

A Cost-Utility Study of Smoking Cessation Interventions for Patients with Chronic Obstructive Pulmonary Disease in Thailand

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Background: Evidence indicates that smoking cessation is the intervention that could slow the decline of lung function in patients with chronic obstructive pulmonary disease (COPD). Several pharmacological therapies for smoking cessation were available in Thailand. However, no cost-effectiveness evidence of smoking cessation intervention in Thailand has been reported.

Objective: To estimate cost-utility of smoking cessation intervention in COPD patients.

Materials and Methods: A lifetime Markov model of varenicline or bupropion in COPD patients willing to quit smoking compared to nortriptyline was conducted from a Thai societal perspective. The model consisted of six health states including 1) mild COPD, 2) moderate COPD, 3) severe COPD, 4) very severe COPD, 5) lung cancer, and 6) death. All inputs were determined by literature sources. The incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained was calculated. One-way and probabilistic sensitivity analyses were also conducted. The willingness-to-pay (WTP) 160,000 Thai baht (THB) was used as WTP threshold.

Results: Compared to nortriptyline, varenicline was cost-effective with ICER of 50,446 THB/QALY gained, while bupropion was not cost-effective with ICER of 841,982 THB/QALY gained. Compared to bupropion, varenicline was also cost-effective with ICER of 14,200 THB/QALY. One-way sensitivity analysis indicated that incidence of lung cancer was a major driver of the model. Probabilistic sensitivity analysis indicated that varenicline had 98% chance to be cost-effective, while bupropion had 87% chance to be cost-effective at the WTP of 160,000 THB.

Conclusion: The authors' findings revealed that varenicline is the most cost-effective strategy for smoking cessation in COPD patients compared to nortriptyline and bupropion. Policy makers should consider varenicline to be in their benefit packages as a smoking cessation intervention for COPD patients.

Keywords: Cost-utility analysis, Smoking cessation intervention, Chronic obstructive pulmonary disease, Thailand

J Med Assoc Thai 2019;102(4): 463-71

Website: <http://www.jmatonline.com>

Chronic obstructive pulmonary disease (COPD) is one of the important respiratory diseases causing mortality and morbidity worldwide. In 2016, COPD caused approximately 3.1 million deaths, which was the third leading cause of death worldwide⁽¹⁾. COPD is also associated with a high economic burden⁽²⁾. The

medical costs associated with COPD in the United States was \$32.1 billion, along with a loss of 16.4 million days of work. Moreover, the projected medical costs related to COPD is going to be \$49 billion by 2020⁽²⁾. In Thailand, COPD was the sixth leading cause of death with 4% of total death⁽³⁾. The estimated prevalence of death related to COPD is 48.0 cases per 100,000 persons⁽⁴⁾.

The primary risk factor for COPD is smoking. Approximately 80% of COPD death are caused by smoking. Individuals who smoke are nearly 12 to 13 times as likely to die from COPD as individuals who have never smoked⁽⁵⁾. Smoking cessation is the

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How to cite this article: Kongsakon R, Sruamsiri R. A Cost-Utility Study of Smoking Cessation Interventions for Patients with Chronic Obstructive Pulmonary Disease in Thailand. *J Med Assoc Thai* 2019;102:463-71.

only evidence-based intervention that could slow the decline of lung function⁽⁶⁻⁸⁾. Supporting individuals to quit smoking could slow COPD progression and reduce the economic burden. There are several interventions available to help people quit smoking including simple counselling, face-to-face counselling, proactive telephone counselling, and pharmacological therapies (including nicotine replacement therapy (NRT), antidepressant, and varenicline). Based on previous studies, a combination of pharmacological and behavioral therapies is recommended for COPD smokers^(9,10).

