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Cost-effectiveness analysis of the first-line therapies for nicotine dependence

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Abstract Background: Nicotine dependence is the major obstacle for smokers who want to quit. Guidelines have identified five effective first-line therapies, four nicotine replacement therapies (NRTs)—gum, patch, nasal spray and inhaler—and bupropion. Studying the extent to which these various treatments are cost-effective requires additional research.

Objectives: To determine cost-effectiveness (CE) ratios of pharmacotherapies for nicotine dependence provided by general practitioners (GPs) during routine visits as an adjunct to cessation counselling.

Methods: We used a Markov model to generate two cohorts of one-pack-a-day smokers: (1) the reference cohort received only cessation counselling from a GP during routine office visits; (2) the second cohort received the same counselling plus an offer to use a pharmacological treatment to help them quit smoking. The effectiveness of adjunctive therapy was expressed in terms of the resultant differential in mortality rate between the two cohorts. Data on the effectiveness of therapies came from meta-analyses, and we used odds ratio for quitting as the measure of effectiveness. The costs of pharmacotherapies were based on the cost of the additional time spent by GPs offering, prescribing and following-up treatment, and on the retail prices of the therapies. We used the third-party-payer perspective. Results are expressed as the incremental cost per life-year saved.

Results: The cost per life-year saved for only counselling ranged from €385 to €622 for men and from €468 to €796 for women. The CE ratios for the five pharmacological treatments varied from €1768 to €6879 for men, and from €2146 to €8799 for women. Significant variations in CE ratios among the five treatments were primarily due to differences in retail prices. The most cost-effective treatments were bupropion and the patch, and, then, in descending order, the spray, the inhaler and, lastly, gum. Differences in CE between men and women across treatments were due to the shape of their respective mortality curve. The lowest CE ratio in men was for the 45- to 49-year-old group and for women in the 50- to 54-year-old group. Sensitivity analysis showed that changes in treatment efficacy produced effects only for less-well proven treatments (spray, inhaler, and bupropion) and revealed a strong influence of the discount rate and natural quit rate on the CE of pharmacological treatments.

Conclusion: The CE of first-line treatments for nicotine dependence varied widely with age and sex and was sensitive to the assumption for the natural quit rate. Bupropion and the nicotine patch were the two most cost-effective treatments.

Keywords Smoking · Nicotine replacement therapy · Pharmacology · Cost-effectiveness · Counselling

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Introduction

Tobacco is the leading cause of preventable death in developed countries. Lowering smoking prevalence is the primary goal in tobacco control. There are two core approaches to reducing prevalence—preventing non-smokers from starting and encouraging current smokers to quit. This study focuses on the second component of a comprehensive approach to tobacco control, the cost-effectiveness of pharmacological smoking cessation aids.

Nicotine dependence is what anchors smokers to their habits and, for many, prevents them from quitting [1].

More than half of all regular smokers express a desire to quit smoking, and most of them report having tried unsuccessfully to give up the habit [2]. It has been recently emphasised that studying the extent to which various tobacco dependence treatments are cost-effective requires additional research [3]. Counselling and pharmacological cessation therapies have been proven to be efficacious as aids for smoking cessation, nearly doubling a smoker's chances of quitting successfully [4, 5, 6, 7]. Recent clinical practice guidelines have identified five first-line therapies [3]. These treatments include four nicotine replacement therapies (NRTs)—gum, patch, nasal spray and inhaler—and bupropion, an anti-depressant which has recently been demonstrated as an effective treatment for nicotine dependence. In today's political and economic climates, marked by fierce competition for limited resources, effectiveness alone is no longer sufficient support for the recommendation of new or preferred interventions. Instead, it is also requisite to provide evidence for cost-effectiveness when presenting policy options that are considered superior to those already in place or to none at all. Few studies—all based on data from Anglo-Saxon countries—have shown that NRT is both effective in practice and cost-effective relative to other common health interventions that are generally funded by third-party payers [8, 9, 10]. However, to our knowledge, no studies have assessed all available first-line pharmacological smoking cessation treatments, i.e., NRT and bupropion. We conducted this analysis as a part of a comprehensive approach to smoking cessation in a European country [11].

