

## ORIGINAL RESEARCH ARTICLE

# Smoking cessation in cardiovascular health

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### ABSTRACT

The World Health Organization has identified noncommunicable diseases (NCDs) as one of the greatest challenges of this century, accounting for 71% of deaths worldwide. Smoking is considered one of the main modifiable risk factors affecting NCDs. There is ample evidence linking smoking to cardiovascular disease, particularly ischemic heart disease. The 2016 European Society of Cardiology Cardiovascular Prevention Guidelines establish smoking cessation as a class I, level of evidence A recommendation. The effect of nicotine generates a strong addiction that triggers a withdrawal syndrome when attempting to quit smoking. Therefore, it is necessary to be familiar with the strategies for the treatment of tobacco addiction, which include: minimal intervention, cognitive-behavioral resources and pharmacological treatment such as nicotine replacement therapy, bupropion and varenicline. At present, there is insufficient scientific evidence to recommend electronic devices.

**Keywords:** tobaccoism; tobacco use cessation; health cardiovascular health

## 1. Introduction

The World Health Organization (WHO) has determined that noncommunicable diseases (NCDs) represent one of the greatest health and development challenges of this century, given the impact they have on human suffering and on the socioeconomic aspects of different countries, especially developing countries<sup>[1]</sup>.

Mortality attributable to NCDs is estimated at 41 million people per year, representing 71% of deaths worldwide. Each year, 15 million people between 30 and 69 years of age die from NCDs, more than 85% of these “premature” deaths occur in low- and middle-income countries<sup>[2]</sup>.

Behavioral risk factors, together with metabolic risk factors, favor the triggering of NCDs. The former includes smoking.

The tobacco epidemic is considered a global problem with serious public health consequences that requires the broadest international cooperation and the collaboration of all countries to join forces in an effective response.

Tobacco is associated with the mortality of 7.2 million people per year, taking into account those who use tobacco directly and those who are exposed to secondhand smoke<sup>[3]</sup>. The effects of tobacco are linked to six of the eight leading causes of death<sup>[4]</sup>.

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According to the latest Global Adult Tobacco Survey (GATS 2017), the prevalence of tobacco use in Uruguay is 21.6% (including daily and occasional users). Consumption is more frequent in men (25.6%) than in women (18.0%), and the age range with the highest consumption is 25 to 44 years old (29.0%). Consumption is significantly lower in the population with tertiary education (14.2%).

When planning health policies, tobacco control is among the prevention measures that have the greatest impact<sup>[4]</sup> on NCDs and at the individual level, quitting smoking is the most beneficial action for the health of any source<sup>[5]</sup>.

As a consequence of this situation, WHO and the World Health Assembly decided to develop the first international public health treaty, the Framework Convention on Tobacco Control (FCTC)<sup>[6]</sup>.

The treaty, in force since 2005, establishes legally binding purposes and principles that must be complied with by the countries (known as Parties) that ratified the treaty, committing themselves to its implementation.

Cardiovascular and cerebrovascular diseases are among the main causes of mortality in smokers, with an increase in risk in accordance with the intensity of consumption<sup>[7]</sup>.

The implementation of control measures and the creation of smoke-free spaces have made it possible to demonstrate the beneficial effects, with a rapid impact on cardiovascular diseases, particularly those related to ischemic heart disease<sup>[8]</sup>.

## **2. Smoking and ischemic heart disease**

There is ample evidence linking smoking to ischemic heart disease. It has been shown that tobacco smoke is associated with platelet activation, endothelial dysfunction, oxidative stress, inflammation, and alterations in the lipid profile and sympathetic nervous system. Consequently, smoking is linked to the processes that trigger atherosclerosis and its consequences at the level of the coronary circulation<sup>[9]</sup>.

Smoking is a highly prevalent risk factor among those suffering from acute coronary syndrome (ACS), with 30% to 50% being smokers at the time of admission and 20% to 40% being former smokers<sup>[10]</sup>.

