Centre for Evidence Based Medicine
University of Lisbon School of Medicine

Clinical Practice Guideline on Smoking Cessation

Inês Reis
Philip Fortuna
Raquel Ascenção
João Costa
António Bugalho
António Vaz Carneiro

CEMBE
Centro de Estudos de Medicina Baseada na Evidência
Faculdade de Medicina de Lisboa – Pisos 4/6
Av. Prof. Egas Moniz
1649-028 Lisboa
PORTUGAL
Tel. 217 940 424 or 217 985 135
Fax: 217 940 424
Email: cembe@fm.ul.pt
Web: www.fm.ul.pt/cembe

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1. Introduction

1.1 Epidemiology

Tobacco is produced in several areas of the world, and is legally marketed in all countries. The World Health Report 2002 refers that at least one third of all disease burden in industrialized countries of North America, Europe and Asia is due to tobacco, alcohol abuse, hypertension, cholesterol increase and obesity. In fact, more than three quarters of cardiovascular diseases (the main cause of global mortality) are due to high levels of cholesterol, tobacco, hypertension or their respective combination. Globally, hypercholesterolemia causes more than 4 millions premature deaths per year, tobacco around 5 millions and hypertension 7 million more.

Despite all efforts to reduce the selling and tobacco use, smoking is still increasing, side by side with the world population. Nowadays, more than 15 billion cigarettes are consumed per day and it is estimated that one third of the adult population has smoking habits[1].

The European Report for Tobacco Control, launched in 2007 by the World Health Organization (WHO), considers the prevalence of smokers (on a daily basis and age ≥ 15 years) within Europe of 28.6%, 40% men and 18.2% women. In young people under 15 the smoking habits prevalence (at least one cigarette per week) is estimated by WHO, in the study *Health Behaviour in School-aged Children* (2001/2002)[2], as 2% from 11 to 13 years, 8% at 13, and 24% at 15. The same study points out rates of prevalence in Portugal of around 18 % in boys and 26% in girls.

In our country the most recent data comes form the 4th National Health Enquiry (NHE) (conducted in 2005/2006), which estimates the smoking prevalence (daily, ages >10) in mainland as 19.6% (28.7% men and 11.2% women). In this geographical area there seems to exist a trend for a decrease in male smokers and an increase in women, already verified in previously conducted National Health Enquiries (1987, 1996, and 1998/1999). In Madeira region, the present estimate of smoking percentages is similar to the one found in the Continent. On the other hand, in Azores these proportions are higher: 24% overall, 36.4% men and 11.9% women. The 4th NHE was the first to include the whole national territory; therefore the Autonomous Regions do not have results corresponding to periods preceding 2005/2006. (National Health Enquiry 2005/2006).

Smoking has been identified as a major factor in diminishing health life expectancy and increasing mortality. Smoking is the main risk factor for premature death in Europe, being responsible for about 1.6 million deaths per year. It is estimated that within the European region of WHO, tobacco is the second more important risk factor, causing, in 2000, 12.3% of the total lost years due to premature mortality and Quality Adjusted Life Years (QALYs),

which equals the loss of around 18.6 million years of life. In 2002, in Portugal, tobacco was also the second more important risk factor, contributing to 10.4% of QALYs [3].

Lung cancer related mortality is still increasing in European countries. In spite of mortality rates due to lung neoplasia in women in Europe being lower than the ones found in men, the actual increase in tobacco consumption amongst teenagers and women is a worrying factor. Considering the time interval between the beginning of smoking habits and the disease manifestations, we can foresee an increase in cancer mortality in this group. The diminishing of the prevalence of tobacco consumption in European men, at least since 1980, has been reflected in the slight decrease noted in mortality rates due to this neoplasic disease in men since 1990.

Nowadays, in Portugal there is an increase in both genders of mortality rates due to respiratory system neoplasias. This fact is connected to the increasing of tobacco consumption amongst women in our country. The non-occurrence of a decrease in mortality rate in men due to these neoplasias is explained by the time lapse between beginning of smoking and its reflex in mortality and morbidity[3].

The price of tobacco to governments, employers and environment includes several kinds of costs such as social security and health systems, absenteeism, diminishing productivity, deflorestation and collection of cigarette-ends. In 1999, smoking was responsible for 6% of health expenses in the United States of America [1].

According to the Family Budgets Enquiry, conducted in our country in the year 2000 by the National Institute of Statistics, the family expenses with tobacco was around 749 euros (4.2% of the total expense). (*Information to the Media, INE, 220 – accessed in May 2007*).

The countries with lower Gross National Product (GNP) per capita present smoking prevalence rates that are higher than 50%, when compared to an average of 34% in richer countries. This fact is reverberated in the higher mortality rate due to tobacco consumption in countries with lower GNP, in individuals aged 35-69 years.

1.2 Tobacco and cardiovascular and/or cerebrovascular risk

Tobacco consumption is an independent risk factor to coronaropathy, cerebrovascular disease and atherosclerotic disease, contributing to the global mortality increase and due to cardiovascular causes [4].

The incidence of **acute myocardial infarction** (AMI) is increased six fold in women and three fold in men who smoke 20 of more cigarettes per day, comparing to individuals who never smoked. In the INTERHEART study, smokers represented 36% of the population at risk to the first AMI[5]. In spite of these data, more than 60% of 737 smokers did not believe they were at higher risk to this nosologic entity.

The risk of **ischemic stroke** also decreases, gradually, after smoking cessation. In a series including smoking women, the accumulated risk disappeared in two to four years after smoking cessation.

Among individuals with no known **coronariopathy**, the reduction of cardiac events associated to smoking cessation varies between 7% and 47%. The cardiovascular risk associated to tobacco smoke decreases shortly after smoking cessation and this tendency is stable during the time of the eviction. In a meta-analysis in which all patients had AMI, coronary artery bypass grafts (CABG), angioplasty or other coronary disease, the relative risk of mortality of smokers who stopped smoking comparing to smokers was 0.64, and this benefit was not affected by age, gender, cardiac index, nationality or year of the beginning of the study[6] .

Tobacco use before **CABG** does not affect survival after surgery, but smokers have an increased mortality risk by any cause (RR 1.68), cardiac death (RR 1.75) and need to repeat revascularization (RR 1.14) comparing to the ones who have stopped smoking at least a year before[7].

After **angioplasty**, persistent smokers face a greater risk of death (1.76) and of Q wave-AMI (2.08) comparing to the non-smokers, and an increased risk of death from any cause and for cardiac causes (1.44 and 1.49 respectively) when compared with the ones who have stopped smoking[8].

Among patients with **left ventricular dysfunction** (FE < 35%), tobacco increases the all cause mortality (RR 1.41 comparatively to non-smokers or ex-smokers) and the incidence of death and hospitalization due to cardiac failure or AMI (RR 1.39)[9].

1.3 Smoking, hypercholesterolemia and diabetes mellitus

Smoking is associated to an increase in serum concentrations of total cholesterol and VLDL cholesterol, and to an increase of insulin resistance, and diabetic patients who smoke have a greater difficulty in controlling glycemia, a greater risk for end stage renal disease and a diminished survival rate as soon as they begin dialysis[10].

In diabetes type 1 patients, tobacco smoke is independently associated with an increase in urinary albumin and non-proliferate retinopathy and, if smoking is discontinued, there is a decrease in the albuminuria to a level similar to the one found in non-smokers.