Several previous cost-effectiveness analysis (CEA) have shown cost-effective smoking cessation interventions in patients with COPD, worldwide^(11,12). However, no CEA was conducted to determine the cost-effectiveness of smoking cessation interventions for patients with COPD in Thailand. Only one CEA related to smoking cessation intervention in Thailand exists⁽¹³⁾. The authors compared cost-effectiveness of seven smoking cessation interventions including, hospital counselling, proactive telephone counselling, nicotine gum, nicotine patch, bupropion, nortriptyline, and varenicline in individuals who were current smokers with more than 10 tobacco cigarettes per day. They found that all interventions could save cost and increase quality-adjusted life year (QALY) compared to self-quit. However, the present study might not be applicable for a specific sub-population such as COPD. Costs and outcomes of smoking cessation interventions in patients with COPD might be different from those in general smokers.

There remains an important question to be answered from a policy maker perspective whether using smoking cessation in COPD patients is worth the money spent in the context of Thailand. To date, again, no evidence for the cost-effectiveness of pharmacological therapies for smoking cessation for patients with COPD has been reported. The present study aimed to estimate the cost-utility of pharmacological therapies for smoking cessation in COPD patients in Thailand.

Materials and Methods

Overall description of cost-utility study

A cost-utility analysis of pharmacological therapies for smoking cessation for patients with COPD in Thailand was undertaken using a lifetime Markov framework under a societal perspective as recommended by the Thailand's Health Technology Assessment (HTA) Guideline⁽¹⁴⁾. The population of interest was current smokers (more than 10 tobacco

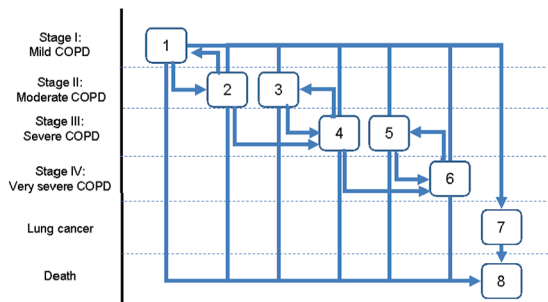


Figure 1. Markov model.

COPD: chronic obstructive pulmonary disease

cigarettes per day) with COPD who were willing to quit smoking. The interventions of interest were, 1) bupropion plus hospital counselling, 2) varenicline plus hospital counselling, and 3) nortriptyline plus hospital counselling as a comparator. The NRT was not included in the study. Based on the present review, no evidence of NRT effectiveness in patients with COPD has been reported. The lifetime cost, life-year, and QALY were estimated. The present study was approved by the Ethics Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

Model structure

The authors' model was developed based on COPD diagnostic criteria, provided by the Global Initiative of Chronic Obstructive Lung Disease⁽⁸⁾ and validated by experts through expert meeting panels as recommended by the Thailand's HTA guideline⁽¹⁴⁾. The model was validated and revised through consultations with health economists and clinicians.

The Markov model with a 1-year cycle length was built to capture lifetime cost and outcomes. A hypothetical cohort of 1,000 patients was simulated. The model consisted of six health states that include 1) mild COPD, 2) moderate COPD, 3) severe COPD, 4) very severe COPD, 5) lung cancer, and 6) death (Figure 1). The model consisted of two sub-model with identical Markov structure for current smokers and smokers who quit. Patients entered to any COPD health states. About 3% of patients entered in mild COPD state, while 26%, 50%, and 21% of patients entered in moderate, severe, and very severe COPD health states, respectively. Each patient could remain at the same health state or progress to the next severer COPD health state. For example, a patient at mild COPD could progress to moderate COPD but could

not progress to severe or very severe COPD. Each patient could also improve to the next better health state. For example, a patient at severe COPD could improve to moderate COPD but could not improve to mild COPD. Any patient at any COPD health states could progress to lung cancer or death. A patient at lung cancer could progress to death but could not improve to any COPD health states. Death served as the absorbing health state, accumulating both disease-specific and background mortality.

Model inputs and assumptions

All model inputs were obtained from systematic review (Table 1). Inputs that had enough information from systematic review were derived by a meta-analysis. All inputs were reviewed by expert panels to determine the best available data sources.