A cohort study with a 50-year follow-up in British physicians showed that mortality from ischemic heart disease was 60% higher in smokers compared to non-smokers<sup>[11]</sup>.

According to epidemiological studies carried out in different countries, it has been shown that exposure to tobacco smoke increases the risk of myocardial infarction by 31% among non-smokers<sup>[12]</sup>.

As of 1 March 2006, Uruguay established a ban on smoking in enclosed public spaces. Subsequent research concluded that admissions for acute myocardial infarction decreased 22% after the measure was implemented<sup>[13]</sup>.

In a recent consultation with the National Resources Fund (NRF) to determine the correlation between smoking and coronary lesions in cardiac catheterizations performed in a population under 55 years of age, we were informed that the risk of coronary lesions tripled in women smokers, on a par with non-smoking men; male smokers have a higher risk of coronary disease, with a 6.85-fold increase in moderate lesions and a 7-fold increase in severe lesions<sup>[14]</sup>.

Other studies state that the relative risk of smokers under 50 years of age is five times higher than that of non-smokers<sup>[15]</sup>.

The 2016 European Society of Cardiology Guidelines on the Prevention of Cardiovascular Disease in Clinical Practice state that “smoking cessation is the most cost-effective strategy for cardiovascular health”, they list it as a class I recommendation with level of evidence type A<sup>[16,17]</sup>.

Smoking cessation rates after ACS are high; however, it has been observed that up to 35% relapse within 30 days of the event<sup>[18]</sup>.

### **3. Tobacco addiction and withdrawal symptoms**

Since the 1970s, there has been sufficient information attributing nicotine's addictive capacity as a key factor in tobacco dependence<sup>[19]</sup>.

Nicotine is an alkaloid found in the tobacco leaf; upon combustion, it vaporizes in the smoke and reaches the lungs, then crosses the alveolar wall to be rapidly absorbed into the pulmonary circulation and enters the systemic arterial circulation. Peak arterial concentrations of nicotine in the arteries are reached within 30 seconds of inhalation<sup>[18]</sup>.

The fundamental action of nicotine is on the central nervous system, acting on the mesolimbic dopaminergic system. It binds to nicotinic acetylcholine receptors in the cell bodies of the ventral tegmentum area. There, action potentials are initiated in dopaminergic neurons that are destined for the nucleus accumbens, where dopamine release generates dependence and a feeling of satisfaction<sup>[18]</sup>.

Smoking cessation causes a tobacco withdrawal syndrome. It is characterized by mood changes and a set of characteristic signs and symptoms including irritability, insomnia, agitation, difficulty concentrating, craving and hunger. This is accompanied by biochemical and physiological changes with reduced heart rate and constipation<sup>[20]</sup>.

Withdrawal symptoms are usually of short duration, peaking in the first few days after cessation of tobacco use, and may persist for two to four weeks<sup>[18]</sup>.

Nicotine is one of the most addictive drugs, surpassing cocaine and heroin. However, most smokers attempt to quit without support<sup>[21]</sup>. Studies in the United States indicate that 62% of smokers who tried to quit did not use any treatment<sup>[22]</sup>. Smoking cessation without support has a low success rate (2% to 3% sustained cessation after one year)<sup>[23]</sup>.

The intervention of the healthcare team is fundamental to increase cessation rates. According to the GATS 2017 survey<sup>[24]</sup>, only 52.0% of smokers who had contact with a health professional in the previous year received cessation advice and only 18.2% received support in the process.

### **4. Tobacco addiction treatment**

Due to the damage it causes to health and the dependence it generates, it is essential to record in the clinical history of each patient whether he/she is a tobacco user and the most important characteristics, such as age of onset and intensity of consumption.

The majority of smokers express their desire to quit smoking, 72% expressed this in a UK study<sup>[25]</sup> and similar data (72.9%) were obtained in the GATS survey conducted in Uruguay<sup>[24]</sup>.

