RECOMMENDATIONS

Pharmacological Tobacco Cessation Treatments: Proposals for Financing

Carlos A Jiménez-Ruiz,[a] Juan Antonio Riesco Miranda,[b] Ángela Ramos Pinedo,[c] Miguel Barrueco Ferrero,[d] Segismundo Solano Reina,[e] José Ignacio de Granda Orive,[f] Jesús Grávalos Guzmán,[g] Lourdes Ramos Casado,[h] Alfonso Pérez Trullén,[i] and Karl O Fagerström[j]

[a]Unidad Especializada en Tabaquismo, Madrid, Spain
[b]Hospital Clinic-IDIBAPS, Ciber-Res CB06/06/0028, Barcelona, Spain
[c]Servicio de Neumología, Hospital Fundación Alcorcón, Madrid, Spain
[d]Servicio de Neumología, Hospital Clínico Universitario, Salamanca, Spain
[e]Coordinador de Neumología, Hospital Virgen de la Torre, Madrid, Spain
[f]Servicio de Neumología, Hospital Central de la Defensa, Madrid, Spain
[g]Servicio de Neumología, Hospital Juan Ramón Jiménez, Huelva, Spain
[h]Servicio de Neumología, Hospital Río Carrión, Palencia, Spain
[i]Servicio de Neumología, Hospital Lozano Blesa, Zaragoza, Spain
[j]Fagerström Consulting, Helsingborg, Sweden

Introduction

Tobacco dependence is a recurring and addictive chronic disease and the leading preventable cause of death in the world. All health professionals are obliged to correctly diagnose and treat smokers to enable them to break the habit.[1,2] In recent years, a wide range of recommendations and guidelines for treating smokers have been published for health professionals.[1,2-5] In 2002 in Spain, a group of scientific societies published the first consensus document on the diagnosis and treatment of tobacco dependence.[6] In 2003, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) updated the current guidelines on treatment of tobacco dependence.[7,8]

All these guidelines agree that treatment of this condition must be on an individual basis and depends essentially on personal motivation for permanent cessation. Therefore, it seems clear that smokers who are preparing to quit should receive 2 types of help: *a)* behavioral therapy, aimed at combating their psychological dependence and *b)* pharmacological therapy to relieve their physical dependence on nicotine (level A evidence).[1-8]

During the last 10 years, there have been important developments in the pharmacological treatment of smoking. New drugs have come onto the market, the modes of use and doses of currently available drugs have been modified, and the indications of the different drugs have even varied slightly. Furthermore, the arrival of new pharmacological options in tobacco cessation has opened an important debate as to whether this option should be financed by the Spanish national health system.[9,10]

Correspondence: Dr C.A. Jiménez Ruiz
Unidad Especializada en Tabaquismo, Instituto de Salud Pública
Santa Cruz del Marcenado, 9
28015 Madrid, Spain
E-mail: carlos.jimenez@salud.madrid.org

Manuscript received July 1, 2007. Accepted for publication September 26, 2007.

These new guidelines on the pharmacological treatment of smoking have 2 main objectives: to analyze the drugs approved by the Spanish health authorities for use as pharmacological treatment of tobacco dependence and to make reasoned proposals based on scientific evidence for public financing of these treatments.

This article sets out the neurophysiological grounding of nicotine dependence and tobacco addiction. It also uses scientific evidence to justify the need for smokers who wish to make a serious attempt at quitting to receive pharmacological therapy when indicated. Similarly, the article reviews the mechanism of action, doses, indications, and contraindications of each of the drugs available in Spain (nicotine gum, tablets, and patches, bupropion, and varenicline) to help smokers quit. The article also examines the results and conclusions of a new approach to the treatment of tobacco dependence: gradual reduction of intake using nicotine gum as a first step towards permanent cessation. Finally, proposals for public financing of pharmacological treatment to help smokers quit are presented.