1.4 Tobacco and pregnancy

Smoking is the most important modifiable risk factor associated to a bad prognosis during pregnancy. The prevalence of tobacco use during pregnancy is around 10% - 20% (it varies according to the data collection method), although it seems to be decreasing slightly. It is estimated that, in populations with high smoking prevalence in women, cessation during

pregnancy might prevent 10% of perinatal deaths, 35% of low weight birth infants and 15% of pre-term labours. Furthermore, active and passive smoking increase the risk for infertility, placenta rupture, premature rupture of this membrane and placenta praevia.

The reduction in fetal oxygenation is the most studied physiopathological cause for the adverse effects of smoking in pregnancy; however, smoking may also damage the genetic material of the fetus, from the direct toxicity of the more than 2500 deleterious constituents of cigarettes.

A meta-analysis of 12 studies detected an increase of the risk of **infertility** in smoking women, relatively to the non-smokers (OR 1.60) and studies in women submitted to *in vitro* fertilization (IVF) have also shown a reduction in the fertility of smokers, the pregnancy rate by number of cycles, in IVF treatment, being significant smaller in this group (OR 0.66)[11].

All pregnant women who smoke have 1.5 to 3.5 times greater probability of having a **low birth weight fetus (LBWF** < 2500 g), and this risk increases with the number of cigarettes consumed. The weight deficit associated to a smoking mother varies between 200 to 300 g. At least 20% of all LBWF are attributable to tobacco exposition during pregnancy, and smoking in the third trimester seems to have a greater impact in this pathology[12].

There is significant evidence that smoking over 10 cigarettes per day may be associated with an increase in the number of **spontaneous abortions**, with a RR of 1.2 to 3.4. Large case-control and cohort studies have shown RR of **fetal death (after 28 weeks of gestation)** of 1.2 to 1.4 in smoking women, with larger risk with heavy smoking. A prospective study has shown, furthermore, that non-smoking women passively exposed to tobacco smoke are at greater risk of intra-uterine death than the ones not exposed (OR 1.53). There is a considerable increase in the risk of preterm premature rupture of membranes (PPROM) amongst smoking women, with a RR of 1.9 to 4.2. Smoking also increases the risk of abruptio placenta with an adjusted relative risk described from 1.4 to 2.5 and has been constantly associated with the occurrence of **placenta praevia** with RR between 1.4 and 4.4.

Pregnant smoking women have 1.3 to 2.5 times a greater probability of having a **pre-term delivery**, particularly before the 32nd week of gestation. It should be noted that smoking and drug abuse are frequently the only potentially modifiable risk factors associated to this intercurrence.

It is not clear yet that smoking effectively increases the risk of **congenital malformations** but the risk of **neonatal death** (in the first 28 days of life) seems increased in smoking women, with RR 1.2 to 1.4 and the **sudden infant death syndrome** has been constantly associated to maternal smoking, with a relative risk of children exposed in utero or during post natal life of 2.0 to 7.2. It has been suggested that pre natal exposure is a greater risk factor than the exposure to passive smoke during childhood at home. Furthermore,

as it was mentioned above, smoking increases other risk factors known as SIDS such as pre term delivery and low birth weight.

The *British Child Development Study* data suggests that maternal smoking habits during pregnancy are associated to an increased risk for **DM2** in offspring from 33 years of age on[13].

Maternal smoking may also have long term implications in the exposed reproductive healthof the offspring. Adult men subjected to tobacco exposure in utero seem to have a 25% reduction of total count of spermatozoids comparatively to the non-exposed, and it was also suggested that there is a possible relationship between reduced feminine fertility and pre natal smoking exposure[14].

Also associated to maternal smoking is a precocious abandon of maternal lactation and other morbidities such as respiratory infections, asthma, otitis media, colic, bronchiolitis, small height, lower scores of reading and speech, lower levels of attention, hyperactivity, school obesity and lower school performance.

Finally, it should be mentioned that, in spite of the existence of meta-analysis that show a significant reduction of **preeclampsia** risk in smoking pregnant women (OR 0.51), this benefit does not supersedes the many clinical and obstetric problems previously described[15].

All the risks mentioned above are insufficient to motivate cessation, and it is estimated that only 20% to 40% women stop smoking completely during pregnancy, and the majority does so before the first pre natal visit.

1.5 Smoking and pulmonary disease

Smoking alters the structure and function of central and peripheral airways, parenchyma, capillaries and pulmonary immunological system, producing an increase of respiratory symptoms amongst smokers. The increase risk of several kinds of **respiratory infections** it is a well known fact, and smoking is an important factor to the development of invasive pneumococcal disease in non elderly immunocompetent adults. Furthermore, it seems to increase the incidence of death due to tuberculosis.

Active smoking is by far the most important risk factor to **chronic obstructive pulmonary disease (COPD)**, being responsible to 80% to 90% of the risk of developing this disease. It is also recognized that smoking is associated to a doubling or tripling of decline rate in FEV_1, and a 2 to 20 times increase in the death risk by COPD[16].

Tobacco is the main cause to the development of **lung cancer (LC)**. It is estimated that smoking is responsible for about 87% of LC cases, and it should be underlined that LC is the most common death cause by neoplasia in the world. Estimates of RR by LC in long time smokers, compared to non-smokers, vary from 10 to 30 times[17]. The cumulative risk for cancer is proportional to the total consumption of cigarettes, and it can attain 30% in

smokers with marked smoking load, comparatively to the risk, lower or equal to 1%, expected during the life of a non-smoking person[17]. Smoking cessation clearly decreases the LC risk of ex-smokers, when compared to active smokers. The size of this reduction is evident after 5 years from the beginning of eviction and varies between 20 and 90%, according to the duration of the abstinence. In smokers who are not able to stop smoking, the reduction might have some effect in the reduction of LC risk. Epidemiological studies have shown that non-smokers exposed to high levels of tobacco smoke present an increased risk of LC when compared to lesser cumulative exposures, and there is a dose-response relation between the intensity of the exposure and the relative risk (as will be referred in the passive smoking chapter).

Strong associations between smoking and the development of **other neoplasias** (e.g. cancer of the mouth, larynx, oesophageal cancer, cancer of the bladder, renal cell cancer, cancer of the pancreas, gastric cancer and cervical cancer) have been found, although the risk is not as high as the risk for LC. The manifestation of a second neoplasia connected to tobacco is more likely to occur when there is a previous history of one of the mentioned malignant tumours[18].

1.6 Passive smoking

Nowadays, 1.3 billion adults in the entire world are smokers, meaning that passive smoking, defined as the involuntary exposure of the non-smokers to the tobacco smoke of active smokers, is inevitable for children or for the 2/3 of non-smoking adults.

The *2006 US Surgeon General's Report* confirms, explicitly, that any exposure to tobacco smoke is harmful to human health. Several assessments of nicotine levels conducted during the last decades show that passive smoking has been largely prevalent in working places and homes. **Lung cancer** has been increasing in non-smokers, and there are around 10.000 cases per year, from which it is estimated that about 2.000 to 3.000 are caused by passive smoking, probably connected to the continuous exposure to tobacco carcinogenic components, with the influence of genetic factors not being excluded. A meta-analysis, including 52 trials, has shown a relative risk of LC for non-smokers exposed to passive smoking of their partner of 1.21, and other – which included 25 trials – referred that the relative risk in the working place was 1.22[19].

