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Review article

Effect of Funding Medications for Nicotine Dependence on Tobacco Control: A Narrative Review

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ABSTRACT

Pharmacological treatments for smoking associated with psychological counseling triple the chances of quitting. However, the accessibility of these drugs is limited by their financial cost. With this review we aim to demonstrate the effect of partial or full funding in terms of efficacy, effectiveness, cost-effectiveness and quality of life. We conducted a literature search for articles related to the issues mentioned above: analysis of the efficacy, effectiveness and cost-effectiveness of pharmacological treatments for nicotine dependence and the effect of their funding. It is shown that the funding of pharmacological treatment can increase the efficacy and effectiveness of smoking cessation interventions. Such funding increases motivation to make a quit attempt. In addition, these strategies can increase self-efficacy, generate social influence and change attitudes toward quitting. Although the funding of pharmacological treatment benefits all smokers, there are certain populations of smokers who are more sensitive to funding strategies such as social groups with lower incomes and lower educational attainment. These funding strategies for smoking cessation interventions have been shown to improve the health and quality of life of the population, as well as the economy, while reducing tobacco use.

Efecto de la financiación de los fármacos para la dependencia a la nicotina en el control del tabaquismo: una revisión narrativa

Palabras clave:
Tabaquismo
Tratamiento farmacológico
Financiación
Eficacia

RESUMEN

Los tratamientos farmacológicos para el tabaquismo asociados al asesoramiento psicológico triplican las posibilidades de abandono del tabaco. Sin embargo, la accesibilidad a estos fármacos está limitada por su coste económico. Con esta revisión pretendemos demostrar el efecto de la financiación parcial o total en términos de eficacia, efectividad, coste/efectividad y calidad de vida. Así se realizó una búsqueda

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bibliográfica de artículos relacionados con las cuestiones mencionadas anteriormente: análisis de la eficacia, efectividad y coste/efectividad de los tratamientos farmacológicos de la dependencia nicotínica y el efecto de su financiación. Se demuestra que la financiación del tratamiento farmacológico puede aumentar la eficacia y la efectividad de las intervenciones para dejar de fumar. Dicha financiación aumenta la motivación para realizar un intento de abandono. Además, estas estrategias pueden incrementar la autoeficacia, generar influencia social y modificar las actitudes hacia el abandono. Aunque la financiación del tratamiento farmacológico beneficia a todos los fumadores, hay ciertas poblaciones de fumadores que son más sensibles a las estrategias de financiación como grupos sociales con menos ingresos y menor nivel educativo. Se ha demostrado que estas estrategias de financiación de las intervenciones para dejar de fumar mejoran la salud y la calidad de vida de la población, así como la economía, a la vez que reducen el consumo de tabaco.

Introduction

Tobacco and nicotine use is a dependence and a chronic disease, requiring systematic diagnosis and treatment. Treatment of nicotine dependence is evidence-based, effective and safe: it combines behavior counseling and medication. In addition, tobacco cessation is one of the most cost-effective medical interventions standing among the 3 highest-ranking preventive services.[1]

While preventing the uptake of smoking by youth is paramount to curb the tobacco epidemic and reduce mortality and disease burden, tobacco cessation has the greatest impact in the short term.[2] The best way to support smokers to quit is to integrate Smoking Cessation Services in National Health Systems that must provide care to smokers quit. Combining tobacco control policies and other population approaches with broad healthcare cessation interventions is synergist and achieves the best public health impact. Notably, wide access to affordable cessation treatments as part of a comprehensive tobacco control national strategy accomplishes a greater decrease in tobacco use.[3]

These Services are key tools for controlling smoking due to two reasons: (a) increasing abstinence rates and (b) can improved population impact in terms of Public Health.

Due to the addictive nature of tobacco/nicotine use smokers suffer from nicotine withdrawal syndrome while attempting to quit and often postpone a quit attempt or relapses. Psychological counseling, pharmacotherapy, and clinical follow up are essential to increase motivation to quit, treat nicotine withdrawal and strengthen coping skills to deal with smoking triggers.[1–3] Multiple systematic reviews and meta-analyses have demonstrated that pharmacological treatment enhances the effectiveness of behavior counseling and can triple the success of a smoking cessation intervention.[4–10] Smoking cessation intervention is an effective strategy to reduce mortality and morbidity associated with tobacco consumption and, consequently, contribute to sustainable healthcare systems and economic development.[11] Recent studies show that smoking cessation is the clinical intervention that prevents most deaths (1 for every 40 interventions while antihypertensive treatment prevents 1 for 700 treatments or cancer screening programs 1 for more than 1000 number of visits). In addition, it reduces the risk and recurrence of ischemic heart disease, recurrence of lung cancer or improvement of chronic diseases such as COPD.[12] Despite this, according to a recent Eurobarometer survey, only a small proportion of smokers (11%) see a healthcare professional and 5% of them use pharmacological treatment when trying to quit smoking. On the other hand, almost 75% of smokers try to quit smoking without help while using methods without scientific evidence.[13] Also, we have to consider that the alerts from the International Drug Regulatory Agencies about certain drugs used in smoking cessation have led to a reduction in their use and, as a consequence, a decrease in the number of smokers who quit tobacco.[14]

