dtbn
DRUG AND THERAPEUTICS BULLETIN OF NAVARRE, SPAIN
25 1993-2018 TWENTY FIVE YEARS OF INDEPENDENT INFORMATION
YEAR 2017
VOL 25, No 4
www.dtb.navarra.es
@DTB_Navarre.es

abstract

Objective: To critically examine scientific evidence on different smoking cessation strategies, with special focus on the safety results obtained in the recent EAGLES trial. **Methods:** We searched MEDLINE and The Cochrane Database of Systematic Reviews in November 2017 for records on nicotine replacement therapy, bupropion, and varenicline. The search was extended to best practice guidelines, publications of the International Society of Drug Bulletins, regulatory agencies databases, updated statistics (Eurobarometer) and other data sources. Finally, GlaxoSmithKline and Pfizer were contacted to gather additional data from the EAGLES trial. **Results:** Abstinence rates seem to improve with some non-pharmacological therapies (brief counselling, intensive support). However, follow-up concluded prior to the typical relapse period. Longer-term comparative studies on smoking cessation pharmacotherapies yield similar abstinence rates. The recommended first-line therapy is nicotine replacement therapy, as more robust long-term evidence is available and its safety profile is more acceptable. The EAGLES trial revealed that no relationship exists between the use of bupropion or varenicline and neuropsychiatric disorders. However, the significant limitations of this study do not allow this controversy to be put to rest. **Conclusions:** Regardless of the smoking cessation method used, smokers must be aware of the substantial health benefits of quitting and understand that success depends on their motivation to stop smoking.

WE GOTTA STOP SMOKIN', STOP, STOP... SMOKING CESSATION STRATEGIES

LUIS CARLOS SAIZ
Pharm D, PhD
Department of Innovation and Organization
Navarre Regional Health Service - Osasunbidea

«Giving up smoking is the easiest thing in the world.
I know because I've done it thousands of times.»
MARK TWAIN (1835-1910)

Introduction

Smoking cessation is the best decision that a smoker can make to improve their health. Success strongly depends on the smoker's determination to quit and, occasionally, on the commitment of policymakers and clinicians to support smokers who want to stop smoking. Tobacco addiction is currently considered a chronic disease[1] and is recognized as such in the International Classification of Diseases (ICD-10) of the World Health Organization (WHO). Thus, tobacco dependence is a challenge of the first magnitude, especially in primary care.

The dimensions of the problem are widely known. Tobacco is the leading cause of avoidable death in Spain, with 53,000 deaths/year attributable to smoking in persons older than 35 years (15% of the total)[2]. Life expectancy of smokers is 14 years shorter than that of non-smokers, with a significant impact on their quality of life[3]. The numerous chemicals found in tobacco have a dramatic impact on human health. Thus, tobacco is linked to 90% of deaths from lung cancer, 60% of deaths from pulmonary disease, one third of deaths from heart disease, and a range of disorders during gestation and at birth. The harmful effects of second-hand smoke have been demonstrated scientifically. Furthermore, recent publications have revealed new disorders associated with passive smoking, including a higher risk of diabetes, liver or colorectal cancer, and immune dysfunction[4].

Active role of public administrations

In the light of the compelling evidence available on the ill health effects of tobacco, public health authorities and agencies are increasingly adopting stronger smoking cessation measures. Based on WHO recommendations, Law 28/2005 on health measures regarding smoking was enacted by the Spanish authorities[5]. This law placed significant limits on tobacco advertising and generalized the ban on smoking in indoor public places[6]. There is evidence that these initiatives are effective in reducing tobacco use and have beneficial health effects, particularly on children, pregnant women[7], and patients with asthma and COPD. The reduction in the number of packs smoked per inhabitant in recent years is also the result of the dramatic economic crisis in Spain (Figure1).

Additionally, the Regional Government of Navarre funds one smoking cessation attempt per year with a choice of several pharmacotherapies. To such purpose, the GP completes a form in the medical record of the patient and asks the patient to commit to attending complementary individual counselling or group therapy sessions[8]. The efficacy of the program will be evaluated after two years and will be compared with the magnitude of the benefits previously reported for this type of program[9]. In this context, the objective of this study was to review evidence supporting the efficacy of smoking cessation strategies in terms of their health benefits and frequent and serious adverse events.