As far as **cardiovascular disease** is concerned, it is estimated that passive smoking is responsible for about 40.000 deaths due to cardiac disease every year in the United States of America[20] and a meta-analysis of the trials conducted to examine the association between passive smoking and coronary disease (CD) estimated an excess of risk for CD of 27% in passive smokers[19]. It was also shown in a study including 60.377 women in

China, that there is an association between **stroke** and their active smoking husbands.

In 2005, the Environment Protection Agency in California established that 22.700 of the 69.000 deaths due to CD in 2000 were caused by passive smoking. The *2006 Surgeon General's Report* refers a 25 to 30% increase in CD risk due to passive smoking[19].

Of the few data existent on the association between **global mortality** and passive smoking, it was suggested an increase of about 15% in the mortality of non-smokers living with smokers, comparative to non-smokers living in a tobacco free household.

Although there is no scientific evidence of exceptional quality yet, all available data suggests that there are clinically relevant consequences due to passive smoking in adults with **chronic respiratory disease**.

Multiple reports in public health have identified specific risks associated to **infant passive smoking**. In an inquiry involving around 17.448 children in the USA, it was seen that children exposed to passive smoking had, in average, two more days of activity restriction, one more day bed driven and 1.4 more days of school abstinence than the non-exposed[21]. Children whose parents are smokers present an increased risk of diseases of the lower respiratory tract (the risk is increased in 50% if both parents are smokers), including a significantly increased frequency of bronchitis and pneumonia during their first year of life. The exposure to passive smoking during childhood is associated to a greater prevalence and seriousness of infant asthma and expression of the latter in adulthood. It is known that the smoking from parents harms the development of pulmonary function during childhood and that there is an association between that exposure and the occurrence of medium otitis.

Passive smoking in healthy non-smoker teenagers may be associated to lower levels of HDL cholesterol and the relation between total cholesterol / HDL cholesterol. There is also increased evidence pointing out that passive smoking influences future cardiovascular risk in children[22].

1.7 Other forms of smoking

Epidemiologic studies have shown that cigarette brands that contain less tar coal and nicotine reduce LC risk only marginally. Likewise, there was only a small difference in the mortality rate between smokers of filter and non-filter cigarettes[18].

Cigar smoke contains the same toxic and carcinogenic compounds found in cigarette smoke and the individuals who smoke four or more cigars per day are exposed to a smoke amount equivalent to 10 cigarettes. Even those who do not inhale cigarette smoke are subject to their own environmental smoke. Cigar use is related to an increase of LC risk, apparently less important than the one found with cigarette use (RR 2.1 and

5.1 in two different trials), the threshold from which the LC risk increases not being defined yet[23].

Pipe tobacco use also increases LC risk, being this similar to the one referred to the use of cigars.

2. Topic / Disease

The disease referred to in this CPG is tobacco dependence, regardless of the way it is used (cigarettes, cigars, cigarillo, pipe, chewed, etc.).

3. Objectives

The purpose of the present CPG is to provide recommendations based in scientific evidence relating to the use and dependence of tobacco treatment.

4. Category

This is a CPG of therapeutic effectiveness.

5. Adaptation

This CPG was not directly adapted from any recommendation, protocol, consensus or CPG published to date. It comes, partially, as an update of the "Clinical orientation guideline to the treatment of tobacco use and dependency" developed by the Institute of Quality in Health (IQS) and CEMBE in 2002.

6. Target population

All users or individuals exposed to tobacco, regardless of gender and age.

7. Potential users of this CPG

- Doctors (family doctors, occupational medicine, internal medicine, cardiology, pneumology, obstetrics, paediatrics, etc.)
- Dentists
- Nurses
- Psychologists
- Pharmacists
- Others.

8. Sources of scientific methodology

The methodological sources of scientific evidence used as basis for this CPG include articles, books and Internet pages of specific organizations. These sources are common to all CPGs, and are included here as information to the users who wish to elaborate this type of documents. It is important to underline that only the ones deemed fundamental by the authors of the present CPG are presented, so the list is, by definition, incomplete.

8.1 Articles Published in Journals or Electronic Databases

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- Australian Government National Health and Medical Research Council: www.nhmrc.gov.au

- Clinical Knowledge Summaries (CKS) Prodigy Guidance: www.cks.library.nhs.uk

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- Institute for Clinical Systems Improvement: www.icsi.org

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- National Institute for Health and Clinical Excellence: www.nice.org.uk
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- Canadian Medical Association Infobase: mdm.ca/cpgsnew/cpgs/index.asp
- Canadian Task Force on Preventive Health Care: www.ctfphc.org
- Guidelines Advisory Committee: www.gacguidelines.ca
- Public Health Agency of Canada guidelines: www.phac-aspc.gc.ca/dpg_e.html
- New Zealand Guidelines Group: www.nzgg.org.nz
- NHS Health Technology Assessment Programme: www.hta.nhsweb.nhs.uk/index.htm
- Scottish Intercollegiate Guidelines Network: www.sign.ac.uk
- Trip Database: www.tripdatabase.com/index.html
- United States Preventive Services Task Force: www.ahrq.gov/clinic/uspstfix.htm

9. Methods for scientific evidence selection

The sources of scientific evidence used as basis for the present CPG include articles, books and Internet pages of specific organizations.

By means of identifying the main randomized and controlled clinical trials, meta-analysis of clinical trials, systematic reviews and clinical practice guidelines that would allow to answer the question on the interventions that promote smoking cessation, we developed a research strategy that was based on the following electronic databases:

- Medline (www.pubmed.com) (1966-3/2007)
- Cochrane Central Register of Controlled Trials (in Cochrane Library issue 1, 2007)

- Cochrane Database of Systematic Reviews (in Cochrane Library issue 1, 2007)
- Database of Abstracts of Reviews of Effectiveness (in Cochrane Library issue 1, 2007)

The research strategy developed for the 4 first mentioned databases was the following:

#1. *Smoking Cessation* [MeSH]
#2. *Tobacco Use Cessation* [MeSH]
#3. *Smoking/drug therapy* [MeSH]
#4. *Smoking/therapy* [MeSH]
#5 OR/1-4

We applied research filters to the results to identify all randomized clinical trials, meta-analysis of clinical trials, systematic reviews and guidelines. Only the trials in adult population (over 18) were considered and they had to be published in Portuguese, French or English. We obtained the synopsis of all the trials identified by the research strategy, in order to select which ones should be included in the analysis. This selection was made by 3 people. After decision was made on which trials to include, the complete publications were requested to be analysed. The research strategy also included the list of references included in the identified trials.

The selection of the scientific evidence was made – additionally – in secondary sources of information, which are defined as the ones that, having selected the articles, papers and trials in the primary databases (Medline, EMBASE, CINAHL, for example), perform critical evaluation of their quality, based on their methodological structure, selecting only those that, through its validity, importance and relevance to clinical practice constitute the evidence considered as the most valid (see below). The base criterion was that the referred sources of secondary scientific evidence were undoubtedly based on scientific evidence and available in printing (journal articles, books) and/or electronically (Internet).

For the final revision, the following secondary sources were included:

- ACP Journal Club
- ACP Medicine
- Agency for Health Care Research and Quality
- Bandolier
- Clinical Evidence
- DynaMed
- Evidence-Based Medicine
- Evidence Based Practice
- Guideline International Network

- InfoPoems
- PIER from ACP
- Scottish Intercollegiate Guidelines Network
- UpToDate.