In this context, strategies and actions are necessary to offer smokers the most effective and safe treatment and, consequently, increase the chances of being able to quit tobacco, while avoiding the use of other methods that keep smokers in nicotine consumption. Among them: promoting a wide network of qualified Smoking Cessation Services and increasing the accessibility of all first-line drugs against nicotine addiction by financing these medications have been identified as very relevant.[1–3] This narrative review aims to evaluate the effect of financing nicotine dependence drugs on tobacco control through four points of view:

a) Effect of financing on the efficacy and effectiveness of smoking cessation interventions.
b) Effect of financing on the cost-effectiveness of smoking cessation interventions.
c) Effect of financing on reducing morbidity and mortality and improvement of quality of life.
d) Public or private financing of smoking cessation medications: tangible health outcomes.

Methodology

The preparation of this document was discussed in online meetings and its methodology was as follows: The main authors carried out a bibliographic search on articles related to the questions mentioned above: analysis of the efficacy, effectiveness and cost-effectiveness of pharmacological treatments of nicotine dependence and the effect of their financing.

The search strategy was carried out in two multidisciplinary databases: Science Citation Index-Expanded of the Web of Science, property of Clarivate Analytics, and the Scopus database of Elsevier (since it fully integrates all Medline/Pubmed). The search equation was performed in the *Topic* field (which includes title, summary and keywords). It was limited to documentary typologies (*article* and *review*) and there was no time limitation, obtaining included articles until 2023. The descriptor terms were: *varenicline, cytisine, bupropion, nicotine replacement therapy financing, efficacy, free access, smoking cessation, stop smoking*. The articles extracted from both databases were reviewed by two independent authors, excluding those that were not pertinent, appropriate or relevant, including only those with robust scientific evidence. Meta-analyses, systematic reviews, clinical trials and observational studies were selected. Randomized clinical trials that do not provide new information were excluded. Articles that generated doubts or discrepancies, articles with a small sample size or absence of adequate conditions to verify smoking abstinence or absence of peer review were excluded (Fig. 1).

The authors complied with ethical principles in the preparation of this manuscript. As it is a narrative review, this manuscript does not require informed consent or approval by the Ethics Committees.

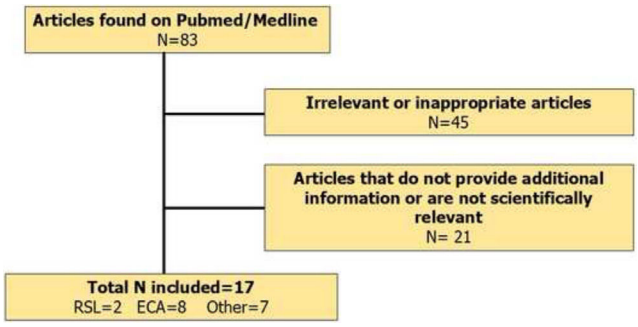

Fig. 1. Flowchart: studies inclusion.

Results

Effect of financing on the efficacy and effectiveness of smoking cessation interventions

Several systematic literature reviews and meta-analyses indicate that there are four drugs that are effective in helping to quit smoking with level 1 scientific evidence. Namely: Varenicline, Nicotine Replacement Therapy (NRT), Bupropion and Cytisine. Strategies such as financing allow a greater number of smokers to have access to these drugs and produce benefits in smoking cessation.

Multiple systematic reviews and meta-analyses have demonstrated that financing pharmacological treatment can increase the efficacy and effectiveness of smoking cessation interventions (Table 1).

A 2017 Cochrane Systematic Review found that financing pharmacological treatment increases verified continuous abstinence at 6 months RR = 1.77 (95% CI 1.37–2.28) I^2 = 33% (n = 9333 participants) without finding differences between total and partial financing but there are differences between partial financing and not financing.[15] Furthermore, studies show that these strategies increase the motivation to quit and thus promote quit attempts, in addition to encouraging its use. That is, free or low-cost medication is a trigger to quit smoking.[16] The mechanism by which economic incentives increase the probability of a smoker quitting tobacco is attributed not only to the increase in the use of medication, but also that these incentives increase self-efficacy, generate social influence and modify attitudes toward cessation.[17]