Given the predisposition of most smokers towards addiction treatment, it is necessary for health professionals to have the necessary information and resources to provide appropriate responses.

Treatment of tobacco addiction can be approached from different levels of intervention. All health professionals should implement at least a minimal intervention. When the professional has more motivation and training, he/she can carry out a more extensive intervention in the scope of his/her usual practice. When necessary or when the professional is not able to accompany the patient in the cessation process, he/she should be referred to the most specialized level of intervention, the smoking cessation unit. At this level, a multidisciplinary team works to provide psychological and pharmacological support, individually or in groups,

all of which multiplies effectiveness.

Evidence correlates time spent in treatment (intensity of intervention) with higher abstinence rate figures<sup>[26]</sup>.

There is evidence that a minimal intervention of less than 3 minutes is sufficient for 40% of smokers to consider quitting and double the abstinence rate at one year compared to no intervention<sup>[27]</sup>.

### 5. Minimal intervention

- It is performed as part of the usual (opportunistic) assistance.
- It can be implemented by all members of the health care team.
- It does not consume more than 3 minutes per intervention.
- It applies to all tobacco users.
- In non-smokers, the objective is to avoid exposure to second-hand smoke.

The first step is to **find out** (A) the person’s link with tobacco, immediately give **brief** advice (B) on cessation and then offer help to achieve **cessation** (C) of consumption. Our country’s National Tobacco Cessation Guidelines call this intervention the ABC of cessation<sup>[16]</sup>.