Nicotine Dependence and Tobacco Addiction

Nicotine acts on acetylcholinergic receptors in the neuronal membranes of the ventral tegmental area of the mesencephalon. These receptors are made up of 5 polypeptide chains. The most numerous are formed by 2 α_4 chains and 3 β_2 chains.[11] We now know that stimulation of these receptors by nicotine increases the release of dopamine in the nucleus accumbens. This response causes the sensation of reward experienced by smokers when they inhale nicotine and explains self-administration.[11,12] Furthermore, self-administration of nicotine is facilitated and boosted when supply is associated with external stimuli.[11-14] In short, administration of nicotine by inhaling cigarette smoke causes organic lesions in the neurons of the ventral tegmental area of the mesencephalon, that is,

an increase in the number and function of the nicotine receptors α_4 and β_2. These lesions make the smoker dependent on nicotine, and this in turn leads to physical and psychological alterations (withdrawal symptoms). Hence the "uncontrolled and unhealthy" search for nicotine through continuous consumption of cigarettes. Therefore, nicotine dependence leads to cigarette addiction, in other words, an addiction to cigarette smoke. There can be no doubt that administration of nicotine by cigarettes or cigars is the quickest and surest way to become dependent on this drug. On the contrary, it is uncommon to become dependent on nicotine if it is consumed in other ways, for example, through nicotine replacement therapy (NRT).[11-14]

Nicotine Replacement Therapy

NRT is recognized as first-line therapy and has been used successfully for many years in the treatment of tobacco dependence. During recent years, new applications have been developed, such as high-dose replacement therapy or, more recently, NRT for reduced consumption as a first step to complete withdrawal. Below, we comment on the pharmaceutical presentations of NRT available in Spain

Nicotine Gum

This is a piece of chewing gum containing 2 mg or 4 mg of nicotine that, when chewed, releases nicotine into the mouth to be absorbed by the oral mucosa. It then reaches the blood from where is stimulates the nicotine receptors of the neuronal membranes of the ventral tegmental area of the mesencephalon, thereby suppressing the withdrawal symptoms experienced by smokers who are trying to quit.

The latest Cochrane review on the subject shows that the odds ratio for withdrawal using nicotine gum is 1.66 (95% confidence interval [CI], 1.52-1.81) (level A evidence).[15] There is also sufficient evidence to recommend gum containing 4 mg of nicotine, compared with 2 mg, for smokers with high physical dependence; in this case, the odds ratio is 2.20 (95% CI, 1.85-3.25) (level A evidence).[15]

Gum allows nicotine to be administered relatively quickly. This is one of its differential characteristics. On the one hand, it can be used on demand to control intense cravings and, on the other, it can be administered gradually to obtain steady plasma nicotine values that will help to relieve the withdrawal symptoms.

Table 1 shows the doses, adverse effects, and contraindications of this type of treatment.[1-8,15-17]

TABLE 1
Nicotine Gum

Efficacy
Odds ratio = 1.66 (95% confidence interval, 1.52-1.81)
Dose
Should be adjusted to the smoker's degree of physical dependence
Smokers of fewer than 20 cigarettes/d or who light their first cigarette more than 30 minutes after getting up are recommended to take 2-mg gum at a dose of 1 piece every 1 or 2 hours while they are awake
Smokers of 20 or more cigarettes/d, or who smoke their first cigarette before 30 minutes after getting up should use 4-mg gum with a similar regimen
Duration of treatment: between 8 and 12 weeks
Less dependent smokers are recommended to use gum for 8-10 weeks
Smokers with a greater degree of dependence are advised to prolong treatment for up to 3 months, although this group could use gum for up to 6-12 months
The dose will be gradually reduced after 4-8 weeks of treatment
Adverse effects[a]
Pain in the temporomandibular joint (4%-12%)
Bad taste in the mouth (2%-20%)
Oropharyngeal discomfort (1%-5%)
Meteorism (3%-15%)
Nausea (3%-8%)
Pyrosis (3%-14%)
Hiccups (2%-14%)
Contraindications
Absolute
Recent diagnosis of myocardial infarction (less than 4 weeks)
Unstable angina
Severe cardiac arrhythmia
Relative
Pregnancy
Breastfeeding

[a]Correct use of nicotine gumhelps reduce the onset of these adverse effects, which are more frequent during the first 2 weeks.

Nicotine Tablets

These tablets contain 1 mg or 2 mg of nicotine. Their mechanism of absorption and their pharmacokinetics are relatively similar to those of 2-mg or 4-mg nicotine gum, respectively, and their efficacy has been verified in a double-blind, placebo-controlled trial,[18] which showed that smokers who used nicotine tablets were twice as likely to quit smoking as those who used the placebo.