10. Methodology of critical evaluation of scientific evidence

A critical evaluation of the evidence - in terms of its validity, importance and applicability of the results - was an essential step in the scientific basis for the preparation of this CPG. Indeed, without a guarantee of quality and scientific methodology of the studies that form the basis of the CPG, the consistent statement of the conclusions could be questioned. The following tables formed the guides to critical evaluation, specific for the type of studies we wanted to examine: in this case, only clinical trials and systematic reviews.

These tables are built up upon questions – *guides* – (primary and secondary), that the trials under review had to respond in detail, so they could be included (or not) in the final analysis and thus serve as scientific basis to this CPG. The review process involved one of four types of possible answers for each guide: **yes, unclear/possibly, no** or **not applicable**. To each of these responses a numerical value of 2.1 or 0 was assigned (table 10.1).

TABLE 10.1 – Codification of responses

Highlight the appropriate code:	2 – Affirmative response = yes 1 – unclear / possibly 0 – negative response = no n/a – not applicable

Each article was then sorted by a score, composed by the sum of all the scores assigned to individual guides, standard for the No. of issues applicable to the specific study, and the final classification was the ratio between the total score and the maximum applicable (Table 10.2).

TABLE 10.2 – Calculation of the final classification of articles

Total score (sum of the assigned scores) _____	[A]
No. of issues applicable (max. 20) _____	[B]
Maximum possible score (2 x B) _____	[C]
FINAL STANDINGS (A/C in %) _____	%

Subsequently, an "evidence table" was built, on which each article was individually included for the final analysis (table 10.3).

TABLE 10.3 – Calculation of the final standings of the articles

Trial (authors and year)	*Design*	*Participants*	*Intervention and comparison*	*Results*	*Final scores*

Only the articles with the higher scores were included in the final database of evidence for the present CPG.

TABLE 10.4 - Grid to the critical evaluation of an article describing a prospective, randomized and controlled clinical trial

VALIDITY OF RESULTS	**Y**	**?**	**N**	**n/a**
1. Was the range of patients well defined?	2	1	0	n/a
2. Was the disease diagnosis well characterized?	2	1	0	
3. Are the inclusion and exclusion criteria logical and clear?	2	1	0	n/a
4. Were the patients randomized?	2	1	0	
5. Was randomization blind?	2	1	0	n/a
6. Were the patients analyzed in the groups for which they had been randomized initially (intend-to-treat)?	2	1	0	n/a
7. Was the randomization method explained?	2	1	0	n/a
8. Was the size of the sample statistically calculated?	2	1	0	n/a
9. Were the patients in comparison groups similar in terms of known prognostic factors?	2	1	0	n/a
10. Except for the study drug, were all patients treated the same way?	2	1	0	n/a
11. Were the patients blinded regarding the group they were included into?	2	1	0	n/a
12. Were the investigators blinded regarding the study groups?	2	1	0	n/a
13. Were the data analyzers blinded regarding the study groups?	2	1	0	n/a
14. Was final follow-up higher than 80%?	2	1	0	n/a
IMPORTANCE OF RESULTS				
15. Was the therapeutic effect dimension (RRR, ARR and NNT) important?	2	1	0	n/a
16. The effect estimate is precise enough (CI)?	2	1	0	n/a
17. Does that effect have clinical relevance?	2	1	0	n/a
APPLICABILITY OF RESULTS				
18. Are the study patients similar to the clinical practice of the individual doctor?	2	1	0	n/a
19. Were all important clinical results considered?	2	1	0	n/a
20. Do treatment benefits over impose to potential risks and costs of implementation?	2	1	0	n/a

Table 10.5 - Grid to critical evaluation of a systematic review

VALIDITY OF RESULTS	Y	?	N	n/a
1. Is the review centered on a clearly focused clinical issue?	2	1	0	n/a
2. Are the inclusion (and exclusion) criteria for studies in the SR appropriate?	2	1	0	n/a
3. Have all important and relevant studies been included?	2	1	0	n/a
4. Was the quality of the included studies correctly evaluated?	2	1	0	n/a
5. Were the critical evaluations of the studies reproducible between the evaluators?	2	1	0	n/a
6. Were the studies' results similar between them?	2	1	0	n/a
IMPORTANCE OF RESULTS				
7. What are the global results of the SR?	2	1	0	n/a
8. What is the precision of the SR results?	2	1	0	n/a
APPLICABILITY OF RESULTS				
9. Can the SR results be applied to our patients?	2	1	0	n/a
10. Were all clinically relevant outcomes duly considered, in view of the question?	2	1	0	n/a
11. Do benefits of the practical application of results compensate potential damages and costs?	2	1	0	n/a

11. Hierarchy scheme for scientific evidence

The hierarchy system for scientific evidence used in the present CPG was based in the recommendations of the *Centre for Evidence-Based Medicine*, Oxford, United Kingdom. Nevertheless it is important to mention that this system is not very different from the one that has been developed internationally, named GRADE[24]. In this CPG we used an adaptation of this system[25], with recommendations good (level 1) or bad (level 2) quality, according to the kind of scientific evidence it is based on, and this evidence is classified with several levels of descending quality, raging from A to D. As such, and for the purpose of the present document, a recommendation graded as level A is considered to be based on high quality evidence, while a level D recommendation only presents low quality evidence.

TABLE 11.1 - Levels of evidence and therapeutic or preventive recommendation degrees

Degree of Recommendation	Level of evidence	Methodological analysis
A	1a	SR* (with internal homogeneity†) of RCTs§
	1b	Individual RCTs (with short CI#)
	1c	All or none¶
B	2a	SR (with internal homogeneity †) of cohort studies
	2b	Cohort individual studies (including low quality RCTs§, e.g. < 80% follow-up)
	2c	Outcomes research §§ and ecological studies
	3a	SR* (with internal homogeneity†) of case-control studies
	3b	Individual case-control studies
C	4	Series of cases (as well as cohort and case control low quality studies**)
D	5	Expert opinion with no previous explanation of the critical evaluations of evidence methodology, o based in basic investigation (extrapolations), or of "primary principles"††

Notes referring to tables

CI: confidence intervals
§ **RCT**: randomized controlled trials
§§ **Outcomes research**: consists in cohort studies with patients with identical diagnosis (stroke, AMY, etc.) which relate their clinical outcomes, whether mortality, morbidity, events, etc., with the received medical care (aspirin, surgery, rehabilitation); this kind of investigation does not use RCT and therefore it is impossible to rate as effective a certain therapeutic manoeuvre. The advantage of this approach is that it allows recognizing if the expected outcomes correspond to the ones found in daily clinical practice.
† **Homogeneity**: low level of heterogeneity in the direction and magnitude of the result of the clinical trials included
††By **primary principles** we consider the physiopathological concepts which preside to medical practice (e.g. blood pressure control in patients with aorta dissection); obviously, these principles, if not tested in rigorous trials, may sometimes lead to wrong practices.
* **SR**: Systematic review: a SR is a literature and scientific review on a certain subject, done in such a way that all biases are reduced to a minimum. The fundamental characteristic of a systematic review is the clear and non-ambiguous explanation of the criteria used on the selection, critical evaluation and inclusion of evidence. As such, a systematic review presents formal and precise objectives, and the inclusion (and exclusion) criteria for the studies are thoroughly explained. The systematic review does not usually present any determined graphic representation.
¶ when all the patients died before the treatment was available, but some of them now survive with it; or when some patients died before the treatment was available, but none now dies when using it.