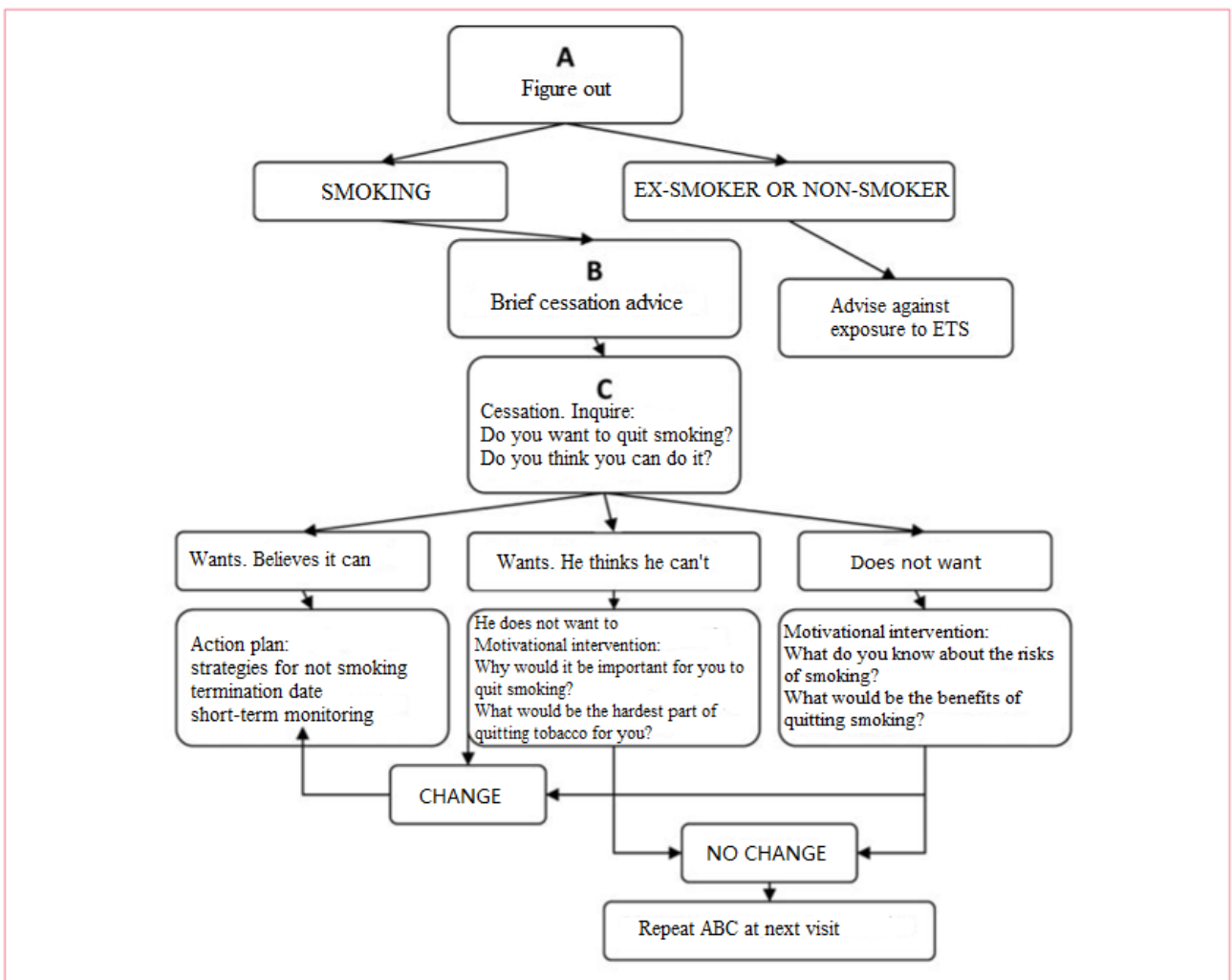


Figure 1. ABC algorithm for smoking cessation.

ETS: secondhand smoke.

**Find out (A):** if the patient is a smoker, whether daily or occasional, or if he/she is exposed to ETS. If it has been more than six months since he/she quit smoking, he/she is considered an ex-smoker. All the answers should be recorded in the clinical history that will be periodically updated.

**Brief advice (B):** should be the first action to be taken by all tobacco users, and should be strongly advised to stop smoking. To be effective, the advice should be: clear, simple and related to the patient's current pathology. Its effectiveness increases when the advice includes the offer of help.

Example: Quitting smoking is the most important thing you can do to avoid another episode. If you agree, I can help you.

**Cessation (C):** the next step is to provide concrete support to the patient or refer him/her to the smoking cessation unit.

The goal is to achieve complete cessation of tobacco use. Effective support consists of several steps, according to the scheme shown in **Figure 1**.

Two questions will suffice in the minimum intervention to assess motivation: Do you want to quit smoking? Do you think you will be able to do it?

People who want to quit smoking and believe they can, even if they have some doubts, are those who are ready for cessation. In them, a concrete action plan and short-term follow-up should be implemented.

## 6. Action plan

- Identify situations and emotions that trigger your desire to smoke (stress, fear, tiredness, boredom, etc.) and look for alternative ways to cope with these situations without smoking.
- The physician can provide simple strategies in preprinted material (see National Guideline).
- Define a cessation date. You can implement 24-hour pre-trials.
- Perform specific follow-up in the short term, no more than one month.
- If the patient has not achieved cessation by the agreed date, pharmacological treatment may be offered or referral to a smoking cessation unit may be made.

## 7. Motivational intervention

In people who do not want or believe they cannot quit smoking, we will carry out a brief motivational intervention and we will propose a follow-up that will depend on whether or not a change in their motivation is achieved.

Motivational intervention is based on questions. The patient has all the answers, we just have to accompany him/her to find them.

If the patient thinks he/she cannot, we can ask:

- Why would it be important for you to quit smoking?
- What would be the hardest part of quitting tobacco for you?

If the patient does not want to quit smoking, we will ask:

- What do you know about the risks of smoking to your health?
- What would be the benefits of quitting smoking?

Simply helping the patient to develop his or her own responses is an effective intervention to promote motivation to change.

We will then ask the patient if he/she still feels the same way about wanting and being able to quit smoking.

If he/she changes, we will proceed with the action plan. If he/she remains unprepared, the brief advice and motivation assessment will be repeated at the next contact for his/her reason for consultation.