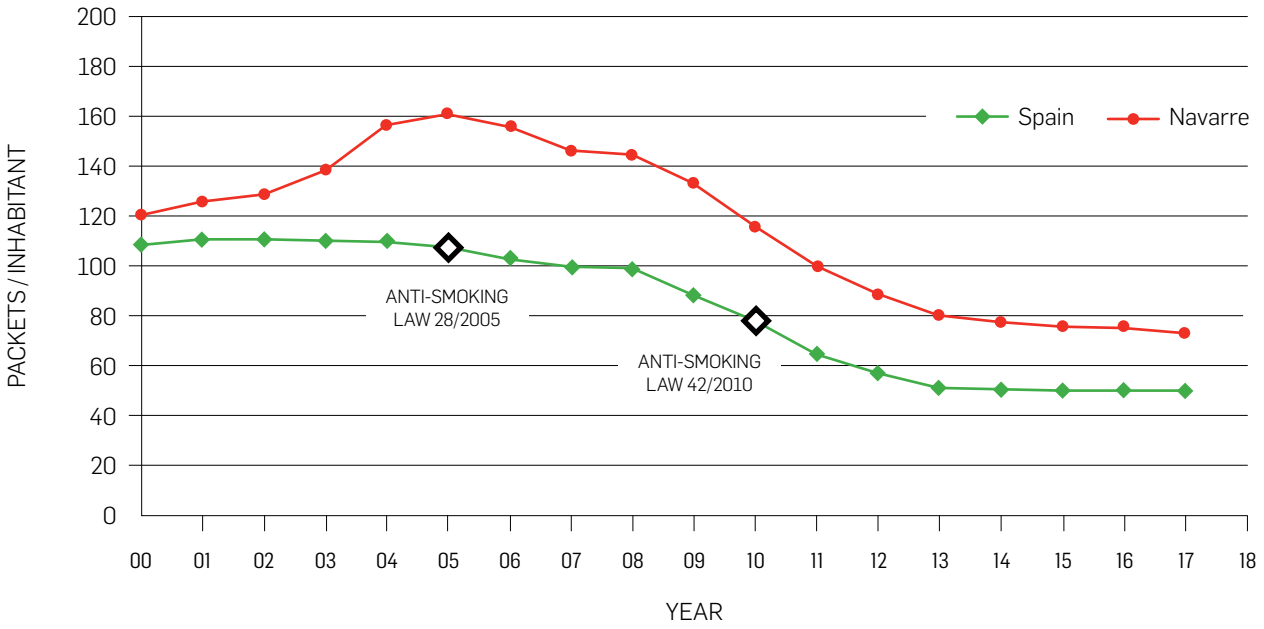
Profile of smokers in Spain

According to a recent European survey on persons older than 14 years[3], half the Spanish population have never smoked, 28% are current smokers (30% men vs. 25% women), and 22% are ex-smokers. Smokers are predominantly middle-aged and have a low economic status and educational level. An average of 12 packaged cigarettes is smoked daily and the majority started smoking before 25 years of age. Of note, 1 out of 6 smokers started smoking younger than 15 years.

In terms of trends, more men than women stopped smoking in recent decades, with the proportion of male and female smokers increasingly becoming more balanced[10]. As compared to other European countries, the prevalence of smoking in Spain fits the European average, below Greece (37%) and France (36%), and far above Sweden (7%) and UK (17%)[3].

The prevalence of smoking in Navarre is similar to that of Spain[10]. The downward trend of smoking is also observed among youngsters[11]. Remarkably, the proportion of female smokers 14 to 17 years of age is more than double that of males (20% vs. 9%).

Figure 1. Comparative analysis of the evolution of sales of 20-cigarette packs/inhabitant.



Note: Data for 2017 in Spain and Navarre were calculated by adding a projection for the month of December (data not available) by assuming the same variation as in December 2016.

Who, When, How, and Why is smoking cessation occurring?

According to the literature[3], abstinence is successfully achieved in Spain at a mean age of 40. About 85% of the population reports having quit more than two years ago, with a mean period of abstinence of 15 years. Half of current smokers attempted to quit in the past, although only 15% have made an attempt in the past 12 months. Smokers with a lower educational level try quitting less frequently and at a later age. Half of the 28% of Spanish residents who currently smoke have never attempted to stop smoking. According to a survey performed among youngsters in Navarre, the main reasons to want to quit are economic and health-related[11].

Figure 2 shows the preferred smoking cessation methods used by Spanish smokers. Spain is the EU country where the most attempts -successful or not- are made without any external aid. Up to 5% report having used electronic cigarettes; 3% have used nicotine replacement therapy (NRT), bupropion or varenicline; and 2% received medical aid, telephone counselling, or used websites. In relation to factors associated with long-term abstinence, successful attempts were made without aid more frequently (78%) than unsuccessful attempts (62%). Nevertheless, these results should be interpreted with caution, as baseline characteristics might differ and therefore possibly affect results. Thus, smokers who smoke a high number of cigarettes per day or recently attempted to quit are more likely to seek external support.

Baseline evaluation

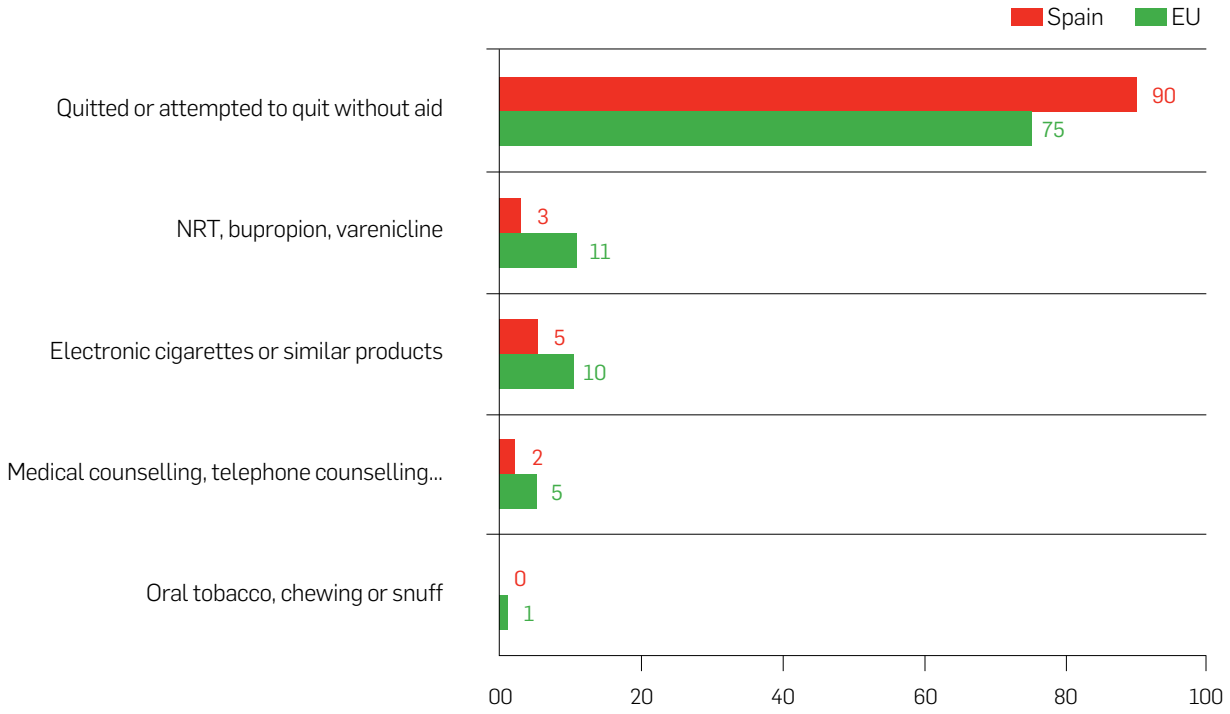
A significant proportion of smokers want to stop smoking and generally try quitting without any external support. In this case, clinicians can use "The 5 A's" protocol[12] to identify tobacco users and address smoking cessation at routine visits. The process includes: 1) asking and documenting tobacco use, 2) advising the patient to quit, 3) assessing the smoker's will to make an attempt and designing a strategy, 4) actively assisting the patient who wants to quit, and 5) arranging follow-up contacts.