Clinical efficacy and transition probabilities: Efficacy of varenicline in patients with COPD was from a randomized controlled clinical trial (RCT) that compared smoking quit rate between varenicline plus counselling and counselling alone⁽¹⁵⁾. The percentage of patients that quit in patients who used varenicline was 24.6%. Efficacy of bupropion was derived by a meta-analysis of two RCTs^(16,17). The percentage of patients that quit in patients who used bupropion was 14.1%. However, the meta-analysis was based on smoking quit rate at 26 weeks. The authors assumed the same smoking quit rate at one year as the rate at 26 weeks. Efficacy of nortriptyline was from a RCT⁽¹⁷⁾. The percentage of patients that quit in patients who used nortriptyline was 13.6%.

Transition probabilities among COPD health states were derived from a previous study⁽¹⁸⁾. The present study was conducted in patient with COPD in the Netherlands. The details of each transition probabilities among COPD health states for continuing smoker and quitters are shown in Table 1. The incidence of lung cancer in patients with COPD was 1.54% in current smoker and 1.24% in quitters⁽¹⁹⁾. The incidence was applied for all other health states except death.

The mortality rate was derived from a Thailand's life table (Ministry of Public Health, Statistical Thailand 2013, 2014)⁽²⁰⁾ and converted to COPD population using data from a previous study conducted by Hoogendoorn et al that reported excess mortality rate of COPD patients in each health states⁽¹⁸⁾.

The authors also incorporated relapse rate of smoking using data from previous studies^(21,22). The authors assumed the relapse rate of patients with COPD to be the same as that of healthy patients. The

average relapse rates of smoking were 6.3%, 2.0%, and 1.0% for first 1 to 5 years, 6 to 10 years, and longer than 10 years, respectively.

Cost: The cost used in this study included the direct medical and the direct non-medical costs. The cost of pharmacological treatment for smoking cessation were calculated based on Thailand's smoking cessation guideline⁽²³⁾. A course of smoking cessation was 12 weeks. The cost of smoking cessation intervention was obtained from a national website of healthcare price⁽²⁴⁾. In summary, the costs of bupropion, varenicline, and nortriptyline were 5,166 THB, 4,733 THB, and 665 THB, respectively.

The direct medical and direct non-medical costs were obtained from a previous Thai study^(13,25) that was conducted to determine costs incurred in 50 patients with COPD in eight teaching hospitals in Thailand. The cost of exacerbation was obtained from another study^(25,26). The present study was conducted to determine cost of COPD exacerbation over 5-year observational period with 183 patients. The average cost of COPD exacerbation was 83,873 THB. All costs were converted to 2016 value using consumer price index⁽²⁷⁾. The details of costs are shown in Table 1.

Utility: Utility of patients with COPD was collected from a previous study by Stahl et al⁽²⁸⁾, while utility of patients with lung cancer was collected from another previous unpublished work at a university hospital at northern part of Thailand. Moreover, the authors incorporated the disutility of exacerbation into the model. The disutility data was obtained from a previous Canadian study⁽²⁹⁾. The disutility value was -0.5 when a patient had a COPD exacerbation. The details of utilities are shown in Table 1.

Statistical analysis

Primary outcomes of interest were lifetime costs, QALYs gained, and the incremental cost-effectiveness ratio (ICER)/QALY gained. For the base-case analysis, the authors calculated the estimated lifetime costs and outcomes for each smoking cessation intervention. All future costs and outcomes were discounted at a rate of 3% per year as recommended by the Thai HTA guideline⁽¹⁴⁾.

The interpretation of cost-effectiveness was based on an official willingness-to-pay (WTP) if the Thai Health Economic Working Group threshold was 160,000 THB per QALY gained.