Nicotine Patches

The nicotine patch is loaded with nicotine that is released through contact with the skin. Three types of patch are available in Spain. These differ in the nicotine concentration, release time, and plasma nicotine levels. Their features are set out in Table 2.[19]

The latest meta-analysis showed that, compared with controls, the odds ratio for withdrawal using nicotine patches was 1.81 (95% CI, 1.63-2.02) (level A evidence).[15] The 24-hour patches are as effective as the 16-hour patches.[15] A recent study has shown slightly increased efficacy of nicotine patches at the end of the first week of treatment when used for 2 weeks before quitting.[20] The patch is a slow and gradual nicotine delivery system.

The following guidelines indicate how to use them correctly[1-8,15-21]:

– They should be used by smokers with a mild-moderate physical dependence. In smokers with a more marked dependence (≥7 points in the Fagerström test), the success

TABLE 2
Types of Nicotine Patch

Company	Novartis	McNeil	GSK
Application time, h	24	16	24
Size, cm^2	30	30	21
	20	20	15
	10	10	7
Total nicotine content, mg	52.5	24	114
	35	16.6	78
	17.5	8.3	36
Nicotine absorbed, mg	21	15	20.6
	14	10	14
	7	5	7

Abbreviation: GSK, GlaxoSmithKline.

TABLE 3
Nicotine Patches

Efficacy
Odds ratio = 1.81 (95% confidence interval, 1.63-2.02)
Adverse effects
Local[a]
Erythema
Exanthema
Pruritus
Eczema
Systemic[b]
Headache
Insomnia. Vivid dreams
Nausea. Hiccups
Bad taste in the mouth
Palpitations
Dizziness
Paresthesia
Myalgia
Contraindications
Absolute
Recently diagnosed myocardial infarction (less than 4 weeks)
Unstable angina
Severe cardiac arrhythmia
Relative
Pregnancy
Breastfeeding

[a]These appear during the first 2 weeks of treatment, are uncommon (3%-18%) and usually self-limiting, and do not require discontinuation of treatment.
[b]These appear less commonly than local adverse effects (1%-9%), are self-limiting, and do not require discontinuation of treatment.

rate did not increase when they were used alone, probably due to the low plasma nicotine concentrations reached. Therefore, in some cases, using 2 patches at the same time is highly recommended

– They should be used for at least 6 to 8 weeks and for no more than 12. Early interruption of treatment with nicotine patches, before 6 to 8 weeks, can lead to relapse, and prolonging treatment for more than 12 weeks does not increase the chances of success

– Patches must be used at high doses during the first 4 to 6 weeks. In the case of 16-hour patches, the recommended high dose is 25 mg/day; this is reached by using a 15-mg patch and a 10-mg patch together. For the 24-hour nicotine patch, the high dose is 21 mg/day

Table 3 shows the adverse effects and contraindications of this treatment.[1-8,15-21]

Ways of Increasing the Effectiveness of Nicotine Replacement Therapy

According to a recent meta-analysis, compared with controls, the odds ratio for withdrawal using the different types of nicotine patch was 1.77 (95% CI, 1.66-1.882) (level A evidence).[15] This effectiveness is not only observed when a health professional offers and monitors NRT in the context of a withdrawal program, it is also maintained when NRT is offered as an over-the-counter medication, with no psychological support. In recent years, several studies have attempted to significantly improve the efficacy of this treatment. Three lines of research have been followed: increasing the dose of nicotine, improving the mode of administration with the aim of reaching higher plasma nicotine peaks more quickly,[22] and analyzing the efficacy of combining different routes of administration.[23]

Reducing Tobacco Consumption as a First Step Toward Complete Withdrawal by Using NRT

Concept. Reduced tobacco consumption is defined as a reduction in the number of cigarettes smoked per day by at least 50% for at least 4 months. This reduction must be verified by a sustained decrease in the levels of carbon monoxide in exhaled breath.[24]

Efficacy and safety of NRT in the reduction of tobacco consumption as a first step toward cessation. In recent years, a large number of clinical trials and studies have analyzed the efficacy and safety of reducing tobacco consumption as a first step to cessation.[25-27] Most show that reducing the number of cigarettes smoked per day not only increases motivation to attempt to quit smoking definitively, but that it also increases the chances of success. These studies also conclude that it is safe to use NRT (mainly nicotine gum) together with cigarette smoking.[25-27] The adverse effects are similar to those observed in studies where NRT is used alone. No signs or symptoms of nicotine poisoning were observed in any case.[25-27] Recently, the Spanish Ministry of Health and Consumer Affairs approved the use of nicotine gum to gradually reduce the consumption of cigarettes as a first step towards complete withdrawal.