When the smoker is not willing to quit, motivational counselling focussing on the relevance of this decision and the barriers to quitting should be provided. In case of failure, motivational counselling should be further provided. If necessary, the Richmond test is a simple instrument to measure patient's willingness to quit[13].

The level of tobacco dependence can be assessed using the Fagerström test or its simplified version[13]. The brief version consists of two questions on the number of cigarettes smoked per day and the time until the first cigarette of the day is consumed. These two variables have been demonstrated to have a good correlation[14].

In this phase, the question arises whether to set a target date to quit abruptly or by gradual reduction. Contradictory results have been obtained in this respect. A systematic review conducted in 2012[15] did not provide evidence of the superiority of a method over the other, whereas a more recent study appeared to favour quitting abruptly[16].

Figure 2. Method(s) used in smoking cessation attempts (%) (marking several options was allowed). Modified from Ref 3 (2017 Eurobarometer)



Similarly, two recent observational studies concluded that the duration of tobacco use better correlates with COPD than with the number of cigarettes smoked per year[17]. Furthermore, the excess relative risk for experiencing a cardiovascular event was already relevant in smokers who only smoked one cigarette per day[18].

Non-pharmacological therapy

A range of non-pharmacological smoking cessation therapies of different intensity and nature are available. These therapies can be implemented alone or in combination with pharmacotherapy. Cochrane has evaluated the specific contribution of many of these strategies, mostly 6 months after their implementation. Unfortunately, this follow up period is too short, as the risk of relapse more than six months after the attempt is very high.

Anti-smoking laws

Structural measures such as the anti-smoking laws 28/2005 and 42/2010 have been proven to have a significant health impact. Of note is the reduction in the rates of admission for heart attack, ischemic heart disease or asthma[19,20] and a lower exposure to second-hand smoke[21]. Cigarette sales fell by 55% per inhabitant/year in Spain and 40% in Navarre. However, cigarette sales have been stable since 2013 (Figure 1).

Smoking cessation without support

Most studies agree that 3-5% of smokers who quit without support will remain abstinent at 6 months. This is consistent with the scarce data available on abstinence at 12 months[22].

Brief medical counselling[23]

Assuming that abstinence is rarely achieved without support, brief counselling in a visit of less than 20 minutes in duration (± 1 follow-up visit at most) could raise the abstinence rates up to 5-6% [17 studies, RR=1.66 95%CI (1.42-1.94)]. Although the size of the effect is small, the benefit of the action is substantial considering the effort made.

Intensive individual[24] or group counselling[25]

Intensive individual counselling is defined as face-to-face interviews with a specialist in an environment different to that of a clinical visit. Intensive individual counselling has been reported to be slightly more effective than brief counselling [27 studies, RR=1.57 95%CI (1.40-1.77)], with abstinence rates of 7-9% at 6 months. No differences were observed between group therapy sessions and intensive individual counselling. In patients receiving NRT[26] an additional benefit of small magnitude was observed in patients who received intensive support [47 studies, RR=1.17 95%CI (1.11-1.24)]. A systematic review revealed a higher benefit when combining pharmacotherapy + intensive support as compared to brief counselling or less inten-

sive support [52 studies, RR=1.83 95%CI (1.68-1.98)][27]. Finally, combining intensive support + NRT yielded higher abstinence rates at six months compared to less intensive support (24.0% vs. 6.4%)[28].

Self-help material[29]
Abstinence rates slightly increase with printed self-help materials not tailored to the characteristics of the smoker as compared to no support [11 studies, RR=1.19 95%CI (1.04-1.37)]. Rates improve when tailored material is used, although the effects remain small (1% increase in abstinence rtes at 6 months). The combination of tailored materials with other strategies does not seem to increase their efficacy.

Telephone[30] **or Internet-based counselling**[31]
Telephone counselling has been documented to be as effective as intensive support methods, especially when it includes several calls and support is proactively provided. As studies on Internet-based interventions assessed abstinence at 4 weeks, their efficacy is less easily evaluated.

Electronic cigarettes
These electronic devices emit vaporized inhalable nicotine or non-nicotine solutions. The use of electronic cigarettes as a smoking cessation strategy attracts much attention for its a priori less toxic effect than tobacco. This devices are currently the subject of intense research[32]. Electronic cigarettes are used by a very small proportion of the population in Spain, mainly younger individuals[3]. The marketing, quality standards and safety of these products have been recently regulated by authorities[33]. A systematic review revealed some efficacy as compared to placebo, although most studies were observational[34]. However, some concerns have been raised in relation to these devices based on the lack of sufficient regulations, the absence of long-term evidence of their safety, the risk of them being an initiation to tobacco smoking, the hypothetical dual use of electronic and tobacco cigarettes, and relapse[35].

Other interventions[35]
Strategies such as physical exercise or anti-nicotine "vaccines" have not as yet been demonstrated to have any direct effect on abstinence rates. The use of mindfulness techniques for reducing withdrawal symptoms and craving are under study.

Another option to increase smoking cessation rates and improve health outcomes in smokers is using medications for that indication. Three options are available in Spain: NRT, bupropion, and varenicline. Below are some general descriptions and instructions for use. For more detailed information, please consult the European public assessment report.

The excess cardiovascular risk of smoking is relevant even when just 1 cigarette per day is smoked

After the implementation of tobacco bans, it has been demonstrated to have a significant impact on health

Nicotine replacement therapy

NRT consists of supplying nicotine at decreasing doses by a method other than smoking. The dose of nicotine is enough to ease the symptoms of nicotine withdrawal and ultimately leads to complete detoxification[13]. In Spain, four NRTs are available on the market: patches, gum, pills and oral inhalers[36].