As it was clear from the previous tables, the recommendation degrees include four levels, in decreasing order of validity (A, B, C and D). Table 11.2 summarizes them, according to the underlying type of clinical trial.

TABLE 11.2 – Degrees of recommendations

A	• Consistent level 1 trials
B	• Consistent level 2 or 3 trials or extrapolation of level 1 trials
C	• Level 4 trials or extrapolation of level 2 or 3 trials
D	• Level 5 trials or inconsistent / inconclusive at any level

12. Methods of analysis and scientific evidence validation

12.1 Included studies

12.1.1 Pharmacological interventions

12.1.1.1 Nicotine replacement therapy (NRT)

West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. Psychopharmacology 2001; 155(2):115-122

Systematic review of 12 clinical trials that concluded, with high degree of evidence, that the oral nicotine dosing forms have reduced the discomfort, irritability and anxiety caused by smoking cessation. It also demonstrated that there is some evidence that these nicotine replacements have a beneficial effect in the decrease of depressive humour and smoking craving.

Hughes JR, Shiffman S, Callas P, Zhang J. A meta-analysis of the efficacy of over-the-counter nicotine replacement. Tobacco Control 2003; 12(1):21-27.

Systematic review whose results have shown that the over-the-counter nicotine replacement therapy has a wider effect in smoking cessation comparing to placebo (OR 2.5, CI 95%, 1.8 to 3.6) and that it produced smoking cessation rates similar, although inferior, to the prescription nicotine replacement therapy (OR 1.4, CI 95%, 0.6 a 3.3).

Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women. Journal of Consulting and Clinical Psychology 2004; 72(4):712-722.

This meta-analysis, which included 21 RCTs, showed that the long term benefits of nicotine replacement therapy decreased more rapidly in

women than in men. The association of intensive non-pharmacological support to pharmacological therapy seemed more important in women.

Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 3

Systematic review of 103 studies showed that all marketed forms of nicotine were effective in smoking cessation. The OR for abstinence with nicotine replacement therapy, compared to control, was of 1.77 (CI 95%, 1.66 to 1.88). In highly dependent smokers (Fagerström score >7) it was shown that the 4 mg gums were more effective than the 2 mg ones. The indirect comparison between the different kinds of nicotine replacement therapy did not reveal a significant difference in their efficacy. There is low evidence that the combination therapy with different forms of nicotine replacement therapy is more effective comparing to the isolated use of one formula. The efficacy of nicotine replacement therapy seems independent of the duration or the context in which the therapy was administrated, as well as the degree of additional support provided to the smoker.

Etter JF, Stapleton JA. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. Tobacco Control 2006; 15(4):280-285.

Meta-analysis, including 12 RCTs, that evaluated the effect a unique course of nicotine replacement therapy in smoking cessation, at the end of 2 to 8 years. The favourable OR to the nicotine replacement therapy, versus control, was of 1.99 (CI 95% 1.50 to 2.64). There was no evidence that the effect varies according to the follow-up time (2 years minimum and 8 years maximum) or the duration go therapy. The rate of global relapses after 12 months was 30.0% (CI 95% 23.5 to 37.5%) which represents an overestimate of the benefit and cost-efficacy relative of nicotine replacement therapy when the abandon rates are only evaluated at 6 and 12 months. Most relapses of tobacco use, after the first 12 months of cessation, occurred during the first or second year, and they were not detectable afterwards.

12.1.1.2 Antidepressants

Scharf D, Shiffman S. Are there gender differences in smoking cessation, with and without bupoprion? Pooled - and meta-analyses of clinical trials of Bupoprion SR. Addiction 2004; 99(11):1462-1469.

Meta-analysis of 12 RCTs that has shown that slow release bupoprion effectively helps smoking cessation compared to placebo (OR 2.49 CI 95% 2.06 to 3.00), with the benefit of this drugs similar in both genders. On the

other hand it was seen that women generally have an inferior success rate in smoking cessation regardless of the treatment used.

Wagena EJ, Knipschild P, Zeegers MP. Should nortriptyline be used as a first-line aid to help smokers quit? Results from a systematic review and meta-analysis. Addiction 2005; 100(3):317-326.

Systematic review and meta-analysis where nortriptyline has shown a significant superior rate of tobacco abstinence, after 6 months, than placebo, with RR 2.4 (CI 95% 1.7 to 3.6), and RD 0.11 (CI 95% 0.07 to 0.15). There was a lesser rate of smoking cessation with nortriptyline compared to bupoprion, but this difference was not statistically significant. The use of nortriptyline in smoking cessation proved to be well tolerated and safe.

Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2007; Issue 1.

Systematic review which included 53 RCTs, comparing antidepressant drugs and placebo or other therapies for smoking cessation. It was demonstrated that bupoprion and nortriptyline helped long term smoking cessation and that, when used in monotherapy, double the rate of eviction (OR 1.9, CI 95%. 1.72 to 2.19 and OR 2.34, CI 95%. 1.61 to 3.4 respectively), with adverse effects rarely serious or a cause to stop the treatment. When comparing bupoprion versus nortriptyline, a benefit was found, although not statistically significant (OR 1.43, CI 95%, 0.9 to 2.27). Both drugs seem to be equally effective and have shown similar efficacy as nicotine replacement therapy; nevertheless, there is no evidence that they provide an additional long term benefit when used concomitantly with nicotine replacement therapy. There was no significant long term benefit with prolonged use of bupoprion to prevent a consumption relapse. Concerning selective serotonin recapture inhibitors, there was no evidence of a facilitator effect in the smoking cessation.

12.1.1.3 Nicotine receptor partial agonists

Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. BMC Public Health 2006; 6:300.

Systematic review to study the relative efficacy of the different available therapies to smoking cessation (nicotine replacement therapy, bupoprion, varenicline), using as primary result the cessation at 12 months. All the methods displayed therapeutic effects. When directly and indirectly compared, bupoprion was not superior to nicotine replacement therapy (OR 1.14, CI 95% 0.20 to 6.42 and OR 0.92, CI 95%, 0.64 to 1.32, respectively) and, on the other hand, varenicline was superior to

bupoprion (OR 1.58, CI 95% 1.22 to 2.05) in smoking cessation at 12 months. In an indirect comparison, varenicline was superior to nicotine replacement therapy when confronted with placebo (OR 1.66, CI 95% 1.17 to 2.36, p=0.004) or with controls (OR 1.73, CI 95% 1.22 to 2.45, p=0.001) at the end of 12 months.

Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2007; 24(1):CD006103.

Meta-analysis proving that varenicline increases long term smoking cessation rates (12 months) compared to placebo (OR 3.22, CI 95%, 2.43 to 4.27) or bupoprion (OR 1.66, CI 95%, 1.28 to 2.16). Nevertheless, there is no clear evidence of its efficacy in the prevention of a relapse. The main adverse effect of varenicline was nausea (mild to moderate degree, decreasing with the drug habituation).

12.1.1.4 Anxiolytics

Hughes JR, Stead LF, Lancaster T. Anxiolytics for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2000; Issue 4.

A systematic review whith 6 RCTs, comparing anxiolytics (diazepam, meprobamate, buspirone, metoprolol, oxprenolol) with placebo. It was shown that there is no consistent evidence that anxiolytics significantly contribute to smoking cessation. Nevertheless, it was not possible to exclude a possible effect form these drugs in dependence cessation.

12.1.1.5 Clonidine

Gourlay SG, Stead LF, Benowitz ML. Clonidine for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 3.