Indications for reduction of tobacco consumption as a first step to cessation. There are 3 types of smoker for whom this approach is indicated: those who do not want to quit but who are willing to significantly reduce the number of cigarettes they smoke per day; those who do want to quit but find it very difficult to do so and feel frustrated at the idea of quitting suddenly; and those who want to quit—although not suddenly—and prefer to reduce their daily consumption gradually.

Clinical considerations. The following points must be taken into account for the clinical management of smokers who are gradually reducing their consumption[28]:

1. The smoker will begin treatment to reduce the daily consumption of cigarettes, but the ultimate goal will be complete cessation.

2. The process should be in 3 phases:

– The first phase is from the day the reduction begins until a 50% reduction has been reached. This should last between 8 and 10 weeks. The smoker must use nicotine gum to help the process along, replacing 2 cigarettes with a piece of gum

– The second phase runs until the day the smoker quits definitively. This should last between 8 and 10 weeks. Similarly, nicotine gum should be used, replacing each cigarette with a piece of gum

– In the last phase, the subject no longer consumes tobacco and gradually quits the nicotine gum. The whole process generally lasts 2 to 3 months

3. Smokers who smoke more than 20 cigarettes per day or who have a high degree of physical dependence on nicotine are recommended to use 4-mg gum, and those who smoke 20 or less, or have a low or moderate degree of dependence, should use 2-mg gum.

4. Confirmation of the reduction. The reduction should be confirmed throughout the process. One method of chemically evaluating the reduction in consumption is CO-oximetry. The technique is based on the fact that as the number of cigarettes smoked per day decreases, the amount of exhaled carbon monoxide decreases, although these reductions are always smaller than the reduction in the number of cigarettes.

5. If there is no significant chemically verified reduction by at least 50% with respect to baseline after 2 to 3 months using gum and cigarettes, the attempt should be considered a failure and treatment should be interrupted.

Bupropion

Bupropion is a bitter white powder in the form of sustained-release tablets containing 150 mg of active ingredient. The mechanism of action of this drug has not yet been accurately determined, although it is known to act on the nucleus accumbens by inhibiting reuptake of dopamine by the neurons; this effect would explain the reduced craving felt by smokers when they use it. It also inhibits neuronal reuptake of noradrenaline in the nucleus ceruleus, thus achieving a significant reduction in the intensity of nicotine withdrawal symptoms.[29] Recent in vitro studies[30] have shown that bupropion is a noncompetitive functional inhibitor of nicotine receptors of acetylcholine. This antinicotinic activity can contribute to its efficacy in treating nicotine dependence.

One meta-analysis showed that bupropion at 300 mg/day for 7 weeks was associated with a significant increase in steady withdrawal until the end of treatment, with an odds ratio of 2.71 (95% CI, 1.88-4.07); at 12 months of follow-up the odds ratio was 2.10 (95% CI, 1.62-2.73).[31] More recently, another meta-analysis evaluating the efficacy of bupropion in 19 clinical trials found an odds ratio of 2.06 (95% CI, 1.77-2.40).[32]

Table 4 shows the doses, main adverse effects, and contraindications of bupropion.[1-8,29,31,32]

Varenicline

Varenicline was recently approved by the United States Food and Drug Administration and by the European Medicines Agency as a specific treatment for smoking cessation. It has been available in Spain for this indication since 2007.

Varenicline was specially developed to help smokers quit smoking. It acts as a selective partial agonist of the nicotine receptors of the neurons in the ventral tegmental area of the mesencephalon. As a partial agonist, it has both agonist and antagonist properties. As an agonist, it can stimulate the nicotine receptor and is therefore able to control craving and withdrawal symptoms, whereas as an antagonist it can block the effects of nicotine on the receptor; therefore, its use during cessation means that relapses are not accompanied by a sensation of pleasure and reward, with the result that this drug prevents a relapse from becoming a failure. Another of its defining characteristics is that it is almost completely eliminated in urine without being metabolized in the liver. This means that it does not present problems of drug-drug interactions.[33]

The most recent meta-analysis by the Cochrane Library shows that using varenicline when trying to quit smoking increases the likelihood of success by 3 after 1 year of follow-up, compared with placebo (odds ratio, 3.22; 95% CI, 2.43-4.27). This drug was also found to help more smokers quit than bupropion (odds ratio = 1.66; 95% CI, 1.28-2.16). The most commonly reported adverse effect was nausea, although this was mostly mild and tended to be self-limiting.[34]

Table 5 shows the doses, main adverse effects, and contraindications of varenicline.[34]

The mechanism of action of varenicline is different from that of NRT and bupropion. Available information shows it to be a first-line, effective, and safe pharmacological treatment for helping smokers quit while preventing relapses.