Transdermal patches[37]
Patches are applied to the skin and slowly release nicotine through the skin. They are applied to clean, dry, hairless, healthy skin for 24 h. Every time a new patch is to be used, it must be applied to a different location of the body. Patches are available in forms that supply a constant dose of nicotine for either 16 hours -while the user is awake- or 24 hours. Patches are available at different doses to adjust the dose of nicotine during the treatment period, which has a maximum duration of 12 weeks. This form of therapy allows for the sustained release of nicotine, which facilitates compliance.

Nicotine gums[38]
Nicotine gums are a type of chewing gum that contains 2 or 4mg of nicotine, depending on the level of nicotine dependence. In monotherapy, the recommended duration of treatment is 3 to 6 months. The gum is chewed when the user needs to have a cigarette, up to a maximum of 15 4-mg pieces or 25 2-mg pieces per day. When chewed, the gum delivers nicotine to the body through the lining of the mouth. Nicotine swallowed with saliva inactivates and can cause stomach discomfort. The correct use is by chewing the piece slowly until it produces a tingling sensation or "peppery" taste. The piece is then tucked in between the cheek and gums. When the tingling ends the gum is chewed again. It is recommended to avoid consumption with acidic drinks such as coffee or soft drinks, which may interfere with nicotine absorption.

Nicotine lozenges[39]
Lozenges are available at doses ranging from 1 to 4mg, cannot be used for longer than 6 months, and range up to 30 tablets for the 1-mg option and 15 for the highest dose. As with nicotine gums, lozenges are chewed until a tingling sensation appears, then they are "parked" and when the tingling ends the lozenge is chewed again. The consumption of acidic foods and beverages should be also avoided.

Inhalers[40]
Like gums and lozenges, inhalers deliver a quick dose of nicotine. The formulation available in Spain allows up to 4 puffs per hour to a maximum of 16 hours of use per day. The user takes a shallow puff and inhales into the back of the throat. Deep inhalation must be avoided to prevent nicotine from entering the respiratory tract.

The efficacy of smoking cessation methods –pharmacological or not– should be evaluated by assessing health outcomes (reduction of mortality rates, cardiovascular events or tumours, to name a few). However, the efficacy of these strategies is generally reported in terms of abstinence duration over different time horizons[41]. Most studies and systematic reviews establish 6 months as the minimum follow-up period required to consider a smoking cessation strategy effective. However, in the light of the criteria established by the European Medicines Agency, this follow-up period is clearly too short[42]. Therefore, for a smoking cessation method to be proven to be effective, abstinence must be continued for at least 1 year.

What is the efficacy of NRT?

A systematic review (2012) of long-term studies which included more than 20,000 patients revealed that nicotine patches [21 studies, RR=1.51 95% CI (1.35-1.70)] and gums [32 studies, RR=1.43 95%CI (1.31-1.56)] are superior to placebo at 12 months follow-up. In absolute terms, abstinence was achieved in 14-16% of patients who used a NRT vs. 9-10% who received placebo[28]. Other studies report results for shorter follow-up periods of at least 6 months. As for active therapies, no differences were observed between 16-h and 24-h patches. In contrast, higher abstinence rates have been reported for 4-mg vs. 2-mg gums [5 studies, RR=1.43 95%CI (1.12-1.83)] and in the combination therapy of two NRTs vs. monotherapy with just one NRT [9 studies, RR=1.34 95%CI (1.18-1.51)]. However, other studies have not confirmed the efficacy of combined NRT therapies[43]. Furthermore, combined pharmacological therapies for smoking cessation have not been approved by health authorities.

In the systematic review mentioned above, no differences were observed between bupropion and varenicline[28]. Abstinence rates of 20-25% have been found in the few long-term follow-up studies performed to compare varenicline vs. bupropion[43,44]. The EAGLES study[45] –which was described in more detail below– showed statistically significant differences in favour of varenicline (22% vs. 16%), although follow up was only 6 months.

Although the magnitude of effect is small, brief counselling is beneficial in relation to the effort it involves

NRT is the first-line therapy due to its long-lasting effects and more acceptable safety profile

Extensive experience of use and very long-term results

The data available should be interpreted from a broader perspective. NRTs have been used for smoking cessation for decades, and more long-term data are available on these methods compared to other more recent options. A relevant meta analysis[46] was performed where studies with follow-up periods from 2 to 6 years were grouped. Although NRTs were found to have a significantly higher relative efficacy than placebo [OR=1.99 95%CI (1.50-2.94)], long-term abstinence decreased due to relapse. Thus, abstinence rates at 6-12 months decreased from 15% to 11% with NRT and from 7% to 4% with placebo. It should be considered that most trials on smoking cessation therapies are promoted and funded by the pharmaceutical industry, for which an impact on results has been demonstrated[47]. These facts should be taken into account when the efficacy of smoking cessation pharmacotherapies are evaluated in real life and the results of studies are interpreted[48].

In addition, well-designed studies have not been conducted on the therapy of choice following the failure of a NRT. In this context, bupropion and varenicline have not been proven to be superior to a new attempt with a NRT.

A therapy with an acceptable safety profile

The adverse events associated with NRT are generally mild and reversible[37,38,39,40]. Oral therapies can cause jaw pain, hiccup, or local discomfort at the site of absorption such as bucal mucosa irritation. Patches can cause pruritus and erythema.

Systemic effects may be similar to those of inhaled nicotine, although milder due to a lower blood concentration. The most relevant adverse events include stomach discomfort, sleep disorders, palpitations, headache, nausea, dizziness, sweating, myalgia or nervousness. It is not always easy to distinguish side effects from withdrawal symptoms. Finally, special attention should be paid to accidental use by children.

Based on all data revealed above, NRT is the therapy of choice (Figure 2). The same recommendation is valid for adolescents and pregnant women[35], although the efficacy of NRTs in the latter has not been conclusively demonstrated and nicotine gums or lozenges are preferred[49,50]. NRT can also be used to reduce the use of cigarettes, which increases the chances of success, although the quality of the evidence available is poor[51].