Methods

Calculation of effectiveness

We calculated the cost-effectiveness of general practitioners (GPs) providing their patients each of the five first-line pharmacological smoking cessation treatments as an adjunct to cessation counselling. We supposed that GPs provided their smoking patients

opportunistic cessation counselling during routine office visits and offered treatment to those for whom it was indicated. Clinical guidelines indicate pharmacological cessation therapy only for smokers who consume at least 10–15 cigarettes per day. The vast majority of daily smokers visiting a GP smoke on average a pack a day [12, 13, 14]. Therefore, we included in our simulated cohorts only patients who smoked, on average, 20 cigarettes per day.

We used a computer-simulated Markov model to generate two cohorts of identical smokers [15]. The reference cohort received only cessation counselling from a GP during routine office visits. The second cohort received the same counselling plus an offer to use a pharmacological treatment to help them quit smoking. The counselling-plus-treatment simulation was run for each of the five therapies. As a result, the two cohorts had different quit rates, which further indicated different mortality rates. We expressed the effectiveness of adjunctive treatment in terms of this resultant differential in mortality rates between the two cohorts. Details of the model can be obtained either directly from the authors upon request or through the following web address (<http://www.hospvd.ch/iump/download/files/rapport/markovmodel.pdf>).

The total cost of offering pharmacological treatments was based on the cost of the additional time spent by GPs offering, prescribing and following-up pharmacological treatment, and on the retail prices of the therapies. The results were expressed as the incremental cost per life-year saved (with both costs and life-years discounted, as described below) that was attributable to the offer, availability, and use of pharmacological treatments, which included the costs associated with patients who were not successful in their treatment-aided quit attempts. Table 1 lists the input variables, base-case assumptions, and ranges for sensitivity analysis used in our study. We assumed a natural quit rate (i.e., cessation without intervention) among smokers of 2.5%. This rate reflected the estimated probability of quitting smoking over the course of 1 year in Switzerland, as well as in other Western countries [12, 16].

Studies have shown that 50–70% of smokers would like to quit smoking [2, 13]. Yet, according to the Stages-of-Change model, a much smaller proportion of these smokers are in the preparation stage—truly ready to make a serious quit attempt—and therefore appropriate candidates for treatment [17]. We made the assumption that 25% of current smokers were in the preparation stage for quitting [18] and used it in the Markov model. We derived the effectiveness of counselling and NRT from the results of two published meta-analyses [4, 5]. We based our analysis of bupropion on the efficacy trial conducted by Jorenby et al., which yielded similar results to a recent meta-analysis based on two bupropion efficacy trials performed by the US Department of Health and Human Services (DHHS) [3, 6]. Each of our reference studies based its measurement of cessation status on the point prevalence at 1 year of abstinence.

Table 1 Variables used in the analysis

Variable	Base case (range for sensitivity analysis)
Natural cessation rate among all smokers, %	2.5 (1–4)
Proportion of smokers in “preparation” stage, %	25 (10–40)
OR* counselling only	1.73 (1.46–2.03)
OR** nicotine gum	1.63 (1.49–1.79)
OR** nicotine patch	1.79 (1.60–2.01)
OR** nicotine spray	2.35 (1.63–3.38)
OR** nicotine inhaler	2.14 (1.44–3.18)
OR** bupropion	2.30 (1.40–3.90)
Smokers still under treatment after first month, %	50 (40–60)
Smokers still under treatment after second month, %	20 (15–25)
Lifetime probability of relapse after 1 year of abstinence, %	35 (10–50)
Time required for counselling, min	10 (5–15)
Total additional physician time required, min	90 (70–110)
Cost per hour of physicians' time, Euro	US \$65 (55.25–74.75)/ Euro 61.25 (52.06–70.44)
Discount rate, %	3 (0–5)