Although financing pharmacological treatment benefits all smokers, there are certain populations of smokers that are more sensitive to financing strategies. Having low income and a lower level of education is associated with a greater number of quit attempts and more use of pharmacological treatment. Among low-income smokers, the odds of abstinence were 1.59 times higher among those randomized to the free NRT sample versus control (95% CI: 0.97, 2.59). This relationship was not found in smokers with higher incomes: (OR = 0.87, 95% CI: 0.39–1.94). Among smokers with a lower educational level, those who received free NRT were 2.23 times (95% CI: 1.30, 3.82) more likely to obtain point prevalence abstinence at six months.[18]

The efficacy and effectiveness of these strategies may vary depending on the drug financed. At the present time, most of the studies have been carried out with NRT. There is less evidence with other drugs such as varenicline.

Efficacy and effectiveness of financing NRT

NRT promotes tobacco cessation by reducing nicotine withdrawal symptoms. Data on NRT show that the efficacy of all types of this medication at standard doses is significantly higher than placebo at 6 and 12 months. OR: 2.01(1.68–2.41) Level of Evidence 1a. It should be noted that nicotine patches are the ones that provide the greatest adherence. Level of evidence 2a. According to a meta-analysis, NRT was associated with higher cessation rates when compared with placebo or without support (17% vs. 10%; RR, 1.55; 95% CI, 1.49–1.61). A meta-analysis with 63 trials and 41,509 participants confirmed that the combination of nicotine patches with fast-acting NRT was associated with better quit rates than when these products were used individually (RR, 1.25; 95% CI, 1.15–1.36).[4,5]

Multiple Randomized Clinical Trials (RCT-s) shown that providing free NRT samples in the clinic improves results in terms of abstinence in the short-medium term this reassures the patients, improves patient confidence, and further motivates them to quit smoking.[16–19] Several studies that analyzing the effect of financing NRT in both slow and fast forms regarding the efficacy and effectiveness, highlighting the following: a)low-income population smokers provided with free nicotine patches achieved higher number of quit attempts versus those who were not provided with it (51% vs. 36%) and b) mean CO levels were lower in the intervention group, point prevalence abstinence higher (8.5% for free nicotine patches and 4.9% in those who were not provided (p = 0.066).[19]

A clinical trial in an older population (n = 1245 smokers followed in 22 South Carolina Primary Care clinics) demonstrated that providing free NRT either patches or rapid forms increases NRT adherence (65% vs. 25% OR; 5.8 CI 3.7–7), promotes a greater number of quit attempts during the first month (24% vs. 18% OR: 1.5 95% CI 1–2.3). The point prevalence abstinence rate at 6 months was significantly higher in the free NRT group (12% vs. 8% OR: 1.5 95% CI 1–2.4).[20]

A study carried out on smoking women who were offered free nicotine patches plus telephone intervention, observed continuous abstinence rate at 3 months of 42% combining both interventions and 28% if only treated with patches.[21]

In a Hong Kong cohort of 1053 participants, smokers who were offered behavioral counseling plus free NRT for one week and referral to an intensive smoking cessation program demonstrated greater abstinence at six months in the intervention group 6.8% compared to 3.6% in the non-intervention OR: 1.96 (95% CI 1.11–3.46, p = 0.02).[22]

Furthermore, providing free NRT favors quit attempts and smoking cessation in both motivated and unmotivated smokers. Thus, a greater frequency of serious quit attempts is observed (77% and 40% higher, in motivated and unmotivated smokers respectively, compared to not financing it). Only 18% try to quit tobacco with unfunded NRT. Likewise, financing NRT promotes a reduction in tobacco consumption of at least 48% in motivated smokers and 31% in unmotivated smokers.[23]

Efficacy and effectiveness of financing nicotinic receptors partial agonist

Recently, numerous publications have shown varenicline as an effective treatment for stopping smoking. Clinical trials such as EAGLES,[10] which provided direct comparisons between different drugs, and systematic reviews with network meta-analysis that provide indirect comparisons, have shown the superiority of varenicline over other drugs. One of them, includes 363 trials for effectiveness analysis (follow-up of 24 weeks or more), concludes that standard dose of varenicline in monotherapy is the most effective aid in helping smokers to quit at 6 and 12 months. OR = 2.83; 95% CI (2.34–3.39), Level of Evidence 1a.[6–10] Few studies analyze the effectiveness of financing varenicline in a smoking cessation programme. A randomized study included a small number of smokers (n = 99) both motivated and not motivated; the intervention group was provided with varenicline free of charge for a period of 2–4 weeks. Adherence to varenicline was higher in the free varenicline group (66% vs. 54%) at 2 weeks and (46% vs.

Table 1
Studies analyzing efficacy of medications for smoking cessation.

