Third, the use of Dutch data, in the absence of Brazilian data, on incidence rates of the diseases considered in the model may have overestimated the base-case ICER. Nonetheless, a deterministic sensitivity analysis showed that this methodological solution did not have a relevant impact on the conclusions of the study.

Conclusions

Although economic evaluations of smoking cessation strategies have been common in high-income countries, limited evidence exists elsewhere. This study showed that varenicline and a combination of transdermal and oral NRT are the most effective alternatives but that varenicline is dominated owing to its higher cost in Brazil. Combined NRT was shown to be cost-effective at a WTP threshold of 0.5 per capita GDP. Further studies of the cost-effectiveness of varenicline and other smoking cessation alternatives (including combined NRT) in low- and middle-income countries are necessary to understand why varenicline does not exhibit its dominance found in high-income settings.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.vhri.2021.07.005.

Article and Author Information

Accepted for Publication: July 6, 2021

Published Online: November 13, 2021

doi: https://doi.org/10.1016/j.vhri.2021.07.005

Author Affiliations: Brazilian National Cancer Institute (INCA), Rio de Janeiro, RJ, Brazil (Fernandes, Szklo, Guerra, Barufaldi, de Albuquerque); Department of Health Policy and Management, University of California, Los Angeles (UCLA), Los Angeles, CA, USA (Seixas); Social Institute of Medicine, State University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil (de Mello Vianna).

Correspondence: Brayan Viegas Seixas, BPharm MSc, Department of Health Policy and Management, University of California, Los Angeles (UCLA), 650 Charles E Young Dr S, Los Angeles, CA 90095, USA. Email: brayanseixas@ucla.edu

Author Contributions: *Concept and design*: Fernandes, Guerra, Barufaldi, Albuquerque, Vianna
Acquisition of data: Fernandes, Szklo, Guerra, Barufaldi, Albuquerque
Analysis and interpretation of data: Fernandes, Seixas, Szklo, Guerra, Vianna
Drafting of the manuscript: Fernandes, Seixas
Critical revision of the paper for important intellectual content: Fernandes, Seixas, Szklo, Guerra, Barufaldi, Albuquerque, Vianna
Statistical analysis: Fernandes
Supervision: Vianna

Conflict of Interest Disclosures: The authors reported no conflicts of interest.

Funding/Support: The authors received no financial support for this research.

REFERENCES

1. Chelland Campbell S, Moffatt RJ, Stamford BA. Smoking and smoking cessation - the relationship between cardiovascular disease and lipoprotein metabolism: a review. *Atherosclerosis*. 2008;201(2):225–235.
2. Fact sheets. Action on Smoking and Health. https://ash.org.uk/information-and-resources/ash-fact-sheets/. Accessed August 26, 2019.
3. Thun M, Carte B, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med*. 2013;368(4):351–364.
4. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2007;298(22):2654–2664.
5. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673–2734.
6. Yu SS, Tang X, Ho Y-S, Chang RC-C, Chiu K. Links between the brain and retina: the effects of cigarette smoking-induced age-related changes in Alzheimer's disease and macular degeneration. *Front Neurol*. 2016;7:119.
7. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. *The Health Consequences of Smoking—50 years of Progress: A Report of the Surgeon General*. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
8. BRASIL, Ministério da Saúde. *Vigitel Brasil* 2017*: Vigilância de Fatores de Risco e Proteção Para Doenças Crônicas Por Inquérito Telefônico: Estimativas Sobre Frequência e Distribuição Sociodemográfica de Fatores de Risco e Proteção Para Doenças Crônicas Nas Capitais Dos 26 Estados b. 1. edição*. Ministério da Saúde; 2018.
9. BRASIL, Ministério da Saúde. *Portaria nº 761, de 21 de junho de* 2016. https://www.inca.gov.br/en/node/1822. Accessed August 6, 2021.
10. Fagerström K, Balfour DJK. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. *Expert Opin Investig Drugs*. 2006;15(2):107–116.
11. Igarashi A, Takuma H, Fukuda T, Tsutani K. Cost-utility analysis of varenicline, an oral smoking cessation drug, in Japan. *Pharmacoeconomics*. 2009;27(3):247–261.
12. Hoogendoorn M, Welsing P, Rutten-van Mölken MPMH. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. *Curr Med Res Opin*. 2008;24(1):51–61.
13. Annemans L, Nackaerts K, Bartsch P, Prignot J, Marbaix S. Cost effectiveness of varenicline in Belgium, compared with bupropion, nicotine replacement therapy, brief counselling and unaided smoking cessation. *Clin Drug Investig*. 2009;29(10):655–665.
14. Von Wartburg M, Raymond V, Paradis PE. The long-term cost-effectiveness of varenicline (12-week standard course and 12 + 12-week extended course) vs. other smoking cessation strategies in Canada. *Int J Clin Pract*. 2014;68(5):639–646.
15. BRASIL, Ministério da Saúde. *Protocolo Clínico e Diretrizes Terapêuticas Dependência à Nicotina*. 2016.
16. 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(6):497–511.
17. BRASIL, Ministério da Saúde. Pesquisa nacional de saúde 2013. Pesquisa nacional de saúde 2013 - microdados. https://ww2.ibge.gov.br/home/estatistica/populacao/pns/2013_vol3/default_microdados.shtm. Accessed June 12, 2018.
18. Wetter DW, Cofta-Gunn L, Fouladi RT, Cinciripini PM, Sui D, Gritz ER. Late relapse/sustained abstinence among former smokers: a longitudinal study. *Prev Med*. 2004;39(6):1156–1163.
19. Krall EA, Garvey AJ, Garcia RI. Smoking relapse after 2 years of abstinence: findings from the VA Normative Aging Study. *Nicotine Tob Res*. 2002;4(1):95–100.