*Odds ratio for smoking cessation at 1 year, relative to no intervention

**Incremental odds ratio for cessation at 1 year, relative to counselling only (identical OR for women and men)

We used odds ratio for quitting as the measure of effectiveness for each treatment. We assumed that quit odds ratios were the same for men and women, the rationale for which has been presented in existing studies [5]. We calculated the quit rates for the pharmacological treatments as adjuncts to counselling by multiplying the quit odds ratios for each of the respective treatments by the odds of quitting for counselling only. For each treatment, we used the 95% confidence intervals for effectiveness as the range for our sensitivity analysis.

The long-term risk of relapse for former smokers has not been well documented. Existing long-term follow-up data suggest that of the subjects who have been abstinent for 1 year, approximately 30% will relapse some time during the following 5 years [19, 20]. Relapse after 5 years does occur, but the rate is insignificantly low [19, 20]. From previous studies, we adopted the conservative assumption of a 35% lifetime probability of relapse after 1 year of validated abstinence [8, 10].

Our assessment of the effects of smoking cessation on mortality rate was based on the results of the American Cancer Society Prevention Study II, as described in the 1990 report of U.S. Surgeon General [19]. This study compared mortality rates for smokers and never-smokers, through age 75 years. Based on Swiss mortality data, we extrapolated the effects of cessation on mortality to extend the mortality curve for smokers through age 100 years. Previous studies have found that the mortality rate for former smokers, whatever the level of previous consumption, progressively approaches and finally rejoins the mortality rate for never-smokers approximately 20 years after quitting [19, 21, 22]. Based on the findings of the American Cancer Society's study, we assumed a conservative approach and applied a phase-in period to never-smokers mortality risk of 25 years after quitting for former smokers who used to smoke on average 20 cigarettes a day [19]. We projected the mortality rate for former smokers during the phase-in period by calculating a weighted average of the incremental differentials between mortality rates of never-smokers and smokers, weighted according to the duration of abstinence.

Cost of smoking cessation therapies

In figuring medical and non-medical costs of smoking cessation therapies, we assumed a third-party-payer perspective, an approach used in several previous cost-effectiveness analyses of NRT [9, 10]. This approach allowed us to compare our results with those of existing studies.

We based the dosage and duration of each pharmacological treatment on current clinical guidelines, which recommend that treatment can last up to 3 months [3]. Physicians commonly recommend that treatment last for a minimum of 1 month, so we assumed that all smokers who agree to undergo treatment incur the cost of at least 1 month of therapy. Previous studies suggest that 50% of smokers who initiate treatment continue for a second month, and only 30% of those who start continue for a third month [23, 24]. These figures reflect the significant rate of relapse within the first several weeks of cessation therapy.

We estimated the price of each treatment based on 2001 pharmacy list prices provided in the drug therapy book for Switzerland [25]. We based the costs associated with GPs' time on average hourly fees in 2001 for medical consultations that do not include any technical procedures [26], as generally performed for other preventive interventions [27]. Cessation counselling and recommendations for pharmacological treatment were delivered by GPs during routine office visits. We assumed that the initial cessation counselling lasted approximately 10 min for all patients. If a patient agreed to undergo pharmacological treatment, an additional 15 min of the GP's time was required during the first consultation, as well as five 15-min follow-up consultations to take place during the remaining course of treatment. In total, pharmacological treatment required an additional 90 min of GP consultation relative to cessation counselling only. Details regarding treatment costs, dosages and duration are detailed elsewhere [28].

Discounting and currency conversion

In this analysis, there is a long period of time between the point at which the costs of the interventions incur and the point at which the benefits in life-years saved are realised. For this reason, it is necessary to calculate the present discounted value of these delayed benefits so that the value of life-years saved is measured on the same relative scale as the cost of the intervention at the time it is undertaken [29, 30]. We applied a 3% discount rate, which is commonly used in these types of prospective cost-effectiveness analyses [29]. To facilitate cross-country comparisons, we conducted the analysis and yielded our initial results using US dollars for all cost data. We then converted all results into Euros (€) by calculating the mean of average monthly exchange rates for 2002, which was 1.0612 Euros to 1 US dollar.