Reference	Participants	Objectives	Design	Results
Cropsey KL et al. Nicotine Tob Res. 2021	*N* = 83	Compare gold standard smoking cessation treatment to four weekly sessions of sampling each short form of NRT	Randomized controlled trial	The number of quit attempts is 51% vs 36% and point abstinence is 8.5% vs 4.9% between providing and not providing free nicotine patches.
Carpenter MJ et al. Addiction. 2020	*N* = 1245, Twenty-two primary care clinics in South Carolina, USA	Compare the effects of NRT sampling plus standard care (SC), relative to SC alone, provided by primary care providers during routine clinic visits.	Cluster-randomized clinical trial	Seven-day point prevalence abstinence rates were significantly higher in the NRT sampling group throughout follow-up, including at 6 months (OR) = 1.5, 95% CI = 1.0–2.4]. NRT sampling increased prevalence of any use of NRT OR = 5.8, 95% CI = 4.3–7.7), with higher prevalence of use at 6 months OR = 2.0, 95% CI = 1.5–2.7). NRT sampling increased the rate of quit attempts in the initial month OR = 1.5, 95% CI = 1.0–2.3
Solomon LJ et al. Prev Med. 2000	*N* = 214 Medicaid-eligible women smokers of childbearing age	Impact of free nicotine patches plus proactive telephone peer support to help low-income women stop smoking.	Clinical trial	At the 3-month follow-up, significantly more women in the patch plus proactive telephone support condition were abstinent (42%) compared to the patch only condition (28%) ($p = 0.03$). Similarly, more women in the experimental condition were abstinent at both the 10-day and 3-month assessments (32 vs 19%, $p = 0.02$).
Luk TT et al. JAMA Intern Med. 2021	*N* = 1053 participants trial in prenatal clinics in 7 public hospitals in Hong Kong	To evaluate the effectiveness of a proactive, combined intervention for smoking cessation in expectant fathers (NRT sampling + Brief Advice, and Active Referral)	Pragmatic randomized clinical trial	Validated tobacco abstinence at 6 months after intervention (NRT sampling + Brief Advice, Nicotine and Active Referral) was significantly higher in the intervention group than in the control group [OR], 1.96; 95% CI, 1.11–3.46; $p = .02$). Self-reported 24-week continuous abstinence at 6 months (OR, 1.87; 95% CI, 1.08–3.23; $p = .03$) and 7-day point prevalence abstinence at 3 months (OR, 1.48; 95% CI, 1.05–2.09; $p = .03$) and 6 months (OR, 1.74; 95% CI, 1.29–2.34; $p < .001$) were also significantly higher in the intervention group.
Jardin BF et al. Nicotine Tob Res. 2014	*N* = 157, motivated smokers wanting to quit in the next 30 days	Efficacy of access to free medication to quit smoking (NRT)	Clinical trial	Frequency of serious quit attempts (77% and 40% in motivated and unmotivated smokers respectively compared to not financing it). Only 18% try to quit tobacco with an unfunded NRT.
Dahne J et al. Prev Med. 2020	*N* = 1245 adult smokers enrolled in the Tobacco Intervention in Primary Care Treatment Opportunities for Providers (TIP TOP) study	Individual-level demographic moderators of the impact of NRT sampling on cessation-related behaviors	Secondary data analysis of the Clinical Trial: Tobacco Intervention in Primary Care Treatment Opportunities for Providers (TIP TOP)	Among low-income smokers, the probability of floating abstinence was 1.59 times higher among those randomized to the NRT sample vs. control (95% CI: 0.97, 2.59). This relationship was not found in higher-income smokers. (OR = 0.87, 95% CI: 0.39–1.94).

Table 1
(*Continued*)