Financing Pharmacological Tobacco Cessation Treatments

Guidelines on treating tobacco dependence from several countries state that there are effective pharmacological treatments capable of helping smokers quit (level A evidence).[1-8] Furthermore, they point out that the cost-effectiveness of this type of treatment is significantly better than that of other treatments for other chronic conditions such as hypertension or hypercholesterolemia (also level A evidence). They also state that treatment to help quit smoking is the best of all the possible preventive interventions (level A evidence).[1-8] Therefore, it is surprising that treatment for hypertension or hypercholesterolemia is financed by both public and private health systems, whereas financing of tobacco cessation treatments is continuously hampered.

TABLE 4
Bupropion

Efficacy
Odds ratio = 2.06 (95% confidence interval, 1.77-2.40)
Dose
Should be used for 7 to 9 weeks at 300 mg/d taken in 2 doses of 150 mg each
Treatment should start 7 to 15 days before definitive cessation
During the first week, the patient must only take 1 tablet of 150 mg per day. The dose is then increased to 2 tablets of 150 mg
A tablet should be taken early in the morning on getting up and the second 8 hours later
The dose should be halved in smokers aged 65 years or more, those with significant hepatic or renal insufficiency, or those who are underweight (<45 kg)
Adverse effects[a]
Dry mouth (7%-12%)
Insomnia (10%-31%)
Instability (3%-8%)
Headache (3%-17%)
Nausea (3%-5%)
Allergic cutaneous manifestations (2%-14%)
Convulsions (0.1%)
Contraindications
Epilepsy
Convulsive disorders
Bulimia or anorexia nervosa
Simultaneous monoamine oxidase inhibitors
Liver cirrhosis
Bipolar disorder
Precautions
Bupropion must be used with caution in the following circumstances:
Smokers in situations that reduce the convulsive threshold (history of alcoholism, history of head injury, smokers withdrawing from benzodiazepines, etc)
Smokers using medication that reduces the convulsive threshold (antipsychotics, theophylline, systemic corticosteroids, quinine, antidepressants, oral antidiabetics, etc)

[a]Dose reduction helps to reduce the onset of these adverse effects.

TABLE 5
Varenicline

Efficacy
Compared with placebo: OR = 3.22 (95% CI, 2.43-4.27)
Compared with bupropion: OR = 1.66 (95% CI, 1.28-2.16)
Dose
First week: subjects can smoke and should use the drug at 0.5 mg once daily for the first 3 days and later at 0.5 mg twice daily until the end of the first week
After this period, the smoker should quit and start to take the drug at 1 mg twice daily until 12 weeks of treatment have been completed
Adverse effects
Nausea[a] (28%)
Flatulence (2%-5%)
Insomnia (13%-15%)
Abnormal dreams (11%-13%)
Contraindications
Hypersensitivity to varenicline

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]This usually appears during the first week of treatment, is mild in more than 70% of cases and do not require treatment to be interrupted, is self-limiting over time, and does not require treatment.

Scientific evidence shows that when pharmacological tobacco cessation treatments are financed (publicly or privately), a greater number of smokers make a serious attempt at quitting, thus increasing the number of ex-smokers and slightly increasing the long-term abstinence rates without an excessive increase in cost (level B evidence).[1,35]

Below, we present 2 proposals for the financing of pharmacological tobacco cessation treatments that we believe should be considered by the public health system.

One possible solution to the problem of financing could involve shared risk contracts between the pharmaceutical industry and health systems for pharmacological treatments. We think that, given the uncertainty over the effect of possible financing of this medication on public expenditure, a shared risk contract between both entities would be a solution. In the contract, both the industry and the public health system would have to accept their responsibilities. The pharmaceutical industry should make a firm commitment in terms of sustainable budgets, return of expenditure in cases of inadequate prescription, and the setting of different prices for different population groups. The public health system, for its part, should accept a price based on the product's incremental innovation and agree that any renegotiation of the price should be bilateral.