Sensitivity analysis

We subjected each input variable in our analysis to sensitivity analysis, which provides an important range of possible results when the input variables are not constant. Sensitivity analysis also reveals which variables are most influential in determining an intervention's cost-effectiveness.

Results

The cost per life-year saved for only counselling ranges from €385 (age 45–49 years) to €622 (age 65–69 years) for men and from €468 (age 50–54 years) to €796 (age 25–29 years) for women (Table 2). Pharmacological therapy used in addition to counselling increases smokers' chances of successful cessation, which, in turn, increases their potential number of life-years saved due to quitting. The cost-effectiveness ratios (Table 3) must be interpreted in marginal terms and reflect only the additional costs and benefits derived from supplemental pharmacological treatment. The marginal cost per life-year saved varies according to treatment, but, in each case, treatment as an adjunct to counselling yields a greater number of life-years saved relative to average gains from counselling only. The cost-effectiveness ratios for the five pharmacological treatments vary from €1768 to €6879 for men, and from €2146 to €8799 for women. The most cost-effective treatment is bupropion, followed by the patch, and then, in descending order, the spray, the inhaler and, lastly, gum. There is a consistent difference in cost-effectiveness between men and women across all treatments, which proceeds directly from the

Table 2 Cost per life-year saved of counselling only (in Euro)

Age category (years)	Men	Women
25–29	540	796
30–34	481	682
35–39	434	595
40–44	402	531
45–49	385	488
50–54	388	468
55–59	418	473
60–64	487	510
65–69	622	596

Table 3 Incremental cost per life-year saved of pharmacological smoking cessation treatments (in Euro)

Age category (years)	Gum		Patch		Spray		Inhaler		Bupropion	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
25–29	5969	8799	4356	6423	5135	7570	5178	7634	2474	3646
30–34	5316	7540	3880	5503	4573	6487	4612	6542	2202	3125
35–39	4804	6571	3506	4795	4132	5652	4168	5700	1990	2722
40–44	4448	5864	3246	4280	3826	5044	3858	5088	1842	2429
45–49	4266	5399	3113	3941	3669	4645	3700	4684	1768	2237
50–54	4298	5178	3137	3779	3698	4454	3729	4492	1781	2146
55–59	4623	5230	3374	3816	3977	4499	4011	4537	1916	2166
60–64	5388	5640	3933	4116	4635	4851	4675	4893	2232	2337
65–69	6879	6588	5021	4809	5918	5667	5968	5715	2851	2730

Table 4 Sensitivity of the cost-effectiveness ratio according to the 95% confidence interval for the efficacy studies (in Euro)

	Gum		Patch		Nasal spray		Inhaler		Bupropion	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
CE ratio 45-year-old	4860	6258	3547	4567	4181	5384	4216	5429	2014	2593
Lower bound	6212	7999	4633	5966	8700	11,201	10,614	13,666	6308	8121
Upper bound	3901	5024	2799	3605	2469	3179	2298	2959	960	1237

shape of their respective mortality curves. The number of cigarettes smoked tends to be higher among men than women. Men, therefore, stand to gain more units of benefit—life-years saved—from cessation, which yields lower cost-effectiveness ratios than for women.

Table 3 also shows the significant differences in cost-effectiveness according to the age of patients at the time of the intervention. Among men, the cost-effectiveness ratio is lowest for each treatment in the 45- to 49-year-old group. For women, the ratio is lowest in each case among the 50- to 54-year-olds. All treatments become progressively less cost-effective as patient age both decreases and increases from the middle-aged groups. Discounting diminishes the cost-effectiveness for the youngest smokers. For the oldest smokers, the greater probability that they will die before realising the benefits of quitting diminishes the cost-effectiveness.