Reference	Objectives	Design	Results
Carpenter MJ et al. Nicotine Tob Res. 2021	To examine the feasibility, uptake, and preliminary outcomes of varenicline sampling.	Clinical trials were recruited and randomized to varenicline sampling versus not, with 12 weeks follow-up. The intervention consisted of mailing one-time samples of varenicline (lasting 2–4 wks),	Varenicline sampling increased motivation ($p = 0.006$) and confidence to quit ($p = 0.02$), and decreased cigarette smoking ($p = 0.02$).
van den Brand FA et al. Cochrane Database Syst Rev. 2017.	Assess the impact of reducing the costs for tobacco smokers or healthcare providers for using or providing smoking cessation treatment through healthcare financing interventions on abstinence from smoking	Systematic review randomized controlled trials, controlled trials and interrupted time series studies involving financial benefit interventions to smokers or their healthcare providers, or both.	Full financial interventions directed at smokers had a favorable effect on abstinence at six months or longer when compared to no intervention (RR 1.77, 95% CI 1.37–2.28). There was no evidence that full coverage interventions increased smoking abstinence compared to partial coverage interventions (RR 1.02, 95% CI 0.71–1.48, $I^2 = 64\%$, 5914 participants), but partial coverage interventions were more effective in increasing abstinence than no intervention (RR 1.27 95% CI 1.02–1.59.
van den Brand FA et al. Tob Control. 2019	To investigate whether mentioning free or lower cost smoking cessation medication as a trigger for thinking about quitting is related to higher medication use, more quit attempts and quit success	Data were derived from survey. Logistic regression analyses were used to assess associations between mentioning in 2013 that free/lower cost smoking cessation medication	37.0% of smokers in the UK and 24.9% of smokers in the Netherlands mentioned free/lower cost medication as a trigger for thinking about quitting. Smokers who mentioned this trigger were more likely to have used cessation medication during a quit attempt both in the UK (OR = 4.19, $p < 0.001$) and in the Netherlands (OR = 2.14, $p = 0.033$). The association between mentioning free/lower cost medication as a trigger for thinking about quitting and actual quit attempts was significant in the UK (OR = 1.45, $p = 0.030$), but not in the Netherlands (OR = 1.10, $p = 0.587$).
van den Brand FA, et al. Lancet Public Health. 2018	To investigate whether financial incentives combined with a smoking cessation group training program (compared with a training program with no incentives) organized at the workplace would increase 12-month abstinence rates in tobacco-smoking employees with different education and income levels.	Cluster-randomized controlled trial	Of the participants in the intervention group, 41.1% had quit smoking compared with 26.4% in the control group. OR: 1.93, 95% CI 1.31–2.85, $p = 0.0009$

38%) at 4 weeks. Relative to the control group, free administration of varenicline increased motivation ($p = 0.006$) and confidence to quit smoking ($p = 0.02$), and decreased cigarette smoking ($p = 0.02$). Smokers who received free varenicline were significantly more likely to achieve a 50% reduction in consumption of cigarettes per day at both baseline and end of follow-up OR = 4.50; 95% CI: (1.56–13.01). Although outcomes were not statistically significant different, there was a 1.5–3-fold increase in quit attempts and abstinence with free varenicline during follow-up. Therefore, financing varenicline allows for a greater number of smokers to be involved in quitting.[24]

Effect of financing in terms of cost-effectiveness in smoking cessation interventions

Table 2 shows the characteristics of the main studies that focus on this topic.

Cost-effectiveness analysis of pharmacological treatment for quitting smoking

Smoking cessation medications are cost-effective. In the United Kingdom, it has been estimated that the additional cost per year of life gained from medical advice or intensive advice to quit smoking compared to doing nothing is less than £1000 (€1439); ranging between £1000 and 2400 pounds (1439–2758 €) for NRT; between 640 and 1500 pounds (921–2158 €) for bupropion; and between 900 and 2000 pounds (1295–2878 €) for combined treatment.[25]

A review[26] including cost-effectiveness analyzes carried out in different countries and based mostly on the Markov and BENESCO model, concluded the following: 12-week therapy with varenicline was more effective and less expensive than bupropion, NRT and behavior modification therapy, in terms of incremental cost per year of life gained or QALY, with a 20-year or lifelong projection. Additionally, 24 weeks of varenicline treatment was superior to bupropion, NRT, or unassisted discontinuation in terms of incremental cost per QALY gained in the US analysis.[27]

A decision analytic model from the United States predicted that, after 2 years, varenicline was more cost-effective than bupropion, NRT, and placebo; and demonstrated that varenicline reduces more costs than other smoking cessation interventions.[28] A recent study analyzed the cost-effectiveness of smoking cessation aids in the United Kingdom adapting a Markov cohort model, results depended on the type of analysis performed. When limited to interventions licensed in the UK, standard dose varenicline and NRT were the most cost-effective.[29] There is less published evidence on the cost effectiveness of treatment with cytisine. A systematic review and network meta-analysis[30] comparing clinical effectiveness and cost-effectiveness of varenicline versus cytisine

Table 2
Summary of studies on the cost-effectiveness of the financing of pharmacological treatment for smoking cessation.