Bupropion

This amphetamine-based drug was initially marketed as an antidepressant. Since 2000, it is also indicated for smoking cessation. The maintenance dose is 150 mg every 12 h. for 7-9 weeks[52]. Smoking tobacco is allowed during the first two weeks of treatment. The dose must be adjusted in patients with renal or liver failure.

A systematic review (2014) of 12-month follow-up studies including 10,000 patients was performed. The study revealed that bupropion was superior to placebo [27 studies, RR=1.59 95%CI (1.44-1.76)], with an abstinence rate of 19% for bupropion and 11% for placebo[53]. Shorter-term comparative studies with other pharmacotherapies revealed no differences as compared to NRT[28,53]. In contrast, differences have been reported with varenicline [4 studies, RR=0.68 95%CI (0.56-0.83)]. In this study, the abstinence rate at six months was 15 % for bupropion and 22% for varenicline.

In the review on bupropion[53], the principal investigator declared that he had received payments from pharmaceutical companies that marketed smoking cessation medications. Cochrane's conflict of interest policy was later strengthened and this scenario is no longer permitted.

Once NRT has failed, there is no evidence that bupropion or varenicline are superior to another attempt with NRT

A therapy with a controversial safety profile

The most common adverse effects associated with bupropion include skin-related hypersensitivity, gastrointestinal disorders, dry mouth, insomnia, anxiety, headache, trembling and dizziness[52].

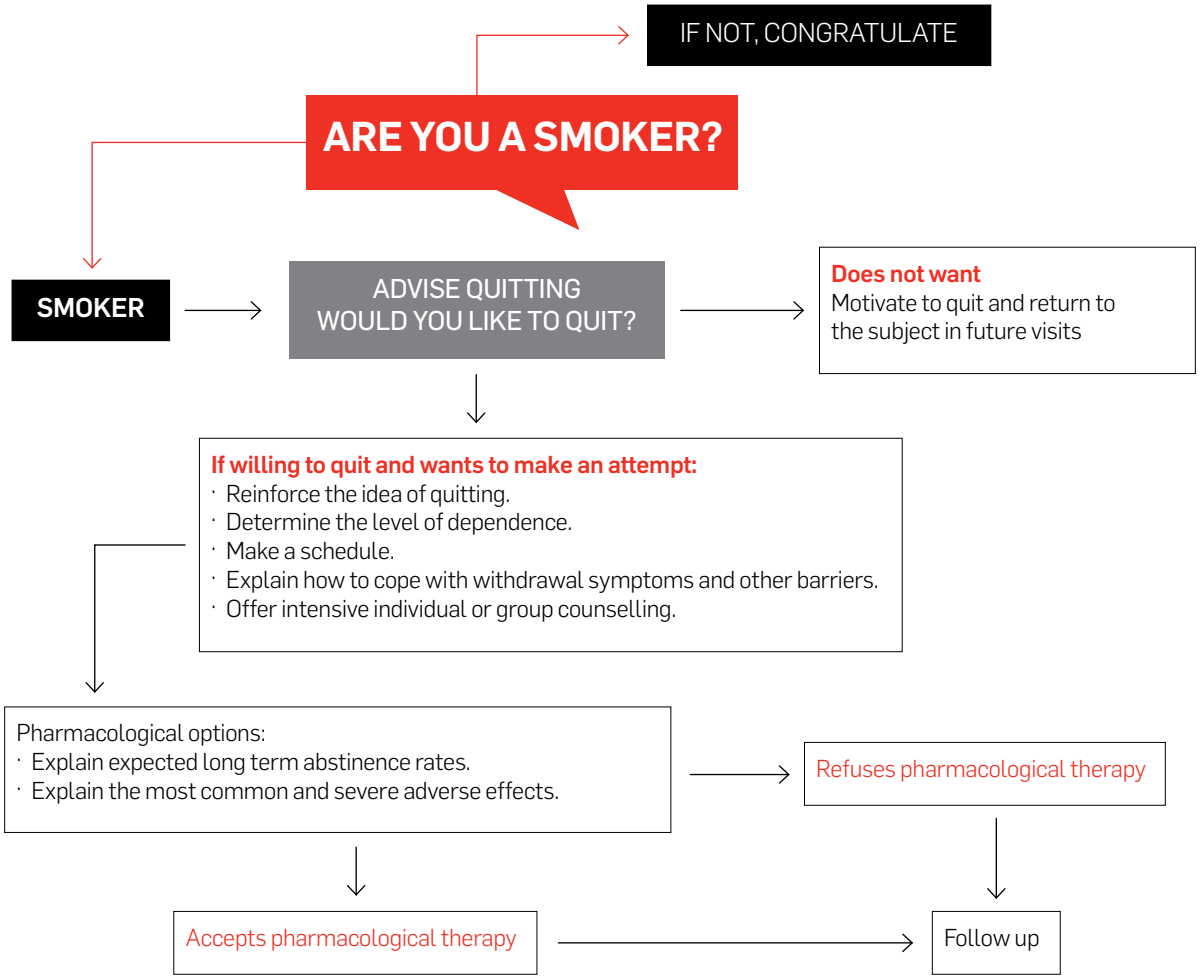
Rare adverse effects include increased blood pressure -occasionally severe- or seizures (1 in 1000 treated subjects) that are aggravated by concomitant alcohol abuse. Congenital cardiovascular malformations have been reported in neonates of mothers who used bupropion during gestation, especially during the first trimester of pregnancy[52,54]. Inconsistent results have been obtained in several observational studies conducted to assess the potential association between congenital malformations and bupropion use.

Finally, severe neuropsychiatric symptoms have been reported including hostility, agitation, depression and suicidal ideation and behaviour[52], symptoms which have also been documented for varenicline. In 2009, the Food and Drug Administration (FDA) included a warning on public information reports on these drugs[55]. Since then, numerous studies have been undertaken to shed light on these adverse effects. The EAGLES study[45] led authorities to lift this warning only partially, as the warning on the risk for suicidal ideation and behaviour is still in force for all antidepressants, including bupropion[56]. Further research is expected to be conducted[57].