There is also significant variation in cost-effectiveness among the five treatments, which is primarily due to differences in retail prices. For example, the treatment cost for a 3-month course of the nicotine patch is €354.54, while the retail price for the same course of treatment with the nicotine nasal spray is €743.02. Notably, physicians' salaries do not account for a significant part of the variation in cost-effectiveness between the various pharmacological therapies in each country.

Sensitivity analysis changes in treatment effectiveness produce major effects for the three recently approved treatments in both countries (i.e., spray, inhaler and bupropion) (Table 4). We based our sensitivity analysis for effectiveness of the treatments on the 95% confidence intervals (CIs) for their respective odds ratios. Very few studies have been conducted regarding the effectiveness of the spray, inhaler and bupropion, and, consequently, their 95% CIs are large. Therefore, the sensitivity analysis for effectiveness of these three treatments produced a significantly wide range of results. This analysis also

demonstrates the strong influence of the discount rate and natural quit rate on the cost-effectiveness of pharmacological treatments. When a 0% discount rate is applied, cost-effectiveness increases for all five treatments by more than 60%. The change in cost-effectiveness from varying the natural quit rate between 1% and 4% is also quite significant, resulting in an overall 35% increase in cost-effectiveness. For example, the ratios for the nicotine patch range from €1730 (4% quit rate) to €4789 (1% quit rate) for men, and from €2281 (4%) to €6009 (1%), for women. Changes in the physicians' fees and treatment costs have minor effects on the cost-effectiveness ratios for the respective treatments (data not shown).

Discussion

Our results provide a comparison of cost-effectiveness between the five first-line smoking cessation therapies. The nicotine patch and bupropion are the most cost-effective pharmacological treatments. The efficacy of the patch is based on a meta-analysis of 23 studies and has a very narrow confidence interval. The cost-effectiveness results for the patch are, therefore, quite robust. The results for bupropion are promising, although it would be premature to draw final conclusions based on a limited meta-analysis [3]. Additional data will strengthen the validity of our findings; but, until further efficacy results are available, sensitivity analysis provides an important range of possible results for the cost-effectiveness of bupropion.

Nicotine spray, inhaler, and gum are less cost-effective than the patch or bupropion. The evidence for effectiveness is strong for both the inhaler and spray, but prices for these two treatments are significantly higher than the others. This raises their respective cost-effectiveness ratios. The effectiveness of the gum is the

weakest of the five treatments, which explains its relatively high cost-effectiveness ratio. It is important to note that in the case of the spray, inhaler and gum, smokers are able to adjust the quantity of treatment they consume based on their individual needs. For this reason, costs may vary substantially between individuals.

We made conservative estimates for the dose and duration of treatment, assuming the highest and longest dosage recommended in recent clinical guidelines [3]. Prices in Switzerland for the five first-line treatments are quite stable, both between pharmacies and over time. In other countries, where competition between pharmacies and promotional offers keep prices very flexible, the situation might differ. The effects of intense competition and the introduction of generic NRT products may induce sufficient pressure on the market to drive the prices down, which could, in turn, lower the cost-effectiveness ratios.

There is continuing debate regarding the real and significant difference in lifetime medical expenditures between smokers and non-smokers. The 1992 report of the US Surgeon General reported that the average lifetime medical costs for a smoker exceeds that of a non-smoker by more than US \$6000 (€7250 in 2002) [31]. Other studies, however, have arrived at the inverse conclusion, suggesting that lifetime medical expenditures are higher for non-smokers than for smokers, due, in part, to the fact that smokers live, on average, fewer years than do non-smokers [32, 33]. To our knowledge, no reliable and definitive data exist regarding the lifetime medical expenditures of former smokers. Therefore, as in other smoking cessation cost-effectiveness research [8, 9, 10], we made the conservative assumption that there are no savings in lifetime medical expenditures associated with quitting smoking.