Reference	Objectives	Design	Results
Fellows JL et al. Tob Control 2007	Cost-effectiveness of offering callers single session versus multisession counseling, with or without free nicotine patches.	Randomized trial included 4614 Oregon tobacco quitline callers and compared brief (one 15-min call), moderate (one 30-min call and a follow-up call) and intensive (five proactive calls) intervention protocols, with or without offers of free nicotine patches (nicotine replacement therapy, NRT). Blinded staff assessed tobacco use by phone at 12 months.	To brief no NRT, the added costs for each additional quit was $2467 for brief NRT, $1912 for moderate no NRT, $2109 for moderate NRT, $2641 for intensive no NRT, and $2112 for intensive NRT.
Cadier B et al. PLoS One. 2016	To estimate the incremental cost-effectiveness ratios of providing free access to cessation treatment taking into account the cost offsets associated with the reduction of the three main diseases related to smoking	A Markov state-transition model that compared free access to cessation treatment to the existing coverage of €50 provided by the French statutory health insurance, taking into account the cost offsets among current French smokers aged 15–75 years.	The incremental cost-effectiveness ratios value for free access to cessation treatment was €3868 per life year gain in the base case.
Altman D et al. Can J Respir Crit Care Sleep Med. 2019	Cost-effectiveness of a health policy of funding smoking cessation pharmacotherapy for all Canadian smokers at no cost to the patient.	A decision model using data from a Cochrane Review meta-analysis incorporating utilization of smoking cessation products, quit rates, six-month continuous abstinence rates, relapse rate, and direct costs of smoking cessation pharmacotherapy and physician visits associated with full funding of smoking cessation pharmacotherapy.	The average incremental cost per life-year gained of funding smoking cessation pharmacotherapy compared to no funding in the overall population was CaD$1030 (range CaD$250–10,040) per life-year gained.
Chen B, et al. J Gen Intern Med. 2022	Cost effectiveness of a primary care nicotine replacement therapy (NRT) sampling intervention.	A Markov cohort simulation model was constructed to conduct cost-effectiveness analyses. Clinical trial results were used to initialize the Markov model.	The intervention cost $75, yielding a discounted lifetime savings of $1065 in healthcare expenditures, and increased both discounted quality-adjusted life years and discounted life years by 0.01.
Jiménez Ruiz et al. Int J Chron Obstruct Pulmon Dis. 2015	Assess the budgetary impact of funding smoking-cessation drugs in COPD patients in Spain	A hybrid model (cohort and Markov) was developed for a 5-year time horizon	The model estimated that 17,756 COPD patients would stop smoking if public funding was available, compared with 1303 without reimbursement. In the reimbursement scenario, the savings accounted for a total of €48.0 million, compensating for expenditures on drugs and medical visits (€40.4 million). Accumulated total additional savings in 5 years (€4.3 million) compared with the scenario without reimbursement was shown.
Cedillo S et al. Eur Addict Res. 2017	To assess the budgetary impact of reimbursing varenicline in patients with chronic obstructive pulmonary disease, type-2 diabetes mellitus or cardiovascular diseases.	A hybrid model was developed using epidemiological data and Markov chains to estimate smoking cessation rates with varenicline during a 5-year horizon.	A total of 68,684 patients stopped smoking in the reimbursed scenario compared with 15,208 without reimbursement. In the reimbursed scenario, total savings accounted for €36.3 million, showing 14.6 million accumulated additional savings compared with the scenario without reimbursement
Trapero-Bertrán M et al. Addiction. 2018	To assess the cost-effectiveness of alternative smoking cessation scenarios from the perspective of the Spanish National Health Service (NHS).	A Markov-based state transition economic model using the European study on Quantifying Utility of Investment in Protection from Tobacco model (EQUIPTMOD)	For every €1 spent on providing NRT sampling, the NHS could recoup €1.17, €2.40 for vareniclina sampling and €2.18 bupropion sampling.

and including 26 clinical trials (none with a direct comparison between drugs) estimates that cytisine is more clinically effective and cost-effective than varenicline. Authors admit that the degree of uncertainty makes direct comparative studies between both drugs necessary. An analysis aiming at estimating the cost-effectiveness of incorporating new treatment strategies in England and the Netherlands concludes that incorporating cytisine treatment could have a net benefit and be cost-effective.[31]

Cost-effectiveness analysis of financing pharmacological treatment for smoking cessation

Financial incentives in work environments, such as staying abstinent more than 12 months, are cost-effective. A study in Holland calculated the increase in cost-effectiveness ratio of giving incentives (the intervention group earned gift vouchers of €350 for 12 months' continuous abstinence. The comparator group received no incentives) shown that in the intervention group, 41.1% had quit smoking compared with 26.4% in the control group. Moreover, the incremental cost effectiveness ratio per quitter was €11,546 from a societal perspective and €5686 from an employer's perspective.[32] Reducing or eliminating the cost of smoking cessation treatment for a smoker can also be highly profitable, assuming an increase in medium-term economic savings for a health system that could be used for other Public Health actions and policies.