20. Miravitlles M. Avaliação econômica da doença pulmonar obstrutiva crônica e de suas agudizações: aplicação na América Latina. *Aplicação Am Lat*;93:274-285.
21. Thun M, Apicella LF, Henley SJ. Smoking vs other risk factors as the cause of smoking-attributable deaths confounding in the courtroom. *JAMA*. 2000;284(6):2000.
22. Ascef B. Qualidade de vida relacionada À Saúde E seus fatores associados: uma análise dos usuários DA atenção básica À Saúde no. *Brasil*; 2015. https://www.scielo.br/j/rsp/a/GJSCDHghfv3M9PdjtwrhNSh/?lang=pt&format=pdf. Accessed August 6, 2021.
23. Salem A, Magno R, Carvalho M, Szklo M, Cavalcante TM, de Almeida LM. Understanding the relationship between sales of legal cigarettes and deaths: a case-study in Brazil. *Prev Med*. 2017;94:55–59.
24. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;2016(5), CD006103.
25. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev*. 2013;(5), CD009329.
26. Neves AC, Fukujima MM, de Jesus PA, et al. Custos do paciente com acidente vascular cerebral no setor de Emergência do Hospital São Paulo. *Rev Neiurociencias*. 2002;10(3):137–140.
27. Reis MF. Análise do custo do tratamento fisioterapêutico de pacientes sequelados por acidentes vasculares cerebrais pelo sistema Único de saúde na cidade de Juiz de Fora, MG. Dissertação de Mestrado, PPG Saúde Coletiva, UFJF, 2015.
28. Araújo D, Teich V, Benitez R, Passos F, Cristina S, Martins O. Análise de custo-efetividade da trombólise com alteplase no acidente vascular cerebral. *Arq Bras Cardiol*. 2010;95:12–20.
29. Ribeiro RA, Mello RGB, Melchior R, et al. Custo anual do manejo da cardiopatia isquêmica crônica no Brasil: perspectiva pública e privada. *Arq Bras Cardiol*. 2005;85(1):3–8.
30. Teich V, Araujo D. Estimativa de custo da síndrome coronariana aguda no Brasil. *Rev Bras Cardiol*. 2011;24(2):85–94.
31. REK I, Crisóstomo M, Ii P, Cristina C, Pereira DA. Estimativa dos custos da assistência do câncer de pulmão avançado em hospital público de referência. *Rev Saúde Publica*. 2017;51:1–11.
32. Marcia P, Ugá MA. Custo do tratamento de pacientes com histórico de tabagismo em hospital especializado em câncer. *Rev Saúde Publ*. 2011;45(3):575–582.
33. Cardoso TDA, Roncada C, Rodrigues E, et al. Impacto da asma no Brasil: análise longitudinal de dados extraídos de um banco de dados governamental brasileiro. *J Bras Pneumol*. 2017;43(3):163–168.
34. BPS. Banco de preços em Saúde. http://bps.saude.gov.br/login.jsf. Accessed September 29, 2020.
35. Higashi H, Barendregt JJ. Cost-effectiveness of tobacco control policies in Vietnam: the case of personal smoking cessation support. *Addiction*. 2012;107(3):658–670.
36. Pichon-Riviere A, Augustovisky F, Garcia-Marti S. Derivation of cost-effectiveness thresholds based on per capita health expenditures and life expectancy, and country-level estimates for 194 countries. https://www.iecs.org.ar/wp-content/uploads/IECS-TechDoc-16-Pichon-Riviere-et-al-CE-Thresholds-June2016-V2.pdf. Accessed May 18, 2018.
37. Linden K, Jormanainen V, Linna M, Sintonen H, Wilson K, Kotomäki T. Cost effectiveness of varenicline versus bupropion and unaided cessation for smoking cessation in a cohort of Finnish adult smokers. *Curr Med Res Opin*. 2010;26(3):549–560.
38. Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model. *Pharmacoeconomics*. 2008;26(6):497–511.
39. Bae JY, Kim CH, Lee EK. Evaluation of cost-utility of varenicline compared with existing smoking cessation therapies in South Korea. *Value Health*. 2009;(12 suppl 3):S70–S73.
40. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaste T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev*. 2014;2014(1), CD000031.