Our evidence for the cost-effectiveness of pharmacological cessation therapies is most pointed when presented in comparison with other common health interventions. For example, a 1991 New Zealand cost-effectiveness analysis demonstrated that the cost per quality-adjusted life-year saved associated with pharmacological hypertension treatments ranged from UK £11,058 to UK £194,989 (€28,187 to €497,036 in 2002 €) [34]. For pharmacological hypercholesterolemia primary prevention treatments, a 1995 Canadian study found the cost per life-year saved to range from CAD \$17,231 to CAD \$155,891 (€17,238 to €155,953 in 2002 €) [35], and a 2000 US study found the cost per quality-adjusted life-year saved to range from US \$54,000 to US \$1,400,000 (€ 53,161 to €1,378,238 in 2002 €) [36]. Furthermore, hypertension and hypercholesterolemia treatments (and their costs) continue throughout the remainder of the patient's life, while smoking cessation treatment (and its costs) lasts only few months. This results in a substantial difference in total lifetime expenditures per patient between the two interventions.

It may also be useful to compare our results with existing cost-effectiveness analyses of NRT, bearing in mind that methodological differences play a significant role in the variation across results. One study found the

incremental cost per life-year saved associated with nicotine gum to range from US \$4167 to US \$9473 (€6445 to €14,652 in 2002 €) [9]. Two other studies found the incremental cost per life-year saved associated with the nicotine patch to be US \$1796 to US \$4391 (€1897 to €4638 in 2002 €) and US \$4390 to US \$10,943 (€4743 to €11,823 in 2002 €), respectively [8, 10]. A 2002 study calculated the incremental cost per life-year saved associated with bupropion to be from US \$920 to US \$2150 (€867 to €2,026) [37].

It is important to acknowledge that some smokers may initiate use of over-the-counter (OTC) NRT independently, thereby missing the benefit of adjunctive cessation counselling provided by physicians [38]. This may lessen the effectiveness of the OTC treatments relative to the treatments that are available only by prescription. Prescription requirements allow physicians to ensure that smoking cessation protocols are carried out as intended.

We concluded that the use of quality-adjusted life years was not warranted in this analysis since the intervention does not have a negative effect on quality of life. The pharmacological treatments have very few side effects, and any that may occur are limited to the short course of treatment. Provided the contraindications are respected, only bupropion has minor significant side effects (e.g., insomnia). The proportion of patients who cannot tolerate side effects is captured in the respective treatment efficacy odds ratios and is thereby accounted for in our analysis. We assumed in our model that the shape of the mortality curve for smokers is simply moved forward in time because of premature death from smoking, versus having a different shape from that of a non-smoker. We determined, then, that the use of life-years-saved is adequate for estimating the benefits of quitting smoking.

One limitation of our study was that we were not able to account for variations in treatment effectiveness across individuals. There are many patient variables that may be associated, both independently and in interaction, with a treatment's potential effectiveness [38], such as age and cigarette consumption, as well as factors of socioeconomic status, culture, race and ethnicity. Until clinical trials have been conducted that account for these influences, treatment efficacy can only be rightly translated into effectiveness for simulated cohorts that match exactly the profiles of study populations used in the existing clinical experiments. Another limitation is that the lack of mortality data for smokers over age 75 years made it very difficult to evaluate the years of life saved for the oldest groups of smokers. We, therefore, developed conservative hypotheses, particularly important in light of our assumption that the mortality of ex-smokers rejoins that of non-smokers 25 years after quitting. Furthermore, we did not include the life-years saved for those smokers who relapse after several years of abstinence. Finally, we only considered savings in mortality and did not include any averted morbidity that is attributable to treatment. Disability-adjusted life-years account for averted death and disability, and would very likely yield better cost-effectiveness ratios in this type of analysis.

We conclude that the cost-effectiveness of first-line treatments for nicotine dependence varied widely with age and sex and was sensitive to the assumption on the natural quit rate. Bupropion and the nicotine patch were the two most cost-effective treatments. These findings may be useful to policymakers in the public and private sectors (e.g., government health systems, health insurance benefits planners) in their efforts to reduce smoking prevalence.

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