One-way sensitivity analysis was performed to explore the effects of uncertainties around inputs with plausible ranges of 95% confidence interval (CI). The results of one-way sensitivity were presented as a

Table 1. Model inputs

Input	Base-case value	SE/range	Distribution	Reference
Efficacy				
Counselling + nortriptyline	13.60%	2.20%	Beta	Wagena, et al. ⁽¹⁷⁾
Counselling + bupropion	14.10%	2.40%	Beta	Wagena, et al. ⁽¹⁷⁾ and Tashkin, et al. ⁽¹⁶⁾
Counselling + varenicline	24.60%	2.70%	Beta	Tashkin, et al. ⁽¹⁵⁾
Progression of COPD				Hoogendoorn, et al. ⁽¹⁸⁾
Current smoker				
• Mild to moderate	2.50%	-	Fixed	
• Moderate to severe	3.70%	-	Fixed	
• Severe to very severe	3.10%	-	Fixed	
Quitted smoker				
• Mild to moderate	2.10%	-	Fixed	
• Moderate to severe	3.40%	-	Fixed	
• Severe to very severe	3.00%	-	Fixed	
Excess mortality risk (per 1,000 patients)*				Suwanla, et al.
Current smoker				
• Mild COPD (male)	22.4	22.4	Beta	
• Mild COPD (female)	22.5	22.5	Beta	
• Moderate COPD (male)	35.5	35.5	Beta	
• Moderate COPD (female)	35.6	35.6	Beta	
• Severe COPD (male)	54	54	Beta	
• Severe COPD (female)	54.3	54.3	Beta	
• Very severe COPD (male)	77.3	77.3	Beta	
• Very severe COPD (female)	77.4	77.4	Beta	
Quitted smoker				
• Mild COPD (male)	22.4	22.4	Beta	
• Mild COPD (female)	22.5	22.5	Beta	
• Moderate COPD (male)	35.5	35.5	Beta	
• Moderate COPD (female)	35.6	35.6	Beta	
• Severe COPD (male)	54	54	Beta	
• Severe COPD (female)	54.3	54.3	Beta	
• Very severe COPD (male)	77.3	77.3	Beta	
• Very severe COPD (female)	77.4	77.4	Beta	
Incidence rate of lung cancer				GLOBOCAN
Current smoker				
Current smoker	1.59%	-	Fixed	
Quitted smoker				
Quitted smoker	1.28%	-	Fixed	
Age-specific mortality				Ministry of Public Health ⁽²⁰⁾
Current smoker				
Current smoker	Varied by age	Varied by age	Varied by age	

COPD=chronic obstructive pulmonary disease

* Assumed SE equals to mean because there were no information on the variation around the inputs

Table 1. (continued)

Input	Base-case value	SE/range	Distribution	Reference
Quitted smoker	Varied by age	Varied by age	Varied by age	
Smoking relapse rate				Wetter, et al. ⁽²¹⁾ and Krall, et al. ⁽²²⁾
Current smoker				
• Up to 5 years	6.30%	1.40%	Beta	
• 6 to 10 years	2.00%	0.60%	Beta	
• 11 years or more	1.00%	0.40%	Beta	
Quitted smoker				
• Up to 5 years	6.30%	1.40%	Beta	
• 6 to 10 years	2.00%	0.60%	Beta	
• 11 years or more	1.00%	0.40%	Beta	
Cost of intervention (Thai baht)				Riewpaiboon, et al. ⁽²⁵⁾ and Tosanguan, et al. ⁽¹³⁾
Counselling + Nortriptyline				
• Direct medical cost	665.34	1,148.72	Gamma	
• Direct non-medical cost	1,442.97	220.86	Gamma	
Counselling + Bupropion				
• Direct medical cost	5,166.28	729.62	Gamma	
• Direct non-medical cost	1,442.97	220.86	Gamma	
Counselling + Varenicline				
• Direct medical cost	4,784.29	671.15	Gamma	
• Direct non-medical cost	1,442.97	220.86	Gamma	
Counselling alone				
• Direct medical cost	399.43	61.14	Gamma	
• Direct non-medical cost	1,442.97	220.86	Gamma	
Cost of COPD*				Patumanond, et al. ⁽²⁶⁾
Mild COPD	10,289	10,289	Gamma	
Moderate COPD	9,596	9,596	Gamma	
Severe COPD	11,839	11,839	Gamma	
Very severe COPD	15,994	15,994	Gamma	
Lung cancer	79,272	79,272	Gamma	
Exacerbation	84,079	84,079	Gamma	
Utility				Stahl, et al. ⁽²⁸⁾ and Spencer, et al. ⁽²⁹⁾
Mild COPD	0.8971	0.0219	Beta	
Moderate COPD	0.7551	0.0346	Beta	
Severe COPD	0.7481	0.0436	Beta	
Very severe COPD	0.5493	0.0652	Beta	
Lung cancer	0.65	0.0655	Beta	
Disutility due to exacerbation	-0.5	-	Fixed	