Systematic review analyzing 6 small RCTs, with potential bias sources, comparing clonidine (oral and transdermal) and placebo. It was shown that clonidine is effective in promoting smoking cessation. Nevertheless, important dose-dependent adverse effects may limit its use for this indication (particularly xerostomia and sedation).

12.1.1.6 Opioid antagonists

David S, Lancaster T, Stead LF, Evins AE. Opioid antagonists for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2006; Issue 4.

Based on the limited data from 4 RCTs, it was not possible to confirm or exclude naltrexone's role in smoking cessation or abstinence in the long term.

12.1.2 Non-pharmacologic interventions

12.1.2.1 Complementary therapies

12.1.2.1.1 Acupuncture

White A.R., Rampes H., Campbell J.L. Acupuncture and related interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2006; Issue 1

Systematic review including 24 RCTs showing that there is no consistent evidence that acupuncture or related techniques (acupression, laser therapy or electro stimulation) are effective interventions in smoking cessation.

12.1.2.1.2 Hypnotherapy

Abbot NC, Stead LF, White A.R., Barnes PC. Hypnotherapy for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 1998; Issue 2

Systematic review which has not demonstrated a superior effect of hypnotherapy in smoking cessation rates at six months versus other interventions or the absence of treatment.

12.1.2.2 Behaviour interventions

12.1.2.2.1 Self-help

Lancaster T, Stead LF. Self-help interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 3

Review based on 60 RCTs demonstrating that the use of self-help material (leaflets or audiovisual media) increases sligthly the smoking cessation rates, when compared to non-intervention. There was no evidence that when associated with other interventions – such as counselling by a health care provider or nicotine replacement therapy – the success rate increases. There is evidence that the use of personalized material is more effective comparatively to the use of non-personalized one, but the effect is still of small dimension.

12.1.2.2.2 Group therapy

Stead LF, Lancaster T. Group behaviour therapy programmes for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2007; Issue 2

Systematic review of 55 RCTs showing that group therapy in smoking cessation presents better results than self-help programmes and other less intensive interventions (with material support but no support face-to-face) – OR 2.04, CI 95%, 1.60 to 2.60; as well as non-intervention – OR 2.17, CI

95%, 1.37 to 3.45. Nevertheless, there is no sufficiently strong evidence to evaluate if this therapy is more effective or more cost-effective than an individual counselling equally intensive; or even if it produces a supplementary benefit with additional forms of therapy (such as counselling by a health care provider or the use of nicotine replacement therapy).

12.1.2.2.3 Telephone support

Solomon LJ, Marcy TW, Howe KD, Skelly JM, Reinier K, Flynn BS. Does extended proactive telephone support increase smoking cessation among low-income women using nicotine patches? Preventive medicine 2005; 40(3):306-313

The results of this RCT are consistent with a meta-analysis of other 4 RCTs, and suggest that proactive telephone counselling, when added to replacement therapy with nicotine OTC patches, has a favourable effect on the smoking abstinence rates in the short term. There was no significant effect in the long term.

Pan W. Proactive telephone counselling as an adjunct to minimal intervention for smoking cessation: a meta-analysis. Health education research 2006; 21(3):416-427

Meta-analysis of 22 trials studying the proactive telephone counselling as an adjunct to minimal intervention for smoking cessation. It was found that this type of intervention is effective in light smokers and younger men.

Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2006; Issue 3

According to the 48 trials analyzed by the authors of this systematic review, proactive telephone counselling increased the success rate of smoking cessation, and there is a dose-response relation. The support lines are an important help source for smokers who wish to stop smoking. The completion of three or more calls increased the probability of cessation comparatively to a minimum intervention (self-help material, counselling minimal intervention, isolate pharmacotherapy).

12.1.2.2.4 Individual counselling

Lancaster T, Stead LF. Individual behavioural counselling for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 2

Systematic review that selected 21 trials related to the individual counselling role in smoking cessation. It was shown that this type of intervention, supplied by trained professionals in smoking cessation,

outside the usual clinical practice environment and lasting over 10 minutes, helps smokers in eviction. There is no evidence of a dose-response benefit for interventions longer than 10 minutes, but the possibility of the existence of a clinically useful effect was not excluded.

12.1.2.2.5 Sequencial based behavioural intervention

Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, Walker A. Systematic review of the effectiveness of stage based interventions to promote smoking cessation. BMJ 2003; 326(7400):1175-1177

The authors of this review, which included 23 RCTs, have concluded that evidence suggests that stage based interventions are not more effective than interventions that do not consider the behaviour changes stages or non-intervention.

12.1.2.2.6 Relapse prevention

Hajek P, Stead LF, West R, Jarvis M, Lancaster T. Relapse prevention interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 1

Systematic review in which the authors concluded that there is not sufficient evidence to support the use of any kind of strategies to prevent relapses in abstinent smokers for a short period of time, in any smoking cessation context. Most trials analyzed cognitive and behavioural strategies to the development of competencies related to the identification of high risk situations for relapse.

12.1.2.3 Aversive therapy

Hajek P, Stead LF. Aversive smoking for smoking cessation: Cochrane Systematic
Review. Cochrane Database of Systematic Reviews 2001; Issue 3

Systematic review with 25 RCTs, comparing aversive therapies (interventions that add unpleasant stimuli to the act of smoking, trying to extinguish the latter), using inactive procedures or aversive therapies of different intensities for smoking cessation. Based on these results, we can conclude that the presently available evidence is insufficient to determine the efficacy of "rapid smoke" (aversive therapy method that requires several smoke inhalations within very few seconds between each inhalation) or the existence of a dose-response to the aversion stimulation. Other aversion methods (lighter forms of the "rapid smoke" method) do not seem to have specific efficacy. In order to achieve a correct evaluation of aversion therapy, we would have to conduct more trials with the adequate methodology.

12.1.3 Special populations

12.1.3.1 Cardiovascular patients

Wiggers LC, Smets EM, de Haes JC, Peters RJ, Legemate DA. Smoking cessation interventions in cardiovascular patients. European Journal of Vascular and Endovascular Surgery 2003; 26(5):467-475.

Systematic review which analysed the few available trials on smoking cessation in cardiovascular patients. In this group, there was no evidence of efficacy for most interventions (nicotine replacement therapy or other pharmacological therapy, self-help materials, individual, group or telephone counselling). There is limited evidence of the efficacy of medical or nurse counselling.

Ludvig J, Miner B, Eisenberg MJ. Smoking cessation in patients with coronary artery disease. Am Heart J 2005; 149(4):565-572

A systematic review of 33 randomized, double-blind clinical trials demonstrated that the auxiliaries to smoking cessation (nicotine in the several marketed forms, bupoprion and behavioural therapy) cause, in patients with coronary artery disease, a modest increase in abstinence rate at 12 months, versus placebo.

Barth J, Critchley J, Bengel J. Efficacy of psychosocial interventions for smoking cessation in patients with coronary heart disease: a systematic review and meta-analysis. Annals of behavioural medicine: a publication of the Society of Behavioural Medicine 2006; 32(1):10-20

Systematic review of 19 RCTs evaluating the efficacy of psychosocial interventions in smoking cessation in patients with coronary heart disease. It was seen that psychosocial interventions (behavioural approaches, telephone support, self-help material) have a positive role in smoking cessation with OR of 1,66 (CI 95%, 1,24 to 2,21), vs. the usual treatment of patients, but they have to be provided during a minimum period of 1 month.