## 8. Pharmacological treatment

A further step in the treatment of tobacco addiction is the use of specific drugs. It is a support to the previously implemented resources. Its objective is to reduce the severity of withdrawal symptoms associated with smoking cessation. Medications that have demonstrated effectiveness and are considered first line are: nicotinic replacement therapies (NRT), bupropion and varenicline.

In a meta-analysis<sup>[28]</sup> in which a review of 267 studies from 2008 to 2012 involving 101,000 smokers was performed in which treatment outcomes six months after initiation and observed side effects were measured, the following results were obtained:

- a) NRT was superior to placebo (OR 1.84; 95% CI 1.71–1.99);
- b) bupropion was superior to placebo (OR 1.82; 95% CI 1.60–2.60);
- c) varenicline was superior to placebo (OR 2.88; 95% CI 2.44–3.47);
- d) varenicline was superior to NRT (OR 1.57; 95% CI 1.29–1.91) and bupropion (OR 1.59; 95% CI 1.29–1.96);
- e) there was no increase in neuropsychiatric or cardiovascular adverse events with either bupropion or varenicline.

The use of the various drugs, side effects and contraindications are extensively described in the 2009 National Guidelines for the Management of Smoking<sup>[17]</sup>.

NRTs are marketed in different presentations, depending on each country: chewing gum, patches, candies, nasal nebulizer, inhaler and sublingual tablets. They are used for a period of approximately three months; in certain cases and depending on the need, it is possible to extend this time<sup>[19]</sup>.

The chewing gum available in Uruguay contains 2 mg of nicotine. The dosage depends on the number of cigarettes consumed daily, up to 24 pieces can be used in a day and the treatment should be maintained for at least eight weeks. It is important that the piece is kept in the mouth for at least 40 minutes and chewed as little as possible. It is started by substituting some cigarettes for chewing gum. When abstinence is achieved, it is recommended to use chewing gum regularly during the day, depending on the number of cigarettes smoked. Effectiveness depends on an adequate chewing technique, which should be explained to the patient. NRT has no absolute contraindications, although caution should be exercised in the first two weeks after acute myocardial infarction, in unstable angina and in severe arrhythmias<sup>[5]</sup>.

Nicotine can be administered with “candies” or “lozenges” that have an absorption and pharmacokinetic mechanism like chewing gum.

Nicotine patches are a mechanism of slow release of nicotine, the presentations are 7, 14 and 21 mg. The duration of use is at least eight weeks. In patients who smoke more than 20 cigarettes a day, it is recommended to start with 21 mg patches for one month and reduce the dose progressively over the following two months<sup>[5]</sup>.

Bupropion is the first non-nicotinic drug that has been shown to be effective in the treatment of smoking<sup>[5]</sup>. Its action is based on the inhibition of neuronal reuptake of dopamine and noradrenaline<sup>[29]</sup>. Treatment should be started 7 to 15 days before the scheduled quit date. During the first three days, 150 mg daily and then 150 mg every 12 hours. It is advisable to maintain the treatment for a period of 7 to 12 weeks. Caution should be exercised in patients with hepatic or renal insufficiency or low weight<sup>[5]</sup>. Bu-propion is contraindicated in patients with a history of seizures, eating disorders (anorexia-bulimia) and bipolar disorder. The authorization of the treating psychiatrist is essential when the patient is using other antidepressants.

Among the nicotinic receptor partial agonists are two drugs, cytisine and its derivative varenicline; the former has been available for several years in some European countries.

These drugs have an affinity for nicotinic acetylcholine receptors in neurons, interrupting the binding of nicotine to the receptor; by this mechanism it decreases the reward at the time of smoking and attenuates withdrawal symptoms<sup>[30]</sup>.