Varenicline

The stop-smoking drug most recently approved in Spain (2007) is varenicline, a partial agonist of nicotinic receptors. The mechanism of action of varenicline eases craving and reduces the rewarding effects of smoking. The recommended duration of treatment is 12 weeks, with dose escalation the first week until a dose of 1mg/12 h. is reached. The dose must be adjusted in patients with renal failure. As with bupropion, smoking is allowed in the first two weeks[58].

Figure 2. Outline of a smoking cessation intervention in primary care (Adapted from recommendations of the Spanish Committee for the Prevention of Smoking (Ref. 2).



The most relevant data on the overall efficacy of varenicline were provided by a systematic review updated in 2016[59]. Sustained abstinence at 12 months of patients treated with varenicline is almost three times higher than with placebo and –as stated above (53) –is 50% higher than the abstinence achieved with bupropion (22% varenicline, 15% bupropion, 9% placebo). This review did not provide additional data on the efficacy of varenicline as compared to NRT beyond that which has been detailed above.

Preventing relapse in patients is crucial, as it is very frequent. Unfortunately, no strategies have been demonstrated to be significantly effective. A Cochrane review[60] cites a study on relapse prevention interventions based on varenicline that provided statistically significant differences vs. placebo [RR=1.18 95%CI (1.03-1.36)]. However, all study subjects were responders to the drug, baseline abstinence was short (12 weeks), 24 weeks of overall treatment were required, and the magnitude of effect at the end of follow-up was small. Also, it is worth mentioning the principal investigator of the systematic review was a co-author of this study[60]. Surprisingly, no declaration is made in the review that the study was financed by Pfizer, the manufacturer of varenicline.

Another therapy –one more– with a questionable safety profile

The most frequent adverse effect of varenicline is nausea, which is experienced by 30% of users, and which is modulated through dose titration. Other common adverse effects include insomnia, abnormal dreams, headache, dizziness, vomiting and other gastrointestinal disorders[61].

Controversy centres on severe rare adverse effects. The systematic review mentioned above[59] reports an excess relative risk of varenicline for serious adverse events of 25% as compared to placebo [29 studies, RR=1.25 95%CI (1.04-1.49)]. This parameter is widely accepted by scientists as suitable for the integration of the most relevant adverse events of a medication. In this case, high-quality evidence was provided, among other aspects, for the risk for infection, tumour or severe injury. Although the authors

considered that these adverse events were not probably related to the therapy, it should not be forgotten that data were obtained in randomized controlled trials where the effects of external factors are minimized.

Another controversial aspect is related to cardiovascular safety. In 2011, a meta-analysis of 14 studies involving more than 8,000 patients[62] attributed a low rate of relevant cardiovascular events to varenicline in absolute terms (1.06% with varenicline vs. 0.82% with placebo), but statistically superior to placebo [OR=1.72 95%CI (1.09-2.71)]. This study received criticism due to the type of statistical analysis performed.

Accordingly, the FDA asked Pfizer to conduct another meta analysis to evaluate the cardiovascular safety of varenicline[63]. The commissioned study published in 2013 revealed no statistically significant differences in terms of cardiovascular safety[63,64]. Although a third meta analysis was performed, concerns about the cardiovascular safety of varenicline have not been definitely resolved[65]. The design of the three reviews differed substantially[66] and a new observational study was recently published suggesting an excess risk for cardiovascular events related to varenicline[67].

It is striking that the fact that a regulatory agency requested the manufacturer of a drug to perform a study in which negative results would lead to the commercial failure of the product is accepted as natural. It would be more logical to resolve controversies on the safety of pharmaceutical products through research conducted by independent research institutes.

Neuropsychiatric adverse events: an agitated decade

Like bupropion, varenicline has been suspected of causing significant neuropsychiatric alterations such as depression, behaviour alterations, agitation, and suicidal ideation and behaviour. The FDA first warned of this potential association in 2007, and in 2009 incorporated the most relevant safety warning (Black Box Warning)[68]. Suspicions were based on a large number of spontaneous reports of adverse events associated with the use of varenicline[69,70]. Such reports are a relevant data source supporting hypotheses that need confirmatory evidence.

In recent years, several studies –two of them commissioned by the FDA– have been performed on neuropsychiatric adverse events linked to varenicline. Most studies had a retrospective cohort design or were reviews of previous studies. Generally speaking, no association was observed in these studies between varenicline and neuropsychiatric disorders[59].

In the most recent trial –EAGLES trial– the FDA commissioned the distributor of varenicline to assess its safety profile in patients with and without previous psychiatric disorders. A detailed analysis of the trial is provided below.

The limitations of the EAGLES study do not make it possible to draw definitive conclusions on the neuropsychiatric safety of varenicline and bupropion

Description of the "EAGLES" trial

This analysis is based on data from the article on the EAGLES trial published in The Lancet on April 22, 2016[45]. To the best of our knowledge, apart from the detailed and non-reader-friendly information provided at ClinicalTrials.gov (NCT01456936), the protocol of the study has not been published elsewhere and only a brief version of the Clinical Study Report (CSR) is available[71].

Throughout 2017, we contacted GSK and Pfizer – co-sponsors of the trial– for the provision of the study protocol, CSR, and anonymized data that allowed comparison of published results. Some months later, Pfizer asked us to provide a statistical analysis plan prior to evaluating our request. As preparing a statistical analysis plan would be time-consuming, we limited our request to the protocol and CSR, which should be publicly available without any further requirement. Unfortunately, we did not receive any response.

Main research question
In smokers with and without stable psychiatric disorders, are varenicline and bupropion associated with a higher rate of adverse neuropsychiatric events as compared to placebo?

Design
A randomized, multicentre, parallel-group, double-blind, triple-dummy study of 12 weeks of treatment and 12-week follow-up.

Setting
140 centres from 16 countries. In decreasing order by number of participants, the regions involved were North America (primarily the USA), several European countries, Latin America, Africa (only South Africa) and Oceania.