COPD=chronic obstructive pulmonary disease

* Assumed SE equals to mean because there were no information on the variation around the inputs

Table 2. Cost-effectiveness analysis results

Comparison	Cost (THB)	QALYs	Incremental costs (THB)	Incremental QALYs	ICER
Base-case analysis					
Varenicline + counselling	174,184	4.46	5,754	0.11	50,446
Bupropion + counselling	172,619	4.35	4,190	0.005	841,982
Nortriptyline + counselling	168,429	4.35	reference	reference	reference
Post-hoc analysis					
Varenicline + counselling	174,184	4.46	1,564	0.11	14,220
Bupropion + counselling	172,619	4.35	reference	reference	reference

THB=Thai baht; QALYs=quality-adjusted life years; ICER=incremental cost-effectiveness ratio

tornado diagram.

Probabilistic sensitivity analysis (PSA) was also performed using a Monte Carlo simulation with 1,000 iterations. The PSA's findings were presented as a cost-effectiveness acceptability curve. The distribution of each input was assigned as 1) beta distribution for probability and utility, 2) gamma distribution for costs, and 3) log-normal distribution for odds ratio of efficacy and survival inputs.

A post-hoc analyses was also performed to compare between varenicline and bupropion.

Results

Base-case analysis

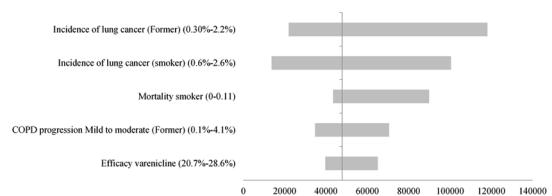
Base-case analysis results are shown in Table 2. Lifetime cost of hospital nortriptyline was 168,429 THB, while the cost of bupropion and varenicline were 172,619 THB and 174,184 THB, respectively. The lifetime QALYs of nortriptyline, bupropion, and varenicline were 4.35, 4.35, and 4.46, respectively. The ICER of bupropion and varenicline compared to nortriptyline were 841,982 THB/QALY gained, and 50,446 THB/QALY gained, respectively.

A post-hoc analysis indicated that ICER of varenicline compared to bupropion was 14,220 THB/QALY gained (Table 2).

Sensitivity analysis

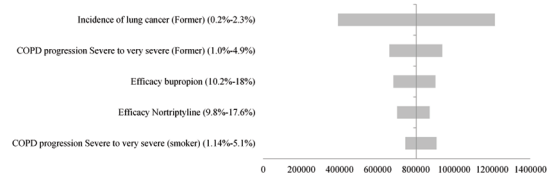
One-way sensitivity analysis indicated that incidences of lung cancer in both quitters and current smokers were important drivers of the results (Figure 2a) when comparing varenicline to nortriptyline. When varying the incidence of lung cancer of quitters from 0.3% to 2.2%, the ICER ranged from 21,953 THB to 118,176 THB, while varying the incidence of lung cancer of current smokers from 0.6% to 2.6%, the ICER ranged from 13,663 THB to 100,491 THB.