Varenicline is available in 0.5 and 1 mg presentations. It is recommended to start its administration seven days before the scheduled quit day. It should be started with 0.5 mg once a day during the first three days; between days 4 to 7, 0.5 mg every 12 hours and then 1 mg every 12 hours for 12 weeks. Among the side effects, the most frequent is nausea, especially during the beginning of treatment<sup>[31]</sup>.

Other drugs that have proven useful in the treatment of tobacco addiction are clonidine and nortriptyline, although they have been used less frequently due to the side effects they produce. Cytisine has been shown to be effective, but it is not available in our environment.

## **9. Electronic devices**

Electronic devices related to the consumption of tobacco products were developed from the idea patented by Herbert A. Gilbert in 1965; later, in 2003, Hon Liky Ruyan Technology, in China, patented what will eventually be known as electronic cigarette (e-cigarettes)<sup>[28]</sup>.

Since then, there have been permanent changes in technology, design and variety of products offered for consumption, achieving exponential growth in sales in several countries.

These devices consist of substituting the combustion of tobacco and the production of gases derived from it by heating a liquid and generating vapor that may or may not contain nicotine.

In some cases the design allows the introduction of tobacco and the heating of the tobacco without combustion. In general terms they are often referred to as “vapers”.

Therefore, we can find electronic devices with and without nicotine, and devices that can accept tobacco in their receptacle to be heated (heat not burn).

In general, the structure of the device consists of a battery, a dispenser and an interchangeable cartridge or capsule that stores liquid inside, usually glycerol, propylene glycol, various additives that give the product different flavors and odors, and different amounts of nicotine or no nicotine at all<sup>[28]</sup>.

Electronic devices are considered “tobacco derivatives”<sup>[32]</sup> and presented as a substitute for tobacco cigarettes because they are considered to be less harmful, and have been promoted as an alternative for smoking cessation.

The evidence available so far and the WHO recommendations<sup>[32,33]</sup> do not support the arguments used by those who promote electronic devices, therefore it is necessary to deepen the studies and obtain more evidence before they can be considered as an alternative in the treatment strategy for smoking. It should be borne in mind that they are not harmless and contain toxic substances.

## **10. Conclusions**

Although progress has been made with respect to tobacco use since the implementation of the Framework Convention on Tobacco Control, we are far from considering it a solved health problem. It is necessary to insist on the implementation of the minimum systematic intervention by the entire health team, as it is the most cost-effective intervention and has the widest population coverage according to the WHO.

## Conflict of interest

The authors declare no conflict of interest.