Another possible solution would involve setting conditions to be fulfilled by the smoker, and even by the health professional who prescribes the treatment. Pharmacological treatment would be financed with the following conditions:

1. Treatment should only be prescribed when the smoker expresses a commitment to quit smoking and sets a date for doing so.

2. Available resources could be maximized by identifying priority groups within the smoking population, such as the following:

– Patients with diseases caused by smoking and whose condition is likely to revert or stop, such as chronic obstructive pulmonary disease, cardiovascular diseases of different types, or cancer that is likely to remit

– Patients with diseases not caused by smoking, but which are exacerbated by smoking, for example, bronchial asthma, diabetes, bronchiectasis, chronic respiratory failure of any cause, sleep apnea syndrome, etc

– Smokers who, while they do not suffer from disease, show a serious desire to quit, have made previous attempts and are unable to control their consumption, whether because of the intensity of the dependence or because of a concomitant psychiatric condition

– Professionals seen as role models due to the influence their profession has on the behavior of the population, for example health professionals or teachers

3. The only treatments used would be those pharmacological treatments that have proven effective and safe and that are recommended in national and international guidelines on the treatment of tobacco dependence. Prescription and mode of use will be according to the indications of these guidelines

4. Pharmacological treatment can be optimized by providing it gradually when the smoker attends follow-up visits. Under no circumstances will the complete course of medication be given to the patient at the start of therapy.

5. If the attempt fails, no new treatment will be financed until 6 months after the date of the first failure.

The initiation of either of these 2 options would involve the recognition of smoking as a chronic disease that can be treated by the public health system. This in turn would enable a greater number of smokers to make a serious attempt at quitting and, thus, considerably increase their chances of success. Similarly, we would like to stress that pulmonology health professionals are perfectly trained to carry out these recommendations and can contribute suitably to optimizing the resources necessary to finance tobacco cessation treatments.