12.1.3.2 Pregnancy

Lumley J, Oliver SS, Chamberlain J, Oakley L. Interventions for promoting smoking cessation during pregnancy: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 4

Systematic review of 64 trials (including 51 RCTs) related to the smoking cessation interventions during pregnancy. The smoking cessation programmes reduced the proportion of smoking women, the occurrence of low weight at birth and pre term labour. The analysis relating to the change in the occurrence of very low weight at birth, stillborns and peri- or neonatal death was not statistically significant.

12.1.3.3 Psychiatric disease

Hitsman B, Borrelli B, McChargue DE, Spring B, Niaura R. History of depression and smoking cessation outcome: a meta-analysis. Journal of Consulting and Clinical Psychology 2003; 71(4):657-663

Meta-analysis of 15 trials which showed that the existence of previous history of major depression does not seem to be an independent risk factor for the cessation failure, in the short or long term, in a smoking cessation programme.

Prochaska JJ, Delucchi K, Hall SM. A meta-analysis of smoking cessation interventions with individuals in substance abuse treatment or recovery. Journal of Consulting and Clinical Psychology 2004; 72(6):1144-1156

Systematic review of 19 RCTs showing that the smoking cessation interventions with individuals in substance abuse treatment programmes where effective in the short term, whether to patients in treatment or in recovery, being nevertheless ineffective in the long run. It was also seen that these interventions seem to promote alcohol or illicit substances long term abstinence.

12.1.3.4 Young people

Sussman S, Sun P, Dent CW. A meta-analysis of teen cigarette smoking cessation. Health psychology: official journal of the Division of Health Psychology, American Psychological Association 2006; 25(5):549-557

Systematic review of 48 trials analyzing the smoking cessation rates in teenagers. There were superior rates of cessation in the short and long run in patients included in smoking cessation programmes; the rates were slightly superior in the programmes lasting longer than 5 sessions, which included a motivational component, cognitive behavioural techniques and social influence approaches, conducted in scholar clinics and within the school class.

Grimshaw GM, Santon. Tobacco cessation interventions for young people. Cochrane Database of Systematic Reviews 2006; Issue 4

Systematic review of 15 randomized and non-randomized clinical trails, evaluating the smoking cessation strategies efficacy in young people under 20. There was no consistent evidence of efficacy of any intervention to increase the rates of smoking cessation for 6 months in a row. Nevertheless, multiple component interventions have shown a degree of persistent abstinence (30 days of occasional abstinence prevalence at 6 months), particularly the one that included elements of the "change stages" model. Presently, there is no available evidence

supporting the use of pharmacological therapy (nicotine or bupoprion) in teenager smokers.

12.1.3.5 Hospitalized smokers

Rigotti NA, Munafo MR, Murphy MFG, Stead LF. Interventions for smoking cessation in hospitalised patients: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2002; Issue 4

Systematic review of 17 trials related to interventions in hospitalised patients. It was shown that behavioural interventions - which include contact during hospitalization and at least one month of follow-up - are effective in promoting smoking cessation in hospitalised patients. Nicotine replacement therapy increased smoking cessation rates.

12.1.3.6 Preoperative patients

Møller A, Villebro N. Interventions for preoperative smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 3

Systematic review of 4 trials related to preoperative smoking cessation. It was seen that preoperative interventions for smoking cessation were only effective in the peri-operative period; the abstinence was not significantly kept in the long run. The data on the smoking cessation effects in the postoperative complications are contradictory.

12.1.3.7 Chronic obstructive pulmonary disease (COPD) patients

Van der Meer RM, Wagena EJ, Ostelo RWJG, Jacobs JE, Van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2001; Issue 1

Systematic review including 5 RCTs, 2 with high quality, analyzing the smoking cessation efficacy in chronic obstructive pulmonary disease (COPD) patients. The authors have concluded that the combination of pharmacological and psychosocial therapy was superior to the psychosocial therapy isolated or the absence of treatment. Nevertheless, there was no sufficiently strong evidence that isolated psychosocial therapy increases the success rate for smoking cessation in COPD patients, when compared to the non-existence of therapy.

12.1.4 Role of health care providers

Gorin SS, Heck JE. Meta-analysis of the efficacy of tobacco counselling by health care providers. Cancer epidemiology, biomarkers & prevention 2004; 13(12):2012-2022

Based on 37 trials' results it was seen that contact and counselling from health care providers increased smoking cessation rates. The most

effective interventions were performed by doctors, followed by multidisciplinary teams, dentists and, finally, nurses.

Mojica WA, Suttorp MJ, Sherman SE et al. Smoking-cessation interventions by type of provider: a meta-analysis. Am J Prev Med 2004; 26(5):391-401

Meta-analysis in which the interventions from psychologists, doctors or nurses have increased smoking cessation rates. Nicotine replacement therapy increased, approximately to the double, the intervention efficacy with most professionals.

Sinclair HK, Bond CM, Stead LF. Community pharmacy personnel interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 1

Systematic review of 2 RCTs concluding that there is evidence (although with a limited weight) that counselling plus support programme with data registry given by trained professionals in the context of a communitarian pharmacy, may have a positive effect on the smoking cessation rates.

Lancaster T, Stead LF. Physician advice for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 4

Systematic review of 39 RCTs, where a brief doctors' counselling compared to the non-existence of counselling, has shown a small yet significant effect in smoking cessation rates (OR 1.74, CI 95%, 1.48 to 2.05). There was no sufficient evidence, from indirect comparisons, to establish a significant difference in medical counselling with the intensity of the intervention, the amount of available follow-up or the use of support materials. A comparison between intensive counselling and minimum counselling has shown a small advantage in the first one (OR 1.44, CI 95%, 1.24 to 1.67). The direct comparisons have also shown a small benefit in follow-up visits.

Carr AB, Ebbert JO. Interventions for tobacco cessation in dental setting. Cochrane
Database of Systematic Reviews 2006, Issue 1

Systematic review of 6 clinical trials evaluating the efficacy of dentists' interventions in smoking cessation, whether in practice or within the school health context. The available evidence suggests that behavioural interventions made by oral health professionals, together with a component of oral/dental evaluation, can increase smoking cessation rates among users of non-smoked types of tobacco (e.g. chewing tobacco). Only one trial included real smokers, and therefore we have no

sufficient evidence to draw any conclusion on the efficacy of the intervention in that group.

Rice VH, Stead L. Nursing intervention and smoking cessation: meta-analysis update. Heart & lung: the journal of critical care 2006; 35(3):147-163

Systematic review of 34 randomized clinical trials. Is spite of the heterogeneous results, it has shown that nursing interventions, whether in the hospital or in ambulatory, increased the smoking cessation probability.

12.1.5 Special topics

12.1.5.1 Community interventions

Secker-Walker RH, Gnich W, Platt S, Lancaster T. Community interventions for reducing smoking among adults: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2002; Issue 2

Systematic review of 37 controlled trials comparing communities with smoking cessation intervention programmes with control communities. It was shown that there is no impact of community interventions in smokers' prevalence. This work suggests that community approach will remain as an important part in health promotion activities but we have to consider its limited effect when planning the magnitude of projects and resources to use.

12.1.5.2 Workplace interventions

Fichtenberg CM, Glantz SA. Effect of smoke-free workplaces on smoking behaviour: systematic review. BMJ 2002; 325:188-190

The analysis of 26 clinical trials showed that totally smoke-free workplaces are associated to reductions of smoking prevalence of 3.8% (CI 95%, 2.8% to 4.7%) and less 3.1 (2.4 to 3.8) smoked cigarettes per day in workers who maintain smoking habits.