## References

1. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: WHO; 2014.
2. World Health Organization. Noncommunicable diseases: 1 June 2018. Geneva: WHO; 2018.
3. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioral, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016; 388(10053): 1659-1724.
4. Beaglehole R, Bonita R, Horton R, et al. Priority actions for the non-communicable disease crisis. *Lancet*. 2011; 377(9775): 1438-1447.
5. Zabert G, Jiménez Ruiz C, Zabert I. What should cardiologists know about pharmacological treatment for smoking cessation? *Rev Urug Cardiol*. 2011; 26(3): 251-262.
6. World Health Organization. Guidelines on protection from exposure to tobacco smoke: purpose, objectives and main considerations. Geneva: WHO; 2007.
7. Ambrose J, Barua R. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004; 43(10): 1731-1737.
8. Sandoya E, Sebríe E, Bianco E, et al. Impact of indoor smoking bans on admissions for acute myocardial infarction in Uruguay. *Rev Méd Urug*. 2010; 26(4): 206-215.
9. Raupach T, Schäfer K, Konstantinides S, Andreas S. Secondhand smoke as an acute threat for the cardiovascular system: a change in paradigm. *Eur Heart J*. 2006; 27(4): 386-392.
10. Teo K, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet*. 2006; 368(9536): 647-658.
11. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004; 328(7455): 1519.
12. Barnoya J, Glantz S. Cardiovascular effects of second hand smoke: nearly as large as smoking. *Circulation*. 2005; 111(20): 2684-2698.
13. Sebríe E, Sandoya E, Hyland A, et al. Hospital admissions for acute myocardial infarction before and after implementation of a comprehensive smoke-free policy in Uruguay. *Tob Control*. 2013; 22(e1): e16-20.
14. National Resources Fund. World tobacco-free day: communication made on May 31, 2018. Montevideo: FNR; 2018.
15. Prescott E, Hippe M, Schnohr P, et al. Smoking and risk of myocardial infarction in women and men: longitudinal population study. *BMJ*. 1998; 316(7137): 1043-1047.
16. Spanish Society of Cardiology. ESC 2016 guideline on prevention of cardiovascular disease in clinical practice. *Rev Esp Cardiol*. 2016; 69(10): 939.e1-e87.
17. Lorenzo García A, Baraibar Penco R, Melgar Álvarez S, et al. Guía Nacional para el Abordaje del Tabaquismo: Uruguay 2009. Montevideo: MSP; 2009.
18. Chow C, Jolly S, Rao-Melacini P, et al. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation*. 2010; 121(6): 750-758.
19. Di Chiara G. Role of dopamine in the behavioral actions of nicotine related to addiction. *Eur J Pharmacol*. 2000; 393(1-3): 295-314.
20. Hughes J. Effects of abstinence from tobacco: valid symptoms and time course. *Nicotine Tob Res*. 2007; 9(3): 315-327.
21. McRobbie H, Thornley S. The importance of treating tobacco dependence. *Rev Esp Cardiol*. 2008; 61(6): 620-628.
22. Shiffman S, Brockwell S, Pillitteri J, Gitchell J. Use of smoking-cessation treatments in the United States. *Am J Prev Med*. 2008; 34(2): 102-111.
23. Hughes J, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*. 2004; 99(1): 29-38.
24. Uruguay. Ministry of Health. Global adult smoking survey: Global Adult Tobacco Survey (GATS) Uruguay 2017. Available online: [http://www.msp.gub.uy/sites/default/files/archi-vos\\_adjuntos/PRESENTACION%20GATS\\_Mayo%202017%20%28edit%29.ppt](http://www.msp.gub.uy/sites/default/files/archi-vos_adjuntos/PRESENTACION%20GATS_Mayo%202017%20%28edit%29.ppt) (accessed on 31 August 2018).
25. Lader D. Smoking-related behaviour and attitudes, 2006: a report on research using the National Statistics Omnibus Survey produced on behalf of the Information Centre for health and social care. Newport, UK: Office for National Statistics; 2007.
26. United States. Department of Health and Human Services. Treating tobacco use and dependence. Rockville, MD: Department of Health and Human Services; 2000.



27. Stead L, Buitrago D, Preciado N, et al. Physician advice for smoking cessation. *Cochrane Database Syst Rev.* 2013; (5): CD000165. doi: 10.1002/14651858.CD000165
28. World Health Organization. Electronic nicotine delivery systems and nicotine-free systems (SEAN/SSSN). In: *Proceedings of Seventh Meeting of the Conference of the Parties to the WHO Framework Convention on Tobacco Control*, Delhi; 7-12 November 2016.
29. Hughes J, Stead L, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev.* 2007; (1): CD000031
30. Rollema H, Hajós M, Seymour P, et al. Preclinical pharmacology of the alpha4 beta2 nAChR partial agonist varenicline related to effects on reward, mood and cognition. *Biochem Pharmacol.* 2009; 78(7): 813-824.
31. Jiménez Ruiz C, Jaén C. Tobacco dependence treatment guide. [Treating tobacco use and dependence: 2008 update. Clinical practice guideline of U.S. Department of Health and Human Services. Public Health Service; 2008.
32. Bhatnagar A, Whitsel L, Ribisl K, et al. Electronic Cigarettes: a policy statement from the American Heart Association. *Circulation.* 2014; 130(16):1418–1436.
33. Doval H, Tajer C. *Evidence in Cardiology (Spanish)*, 8th ed. Buenos Aires: GEDIC; 2016.