REFERENCES

1. Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, et al. Treating tobacco use and dependence. Clinical practice guideline. Rockville: US Department of Health and Human Services. Public Health Service; 2000.
2. Tønnesen P, Carrozzi L, Fagerström KO, Gratziou C, Jimenez-Ruiz CA, Nardini S, et al. Task Force Recommendations: Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. Eur Respir J. 2007;29:390-427.
3. Akehurst RL, Bernett D, Berry C, Bird S, Buxton M, Claxton K, et al. Guidance on the use of nicotine replacement therapy and bupropion for smoking cessation. National Institute for Clinical Excellence. www.nice.org.uk. Accessed December 2007.
4. West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. Thorax. 2000;55:987-99.
5. Pérez Trullén A, Clemente Jiménez L. Presente y futuro de los tratamientos para dejar de fumar. Arch Bronconeumol. 2001;37: 241-6.
6. Jiménez Ruiz CA, Barrueco Ferrero M, Solano Reina S, Torrecilla García M, Domínguez Granda F, Díaz-Maroto Muñoz JL, et al. Recomendaciones en el abordaje diagnóstico y terapéutico del tabaquismo. Documento de consenso. Arch Bronconeumol. 2003;39:35-41.
7. Jiménez Ruiz CA, Solano Reina S, González de Vega JM, Ruiz Pardo M, Flórez Martín S, Ramos Pinedo A, et al. Normativa para el tratamiento del tabaquismo. Arch Bronconeumol. 1999;335: 499-506.
8. Jiménez Ruiz CA, Granda Orive JI, Solano Reina S, Carrión Valero F, Romero Palacios J, Barrueco Ferrero M. Recomendaciones para el tratamiento del tabaquismo. Arch Bronconeumol. 2003;39: 409-18.
9. Cornuz J, Pinget C, Gilbert A, Paccaud F. Cost-effectiveness analysis of the first-line therapies for nicotine dependence. Eur J Clin Pharmacol. 2003;59:201-6.
10. de Granda Orive JI, Gutiérrez Jiménez T, Martínez Albiach JM. La financiación de los tratamientos para dejar de fumar a través del sistema nacional de salud puede incrementar su éxito. Arch Bronconeumol. 2006;42:666.
11. Fagerström KO, Balfour D. Neuropharmacology and potential efficacy of new treatments for tobacco dependence. Expert Opin Investig Drugs. 2006;15:107-16.
12. Cadoni C, di Chiara G. Differential changes in the accumbens medial shell and core dopamine in behavioural sensitization to nicotine. Eur J Pharmacol. 2000;387:R23-R5.
13. Caggiula AR, Donny EC, Chaudrin N, Perkins KA, Evans Martin FF, Sved AF. Importance of nonpharmacological factors in nicotine self-administration. Physiol Behav. 2002;77:683-7.
14. Rose JE, Behn FM, Westmen EC, Johnson M. Dissociating nicotine and nonnicotine components of cigarette smoking. Pharmacol Biochem Behav. 2000;67:71-81.
15. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004;(3):CD000146.
16. Fagerström KO, Jiménez Ruiz CA. Tratamiento farmacológico del tabaquismo. In: Jiménez Ruiz CA, Solano Reina S, editors. Monografías Neumomadrid. Tabaquismo. Madrid: Ergón; 2004. p. 101-10.
17. Shiffman S, Shadel WG, Niaura R, Khayrallah MA, Jorenby DE, Ryan CF, et al. Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. Psychopharmacology. 2003;166:343-50.
18. Dautzenberg M. Multicentre controlled study with nicotine pills. Proceedings of the 3rd SRNT European Conference; 2001; Paris.
19. Shiffman S, Fant R, Buchhalter R, Girchell J, Henningfield J. Nicotine delivery systems. Expert Opin Drug Deliv. 2005;2:563-77.
20. Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. Nicotine Tob Res. 2006;8:89-101.
21. Tonnessen P, Paoletti P, Gustavsson G, Russell MA, Saracci R, Gulsvik A, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE-trial. Eur Respir. 1999;13:238-46.
22. Niaura R, Sayette MA, Shiffman S. Comparative efficacy of rapid-release nicotine gum vs. Nicorette in relieving smoking cue-provoked craving. Proceedings of the Annual Meeting of the Society for Research on Nicotine and Tobacco; 2003, February 19-22; New Orleans. New Orleans: Society for Research on Nicotine and Tobacco; 2003.
23. Kornitzer M, Boutsen M, Dramaix M, Thijs JK, Gusstavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. Prev Med. 1995;24:41-7.
24. Jiménez Ruiz CA, Fagerström KO. Reducción hasta dejarlo: árbol de decisión. Prev Tab. 2006;8 Suppl 1:34-7.
25. Pisinger C, Vestbo J, Borch-Johnsen K, Jorgensen T. Smoking reduction intervention in a large population-based study. Prev Med. 2005;40:1128.
26. Bolliger CT, Zellweger J-P, Danielsson T, van Biljon X, Robidou A, Westin A, et al. Smoking reduction with oral nicotine inhalers: double blind, randomized clinical trial of efficacy and safety. BMJ. 2000;321:329-33.
27. Rennard SI, Glover E, Leischow S, Daughto DM, Glover PM, Muramoto M, et al. Efficacy of nicotine inhaler in smoking reduction: a double-blind, randomized trial. Nicotine Tob Res. 2006;8:555-64.
28. Jiménez Ruiz CA, Fagerström KO. Un nuevo planteamiento del tratamiento del tabaquismo. Prev Tab. 2006; 8 Suppl 1:1.
29. Lerman C, Shields PG, Wileyto EP, Audrain J, Hawk LH, Pinto A, et al. Effects of dopamine transporter and receptor polymorphisms on smoking cessation in a bupropion clinical trial. Health Psychol. 2003;22:541-8.
30. Balfour D. The neurobiology of tobacco dependence: a pre-clinical prespective on the role of dopamine projections to the nucleus accumbens. Nicotine Tob Res 2004;6:899-912
31. Jarvis M, Powell S, Marsh H. A meta-analysis of clinical studies confirms the effectiveness of bupropion SR in smoking cessation. Proceedings of the 7th Annual Conference of the Society for Research on Nicotine and Tobacco; 2001, March 23-25; Seattle. Seattle: Society for Research on Nicotine and Tobacco; 2001.
32. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Sys Rev. 2004;(4):CD000031.

33. Zierler-Brown SL, Kyle JA. Oral varenicline for smoking cessation. Ann Pharmacother. 2007;41:95-9.

34. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonist for smoking cessation. Cochrane Database Sys Rev. 2007;(1): CD006103.

35. Kaper J, Wagena EJ, Severens JL, van Schayck CP. Healthcare financing systems for increasing the use of tobacco dependence treatment. Cochrane Database Sys Rev. 2005;(1):CD004305.