A Canadian study evaluated the cost-effectiveness of universal financing of all first-line pharmacotherapy used in smoking cessation (NRT, varenicline and bupropion). The average incremental cost per life year gained of funding smoking cessation pharmacotherapy compared to no funding in the general population was 1030 Canadian dollars (range 250–10,040 Canadian dollars) per life year gained.[33]

Using a Markov model, the cost-effectiveness of free access to NRT in a US Primary Care setting was analyzed and a cost per treatment of $75 was observed. This generated a discounted lifetime savings of $1065 in care expenses and increased both discounted quality-adjusted life years and discounted life years by 0.01.[34]

In France, cost-effectiveness was analyzed using a Markov model assuming free access to smoking cessation treatment with the existing €50 coverage provided by French compulsory health insurance. Potential cost savings for lung cancer, COPD, and cardiovascular diseases ranged from €15 to €215 million over a five-year horizon for an initial dropout treatment cost of €125 to €421 million.[35]

Financing varenicline in special populations (COPD, cardiovascular diseases and Diabetes Mellitus) shows that the number of patients who stop smoking in a funded scenario is 68,684 patients compared to 15,208 without financing. Total savings amounted to 36.3 million euros, showing an additional accumulated savings of 14.6 million compared to the scenario without financing.[36]

A Spanish study estimated that 17,756 COPD patients would quit smoking if public funding were available, compared to 1303 without funding. In the financing scenario, savings amounted to a total of 48.0 million euros, offsetting expenses on medications and medical visits (40.4 million euros). There is a total additional savings accumulated in 5 years (4.3 million euros) compared to the unfinanced scenario. Sensitivity analyzes supported the robustness of the results.[37]

A European study on the quantification of the usefulness of investment in a protection model against smoking (EQUIPTMOD) shows that for every euro spent on financing NRT, 1.17 euros are recovered in the medium term. In the case of varenicline, 2.40 euros are recovered and with bupropion 2.18 euros.[38]

Effect of financing smoking cessation interventions on morbidity and mortality and quality of life of smoker population

Financing strategies for smoking cessation interventions have been shown to promote quit attempts, increasing the adherence to pharmacological treatments and increasing the number of those who quit. Therefore, by expanding the number of smokers who have access to the best treatment to quit can further foster smoking cessation. Consequently, a smoking cessation financing-policy will improve population health and quality of life, as well as the economy, while reducing tobacco health burden and the direct and indirect costs of smoking.[15,39–41]

Mortality attributable to tobacco consumption

Multiple studies observe a significant reduction in the number of deaths associated with smoking as a consequence of smoking cessation. This risk of death is influenced by the age of cessation, with a decrease in this ranging from 90 to 40%.[39] Thus, a recent study observes reductions of 90% in excess mortality compared to continuing smoking at ages under 45 year and more than 60% compared to continuing smoking at ages between 45 and 65 years. Even at ages over 60 years, premature mortality could be reduced to 40%.[40] On the other hand, a study relates to tobacco associated mortality to economic inequalities, with 50% of deaths occurring in the group with fewer socioeconomic resources. This may be partly explained by the reduced opportunities of those socially deprived to access the most effective cessation treatments while maintaining tobacco consumption.[41] Therefore, providing the most optimal treatment to smokers is correlated with a higher percentage of them quitting tobacco and a reduction in the number of deaths.[41]

Several studies show that providing free medications for smoking cessation significantly reduces morbi-mortality rate of smoking related disorders[36–38,40–43] (Table 2).

A Spanish study showed that expanding access to smoking cessation interventions to up to 35% of smokers through different methods such as financing of drugs by the National Health System (SNS) achieves a reduction in deaths of 2613 after one year; more than 9000 at 5 year and more than 17,000 at 10 years.[41,42] This strategy has been shown to increase the number of smokers who quit from 15,208 to more than 68,000 over a 5-year period, reducing the risk of mortality associated with tobacco more than four times compared to an unfunded scenario.[36] In other study involving COPD patients, it is estimated that in a funded scenario the number of smokers who will quit tobacco per year is more than 10 times higher than in a non-financed scenario, resulting in a significant reduction in the number of deaths associated with tobacco in subsequent years.[37]

Smoking related disorders

After quitting smoking, patients with cardiovascular disease (CVD) reduced their risk of developing a new acute CVD episode up to three times. Likewise, in these patients, as a consequence of smoking cessation, mortality is reduced to 46%.[42]

In COPD patients, quitting is associated with an improvement in lung function and an increase in survival. A Spanish study shows that smoking cessation reduces the number of annual exacerbations and their severity. In addition, it demonstrates a lower average number of days of hospitalization, a lower frequency of medical visits, and a decrease in the use of pharmacological treatment, and home respiratory therapies in those COPD who stop smoking.[38]

There is robust scientific evidence on the efficacy and effectiveness of smoking cessation drugs on these special populations (COPD, cardiovascular and psychiatric patients) that can achieve continuous abstinence rates ranging between 35 and 40%. Financing smoking cessation drugs among these patients encourage them to use medication, and multiply their chances of succeeding in an quit attempt.