One-way sensitivity analysis (Varenicline + counselling vs. Nortriptyline + counselling)



a. Varenicline + counselling + Nortriptyline + counselling

One-way sensitivity analysis (Bupropion + counselling vs. Nortriptyline + counselling)



b. Bupropion + counselling + Nortriptyline + counselling

Figure 2. The results of one-way sensitivity analysis.

Comparing bupropion to nortriptyline, the important drivers of the results were incidence of lung cancer in quitters and COPD progression probability from severe to very severe in quitters (Figure 2b). When varying the incidence of lung cancer of quitters from 0.2% to 2.3%, the ICER ranged from 392,484 THB to 1,214,722 THB. When varying COPD progression probability from severe to very severe in quitters from 1.0% to 4.9%, the ICER ranged from 662,205 THB to 938,588 THB.

The results of 1,000 iterations of probabilistic sensitivity analysis indicated that both bupropion and varenicline were higher costs and higher QALYs compared to nortriptyline (Figure 3). The cost-effectiveness acceptability curve indicated that at the WTP threshold of 160,000 THB, bupropion had 87% chance to be cost-effective, while varenicline had 98% chance to be cost-effective (Figure 4). Varenicline was

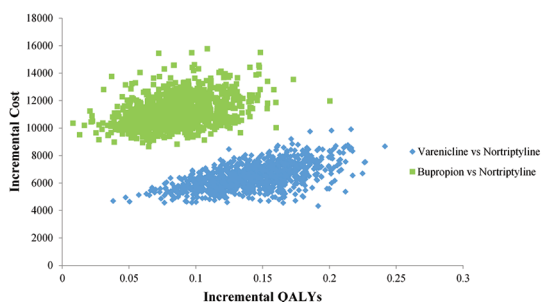


Figure 3. The results of probabilistic sensitivity analysis between bupropion vs. nortriptyline and varenicline vs. nortriptyline.

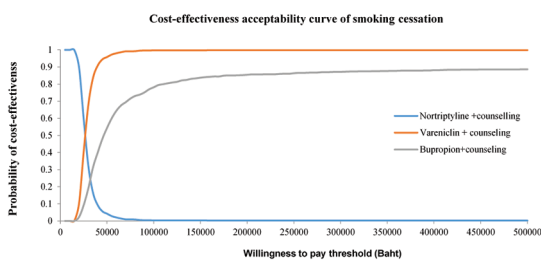


Figure 4. The results of cost-effectiveness acceptability curve of all smoking cessation interventions.

dominant to bupropion.

Discussion

The present study was the first study estimating the lifetime cost, QALYs, and ICER/QALY gained for pharmacological therapies plus counselling for smoking cessation in COPD patients in Thailand. The findings were that lifetime cost of varenicline was highest, while cost of nortriptyline was the lowest among the pharmacological therapies for smoking cessation. Varenicline could gain the highest QALYs compared to other therapies. Based on ICER, varenicline was cost-effective compared to nortriptyline according the Thailand's WTP at 160,000 THB, while bupropion was not cost-effective.

The authors' findings were similar to previous cost-effectiveness studies of smoking cessation in several countries⁽³⁰⁻³²⁾. The studies indicated that varenicline was cost-effective for smoking cessation in COPD patients compared to placebo, NRT, or even bupropion. The authors' findings were also similar to a previous Thai study⁽¹³⁾ that was conducted in Thai smokers to determine the cost-effectiveness of smoking cessation interventions. They found that smoking cessation could save healthcare cost and

gain health outcomes. The present study supported that smoking cessation could also be a cost-effective strategy, especially for varenicline, even though the smoking quit rate of COPD patients was lower than the general population⁽¹³⁾.