Inclusion and exclusion criteria
Adult smokers of at least 10 cigarettes per day willing to stop smoking. The cohort of patients with psychiatric disorders was composed of patients with stable schizophrenia, major depression, bipolar disorder, anxiety or per-

sonality disorder. Exclusion criteria were mental disorders other than the ones considered in the inclusion criteria, substance abuse, baseline suicidal behaviour and suicide risk, risk of seizures, severe COPD or recent cardiovascular disease.

Intervention
Between November 2011 and January 2015, 8144 participants were randomized to either the psychiatric (4,116) or the non-psychiatric cohort (4,028). In the two cohorts, subjects were assigned to a 1:1:1:1 ratio to four treatment arms, namely: varenicline 1mg/12h, bupropion 150mg/12h, nicotine patches 21mg/24h. with gradual dose reduction or placebo.

Outcomes
The primary endpoint was a composite variable of 16 neuropsychiatric symptoms based on reported cases of smokers who had used varenicline and bupropion. Symptoms were classified as mild, moderate or severe based on the estimated level of effect, except for four symptoms which were always considered severe (anxiety, depression, hostility and abnormal sensations). Secondary outcomes included the total number of severe adverse events and the outcome of every particular symptom. Cardiovascular safety data have not been published yet, while efficacy data were analyzed above.

Sample size
The rate of neuropsychiatric events in the placebo group was 3.5% for the non-psychiatric cohort and 7% for the psychiatric cohort. We estimated that a sample of 2000 subjects was required to detect a 75% increase in the rate of neuropsychiatric events. Safety analyses were performed taking into account the population treated in the study.

Results
Up to 79% of non-psychiatric patients and 74% of psychiatric patients completed the study. Of the latter, 71% met the criteria for mood disorder, 19% had anxiety, 9% had a psychotic disorder, and the remainder 1% had a personality disorder.
No differences were observed in the overall incidence of neuropsychiatric events for the four treatment arms (varenicline 4.0%; bupropion 4.5%; NRT 3.9%; placebo 3.7%). More neuropsychiatric events were reported in the psychiatric cohort (5.8%) than in the non-psychiatric cohort (2.1%) (Table 1). The percentage of severe neuropsychiatric events was lower in the non-psychiatric cohort, with no differences among treatment arms. In relation to the incidence of each symptom, the most common events were abnormal dreams in the varenicline and NRT arms as compared to placebo.

Authors' conclusions
The study did not show any significant increase in the incidence of neuropsychiatric events attributable to varenicline or bupropion as compared to NRT or placebo.

Research should be performed to identify the factors that led so many ex smokers to successfully stop smoking

Critical review of the EAGLES trial

The EAGLES trial was commissioned by the FDA, which approved the final design of the trial proposed by the pharmaceutical companies.

Conflicts of interest
The EAGLES trial was co-financed by Pfizer -manufacturer of varenicline- and GSK –distributor of bupropion. Six of the ten co-authors of the study worked for the two companies, whereas the other four were scholars from different universities, all of whom declared that they had received payments from the two companies[45]. More specifically, the principal investigator received increasing payments from Pfizer between 2013 ($2,030), through 2014 ($6,890), 2015 ($17,345) and 2016 ($52,685)[72]. Another investigator from the academic community signed the Cochrane systematic review on relapse prevention in smoking cessation while involved in the study[60].
Finally, statistical analyses were reportedly performed by employees of the two pharmaceutical companies, one of whom was a stakeholder of the company. Although FDA agents had the opportunity to review the entire dataset, other agents assumed control over key phases of the trial. This does not seem the most appropriate behaviour, particularly given that the Institute for Safe Medication Practices (ISMP) had reported a potential mala praxis of this laboratory in relation to reports to the regulatory agency[70,73].

Insufficient duration of the study
The EAGLE trial included a three-month follow-up period after the administration of the therapy. This follow-up period is inferior to that recommended by the EMA, where a follow up period of 6 to 12 months is established to explore potential psychiatric adverse events[42].

Insufficiently validated primary endpoint
The study design is based on this endpoint. The sample size was estimated as a function of this endpoint, at which outcomes can be accepted with more certainty. The estimator used in the EAGLES trial was designed by the

manufacturer of varenicline[74], which had not been previously validated. The incidence of neuropsychiatric events was assessed by a semi-structured 25 item interview conducted by a group of interviewers who subjectively determined the severity of events.
For example, regarding the symptom "hostility", it is striking that none of the 2,000 subjects assigned to the placebo group -i.e. exposed to withdrawal symptoms without any drug-based therapy- experienced a severe event of hostility. In sum, some doubt arises as to the ability of this composite endpoint to provide the information sought with the appropriate accuracy and reliability[73].

Insufficient statistical power

It is known that trials are designed so that low-incidence adverse events can be detected, taking into account the limited number of participants and the relatively short follow-up duration allowed. In the case of the EAGLES trial, its statistical power was calculated to rule out moderate to severe intensity neuropsychiatric events based on a relative risk of 1.75 for varenicline vs. placebo[75]. However, a much lower incidence of adverse events such as suicidal ideation are expected[73]. As no differences were found among the different treatment arms, no relevant information was obtained on the real magnitude of the incidence of severe adverse effects[76]. Considering reports on suicidal ideation in the psychiatric cohort, it is unclear whether statistically significant and clinically relevant differences would have been obtained with a higher power[76].

Limitations to external validity

The exclusion criteria used limit the external validity of the study, as patients with unstable psychiatric disorders or high suicidal risk –among others– were excluded[45]. Future research in patients with a broader profile is needed to ensure a favorable risk/benefit balance in patients with more complex psychiatric disorders[76]. Also, some of the recruitment methods employed were aimed at patients with a very specific profile that is scarcely representative of the average smoker. It should also be taken into account that light smokers using less than 10 cigarettes per day were also excluded.