Smoking at the time of surgery is associated with postoperative complications. Quitting smoking before surgery is linked to fewer complications during the hospital stay. A Spanish study analyzed whether a smoking cessation intervention before surgery is economically worthwhile when funded by the National Health System. Smoking cessation increased by 21.7% with funding; the rate was 32.5% when funded *versus*10.7% without funding, producing 9611 extra quitters. The cost per averted smoker was €1753 with a benefit of €503, achieving a net economic benefit of €4.8 million per year. The return on investment was 28.7% annually, equivalent to €1.29 per €1 of investment.[43]

Quality of life

Smokers have a worse quality of life compared to former and non-smokers. Quitting tobacco for a period of more than 8 years achieves better scores in satisfaction questionnaires.[44] Study carried out in Spain on more than 19,000 medical records showed that ex-smokers had a better state of health than smokers.[45]

Public or private financing of smoking cessation medications: tangible health outcomes

Despite of the available scientific evidence, the majority of health services, both public and private, do not consider financing tobacco cessation because they measure its impact on health through predictive models and not tangible outcomes. They argue that these benefits mainly refer to monetary measures, such as costs avoided in various pathologies by quitting smoking, cost per years of life gained or quality-adjusted life years gained (QALY) and calculation of return on investment.

It is important to consider that the benefits are usually undervalued since, in general, they only refer to some tobacco

related disorders (cardio-vascular and pulmonary diseases) without taking into account other diseases also related with tobacco consumption.[33–38,42]

There are relevant examples that demonstrate that the implementation of a Global Tobacco Control Programme at regional or national levels work very well and all of them contains measures of public or private financing of smoking cessation medications.[46–48] The pioneer Californian Tobacco Control Program, US, was based in four main goals: (a) to limit the influences that promote tobacco, (b) to reduce exposure to secondhand smoke and tobacco products, (c) to reduce the availability of tobacco products and (d) to promote tobacco cessation, including the provision of free smoking cessation assistance. This program achieved a reduction in tobacco consumption from 22.7% to 11.9% between 1988 and 2010, which translated into a reduction in deaths due to cardiac disease[46] and in the prevalence of lung cancer, the latter being reduced four times faster than in the rest of the states that had not started the Tobacco Control Program at that time.[47]

We also highlight the results of a tobacco prevention and cessation program established in Massachusetts in 2006 containing free telephone advice and pharmacological treatment to quit smoking with a minimal co-payment for Medicaid beneficiaries: (a) it was used by a 37% of potential beneficiaries and achieved a 10% reduction in the smoking rate[48]; (b) using estimating equations, changes in hospitalization trends were examined among 21,656 Medicaid beneficiaries before and after the program, adjusting for demographics, comorbidities, seasonality, and other factors; (c) the follow-up of the study participants reached an average of four years, (d) and it was found that participation in the program was associated with statistically significant reductions in hospital admissions for: acute myocardial infarction (46%, $p < 0.05$), coronary atherosclerosis (49%) and other heart diseases (32%, $p < 0.05$), and up to 32% due to non-specific chest pain, $p < 0.01$.[48]

A current systematic review demonstrates that the financial incentive increases the effectiveness of smoking cessation interventions with a high level of evidence (OR: 1.46, 95% CI 1.15–1.85; 19 studies $n = 8877$ patients).[49] Moreover, in a recent published guide it was shown that financing smoking cessation drugs is profitable and is associated with greater abstinence from a non-individual population perspective (Level of Evidence 2a).[50]

Conclusions

The main conclusions of this paper are as follows:

- Several systematic literature reviews and meta-analyses indicate that there are four drugs effective in helping smokers to quit (Level 1 scientific evidence) Namely: Varenicline, Nicotine Replacement Therapy (NRT), Bupropion and Cytisine.
- Multiple systematic reviews and meta-analyses demonstrate that financing pharmacological treatment can increase the efficacy and effectiveness of smoking cessation interventions.
- Financing smoking cessation medications can increase the motivation to make a quit attempt and encourages its use. Also, these strategies can increase self-efficacy, generate social influence, and modify attitudes toward cessation.
- Although financing pharmacological treatment benefits all smokers, there are certain populations of smokers that are more sensitive to financing strategies. For instance, having low income and a lower level of education is associated with a greater number of quit attempts and more use of pharmacological treatment if these medications are financed.
- Financing strategies for smoking cessation interventions has been shown to improve population health and quality of life, as well as the economy, while reducing tobacco health burden and the direct and indirect cost of smoking.
- Global Tobacco Control Programmes at regional or national levels work very well. It is crucial that they contain measures of public or private financing of smoking cessation medications.

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