Smoking cessation, especially in patients with chronic diseases such as COPD in Thailand, should be encouraged because evidence indicates that quitting smoking increase life expectancy and decrease the risk of lung cancer and oral cancer⁽³³⁾. The present study supported the information that patients who participate in smoking cessation using one of the medications including varenicline, bupropion, and nortriptyline could increase about 4.35 to 4.46 QALYs. However, the present study indicated that varenicline might be the most cost-effective strategy according the ICER the authors observed. These findings drew Thai policy makers' attention that they might consider varenicline to be in the benefit packages as smoking cessation intervention for COPD patients.

The authors believe that our findings are highly accurate and relevant to Thai contexts. The authors conducted the present study with stakeholders' involvement throughout the authors' process according to the Thai HTA guideline⁽¹⁴⁾. Experts and different types of stakeholders were invited to provide their thoughts. This process gains validity of study's scope and inputs. Moreover, this process increases transparency of the present study. The authors also used local data as much as possible. The authors collected several inputs from Thai studies. The authors' age-specific mortality was from Ministry of Public Health (MOPH), which is specific to Thai population. The authors also collected cost data from several local data sources. The authors collected smoking cessation costs from previous Thai studies⁽¹³⁾, cost of COPD treatments from other previous Thai studies⁽²⁶⁾, with information from Drug and Medical Supplies, MOPH⁽²⁴⁾. The authors also collected utility data of lung cancer patients from an unpublished Thai study. These make our result more relevant to Thai context.

A number of limitations of the present study should be addressed. First, although the authors tried to collect local data as much as possible, the authors could not find any efficacy data of each smoking cessation intervention in Thailand. The efficacy data were from other countries. The efficacy of each smoking cessation intervention from other countries might be different from Thai context. Even, the authors found that there was a Thai study conducted to determine effectiveness of smoking cessation

intervention on quit rate. However, the present study was conducted using observational study design with some scientific flaws. The authors do not think the data should be applicable for the present study. However, the authors did sensitivity analysis using the Thai study data (but not shown in the authors' findings) and the authors found similar findings that varenicline was cost-effective. Therefore, the authors believe that the efficacy inputs were the best available data sources and were applicable to the present study. Second, the authors could not find any COPD-related mortality in Thai population. The authors used age-specific mortality from MOPH and adjusted to COPD-related mortality using data from the Netherlands. The COPD-related mortality the authors used might not be the true estimates for Thai population. However, again based on limited available data, the authors believe that the approach was appropriate to estimate the mortality. Third, the authors used utility data of lung cancer from a single-center unpublished study. The data might not be representative of Thai patients with lung cancer. Fourth, the authors assumed the same smoking quit rate of bupropion at 1 year and the rate at 26 weeks. This assumption might not be accurate because quitters might re-smoke after 26 weeks. The efficacy used in this model might be over-estimated. Last, the authors assumed the same relapse rate for COPD patients and general population, which might not be accurate because COPD patients are likely to have been addicted to smoking longer than the general population. The relapse rate of COPD patients might be higher than the general population. However, there is no study related to relapse rate of COPD patients available. Further studies aiming to determine the relapse rate of smoking in COPD patients are warranted.

Conclusion

In conclusion, the authors' findings found that varenicline is the most cost-effective strategy for smoking cessation in COPD patients compared to nortriptyline and bupropion. Policy makers should consider varenicline to be in their benefit packages as a smoking cessation intervention for COPD patients.

What is already known on this topic?

COPD is one of important respiratory diseases causing mortality and morbidity worldwide. The primary risk factor for COPD is smoking. Supporting individuals to quit smoking could slow COPD progression and reduce the economic burden.

However, policy makers are still concerned

whether using smoking cessation in COPD patients is worth the money spent in the context of Thailand.

What this study adds?

The findings support that varenicline is the most cost-effective strategy for smoking cessation in COPD patients in Thailand. Policy makers should consider varenicline to be in their benefit packages as a smoking cessation intervention for COPD patients.

Conflicts of interest

The authors declare no conflict of interest.

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