FDA public assessments

Once the EAGLES trial was completed, the FDA held a meeting to decide whether the Black Box Warning included in public reports on varenicline should be removed or not. Although the Institute for Safe Medication Practices (ISMP) advocated maintaining the warning[73], after a tight vote –10 vs. 9–, it was decided to remove the warning[56]. However, the FDA and full members of the committee listed a large number of weaknesses of the study, namely: incomplete data on some events, underestimation of the severity of some adverse events, encoding problems, large heterogeneity unexplained by the rate of neuropsychiatric events by the participating centre, the lack of validation of the primary endpoint, and insufficient statistical power[75,76]. Nevertheless, the FDA label still recommends monitoring neuropsychiatric symptoms in patients treated with varenicline, including behavioural disorders, hostility, agitation, depression or suicidal behaviours.

Counterpoint: is (smokeless) life possible without medication?

We have provided so far scientific evidence supporting to a greater or lesser degree the use of pharmacological and non-pharmacological therapies by smokers who want to quit. However, some consideration should be given to the values of motivation and willingness. In his book "Man's Search for Meaning", the Austrian neurologist and psychiatrist Viktor Frankl affirms that people who have a why to life can tolerate any how. Similarly, some authors sustain the hypothesis that having a good reason to quit may be a more determinant factor than the smoking method employed[77].

This theory is supported by scientific evidence that 9 out of 10 smokers choose to quit without any external support[3]. This does not mean that smokers willing to quit do not need support; they need proactive assistance from health professionals. This assistance must be combined with more global approaches including tobacco taxes, bans/restrictions or public awareness campaigns[78].

Table 1. Results for the primary endpoint (neurophsychiatric adverse events) in the EAGLES trial.

	Events (n)	Total (n)	ARR (% [95% CI])
COHORT WITHOUT MENTAL ILLNESS			
TSN / Placebo	25 / 24	1006 / 999	[-0.21 (-1.54 to 1.12)]
Bupropion / Placebo	22 / 24	989 / 999	[-0.08 (-1.37 to 1.21)]
Varenicline / Placebo	13 / 24	990 / 999	[-1.28 (-2.40 to -0.15)]
COHORT WITH MENTAL ILLNESS			
TSN / Placebo	53 / 50	1016 / 1015	[0.37 (-1.53 to 2.26)]
Bupropion / Placebo	68 / 50	1017 / 1015	[1.78 (-0.24 to 3.81)]
Varenicline / Placebo	67 / 50	1026 / 1015	[1.59 (-0.42 to 3.59)]

ARR = Absolute risk reduction.

Although the efficacy of brief counselling and professional assistance of different intensities is unclear, these methods do not pose severe safety risks. The question is: What role should pharmacotherapies play? In accordance with the studies analyzed, pharmacotherapies seem to improve the chances of success, although their effect should not be overestimated. Thus, we should take into account that: 1) In trials, abstinence rates are calculated on the basis of a specific follow-up period which is often shorter than real time to relapse. 2) Blinding does not work appropriately, as many study participants can identify the drug used based on their effects. 3) Most trials were sponsored by the pharmaceutical industry, which correlates with better abstinence outcomes[78]. 4) Relapse after smoking cessation with or without aid is common, although it can help smokers in their next attempt. 5) Observational studies invalidate the hypothesis that higher abstinence rates are achieved with pharmacotherapy, although they have a low level of evidence[79].

From this perspective, we invite research institutes to further investigate the factors that have led so many ex-smokers to successfully stop smoking without any psycho-pharmacological aid. Similarly, we recommend that health professionals emphasize motivational factors that provide smokers willing to quit with solid whys. This would result in more frequent quit attempts that –after some probable relapses– would provide the smoker with the experience and learning necessary to definitively stop smoking[77].

Conclusions

Smoking is the most influential avoidable factor of related morbidity and mortality. Many smokers want and try to quit, most without external support. Health professionals can take advantage of visits for other reasons to explore the desires and expectations of smokers and motivate them to quit by providing active support.

Social-based smoking cessation strategies have been proven to have a greater and long-lasting impact. Nevertheless, tobacco consumption has not been eradicated yet.

Brief medical counselling and intensive individual or group counselling have been demonstrated to be somehow effective in increasing 6-month abstinence rates. However, their efficacy is insufficient, given the high risk of relapse. The efficacy and safety of electronic cigarettes requires further research.

The efficacy of nicotine replacement therapies (NRT), bupropion, and varenicline at 12 months is similar. When appropriate, NRT is the therapy of choice, given the consistent evidence on its long-term efficacy and more acceptable safety profile.

Varenicline and bupropion are suspected to cause rare but severe neuropsychiatric events. The results of the EAGLES trial contradict this hypothesis, but the use of a non-validated endpoint, its low statistical power, the weaknesses detected by the FDA and the evident conflicts of interest of the investigators of the study suggest that the results of this study should be interpreted with caution.

The evidence available on the role of psychopharmacological support in smoking cessation leads us to recommend that the pros and cons of the different methods be evaluated before making a therapeutic choice. The fight against smoking requires the adoption of courageous and global policies by public administrations, the active involvement of health professionals in terms of motivational aspects, and the belief by smokers that they can successfully quit smoking.

Annex 1: Contraindications in the labelling of pharmacotherapies indicated for smoking cessation.

Nicotine replacement therapy (patches)[37]
Non-smokers and light smokers
Children < 12 years

Bupropion[52]
Pregnancy
Children and adolescents < 18 years
Current seizure disorder or history of seizures
Patients undergoing quick withdrawal of drugs associated with seizures (e.g. benzodiazepines).
Central nervous system tumor
Patients undergoing abrupt alcohol withdrawal
Diagnosis of bulimia or anorexia nervosa
Severe liver cirrhosis
Concomitant use of monoamine oxidase inhibitors (MAOIs)
Patients with a history of bipolar disorder
Patients receiving other bupropion-containing therapies

Varenicline[58]
The use of varenicline during pregnancy should be avoided, as it has been demonstrated to have reproductive toxicity in animals.
Children and adolescents < 18 years
End-stage renal disease

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1138-1043

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Servicio Navarro de Salud / Osasunbidea
Plaza de la Paz, s/n
31002 Pamplona
T 848429047
F 848429010

E-mail
farmacia.atprimaria@cfnavarra.es

Web site
www.dtb.navarra.es