Smedslund G, Fisher KJ, Boles SM, Lichtenstein E. The effectiveness of workplace smoking cessation programmes: a meta-analysis of recent studies. Tobacco control 2004; 13(2):197-204

Meta-analysis of 19 clinical trials, showing that workplace interventions for smoking cessation have a short term benefit. This was found both in the randomized and in the non-randomized groups of trials, and they both presented an adequate statistical homogeneity. The beneficial effect seems to vanish with time, disappearing after 12 months.

Moher M, Hey K, Lancaster T. Workplace interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 2

Review studying the efficacy of workplace interventions for smoking cessation; all the interventions already considered effective, such as group therapy, individual counselling and nicotine replacement therapy have shown to be equally effective in the workplace. Self-help methods have been less effective. Prohibition and smoking restrictions in workplace have reduced smoking incidence in workplace but it was not clear that the active use prevalence or total smoking load have been reduced. Social and environmental interventions, incentives, competitions and programmes with different types of interventions do not present evident advantages.

12.1.5.3 Incentives

Kaper J, Wagena EJ, Severens JL, Van Schayck CP. Healthcare financing systems for increasing the use of tobacco dependence treatment: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 1

Systematic review analyzing RCTs, CTs and ITS that has shown evidence (although with a limited weight) that the use of financing systems that eliminate the smoking cessation programme costs for the patient may increase smoking cessation rates in the long term, when compared to systems that only reduce or do not change that treatment cost. Presently, there is no sufficient evidence in order to evaluate the effects of monetary incentives given to health care providers in order to identify and treat smoking people.

Hey K, Perera R. Competitions and incentives for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 2

Systematic review of 15 RCTs, concluding that economical incentives and competitions do not seem to increase smoking cessation rates in the long term; nevertheless, they may increase recruiting rates for cessation attempt, and indirectly the absolute number of individuals that successfully cease smoking.

Hey K, Perera R. Quit and Win contests for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 2

4 RCT selected to study the impact of contests "Quit and Win" in smoking cessation. The authors concluded that local and regional contests seem to increase smoking cessation rates; nevertheless, the impact in the

smoking prevalence in the population is small. These contests can induce deception levels in the participants that may compromise the validity of the intervention. International contests may be an effective mechanism, mainly in developing countries, but we can not draw safe conclusions, as there are no adequate studies available.

12.1.5.4 Biomedical risk assessment

Bize R, Burnand B, Mueller Y, Cornuz J. Biomedical risk assessment as an aid for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2005; Issue 4

Systematic review of 8 RCTs, concluding that, to date, there is no good evidence on the biomedical risk assessment efficacy (physiological parameters determination aiming to provide smokers with a measure of the smoking harmful effects) as an incentive to smoking cessation.

12.1.5.5 Partner support

Park E-W, Schultz JK, Tudiver F, Campbell T, Becker L. Enhancing partner support to improve smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 3

Systematic review of 9 RCTs, in which the interventions to enhance non-smoking partner support to improve smoking cessation do not show increases in long term cessation rates. Nevertheless, we can not draw conclusions on the real impact of this strategy, since limited data from some trials suggest that these interventions did not successfully change the support provided by the partners.

12.1.5.6 Physical exercise

Ussher M. Exercise interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2007; Issue 1

Systematic review in which only 1 of the 11 RCTs analysed presented evidence that exercise was beneficial to smoking cessation on the long term. All the other trials presented several methodological limitations or included only a moderate exercise programme, insufficient to attain the desired level of exercise; therefore, we can not trustworthily exclude an effect of this type of intervention.

12.1.5.7 Health care provider training

Lancaster T, Silagy C, Fowler G. Training health professionals in smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2000; Issue 3

This review concluded that specifically trained professionals in smoking cessation have a greater probability of identifying smokers and

consequently to propose abstinence strategies. Nevertheless, there is no significant evidence that the mentioned training may in any way change the smoking habits of their patients.

Anderson P, Jane-Llopis E. How can we increase the involvement of primary health care in the treatment of tobacco dependence? A meta-analysis. Addiction 2004; 99(3):299-312

Systematic review of 19 trials in which primary health care professionals were involved in the treatment of smoking addiction increasing the tracing rates, counselling and cessation of their patients. The administration of educational interventions, to learning professionals, and the combination of these with practical support, to established professionals, has proven to be an efficient strategy.

12.1.5.8 Passive smoking

Roseby R, Waters E, Polnay A, Campbell R, Webster P, Spencer N. Family and career smoking control programmes for reducing children's exposure to environmental tobacco smoke: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2002; Issue 3

Systematic review of 18 RCTs on all kinds of mechanisms eventually involved in the prevention of children's exposure to environmental tobacco smoke, including active children care providers (0-12 years). Presently we have no sufficient evidence to conclude which is the most effective intervention to reduce parents' smoking within children health practice environment.

12.2 Excluded trials

Stead LF, Hughes JR. Lobeline for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 1997; Issue 3

This drug is not available in Portugal.

Lancaster T, Stead LF. Silver acetate for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 1997; Issue 3

This drug is not available in Portugal.

Lancaster T, Stead LF. Mecamylamine (a nicotine antagonist) for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 1998; Issue 2

This drug is not available in Portugal.

Rosen CS. Is the sequencing of change processes by stage consistent across health problems? A meta-analysis. Health psychology: official journal of the Division of Health Psychology, American Psychological Association 2000; 19(6):593-604

This review refers only to the analysis of the intervention method by stage per si.

Melvin CL, Dolan-Mullen P, Windsor RA, Whiteside HPJ, Goldenberg RL. Recommended cessation counselling for pregnant women who smoke: a review of the evidence. Tobacco control 2000; 9 Suppl 3: III80-III84

This study was excluded since it was a narrative review.

Wilson K, Gibson N, Willan A, Cook D. Effect of smoking cessation on mortality after myocardial infarction: meta-analysis of cohort studies. Arch Intern Med 2000; 160(7):939-944.

This study approaches the benefits but not the smoking cessation methods.

Khuder SA, Mutgi AB. Effect of smoking cessation on major histologic types of lung cancer. Chest 2001; 120(5):1577-1583

This study approaches the benefits but not the smoking cessation methods.

McClure JB. Are biomarkers a useful aid in smoking cessation? A review and analysis of the literature. Behavioural medicine (Washington, DC) 2001; 27(1):37-47

This study was excluded since it was a narrative review.

Wagena EJ, Zeegers MP, Huibers MJ, Chavannes NH, Van Schayck CP. Bupoprion: an effective new aid for smoking cessation. Nederlands tijdschrift voor geneeskunde 2001; 145(2):103-104

The article was written in Dutch, there was no international language translation available.

Sansores RH, Ramirez-Venegas A, Espinosa-Martinez M, Sandoval RA. Treatments to quit smoking, available in Mexico. Salud pública de México 2002; 44 Suppl 1:S116-S124

This study was excluded since it was a narrative review.

Le Foll B, Aubin HJ, Lagrue G. Behavioural and cognitive therapy to break the smoking habit. Review of the literature. Annales de médecine interne 2002; 153(3 Suppl):1S32-1S40

This study was excluded since it was a narrative review.

Maeda K, Noguchi Y, Fukui T. The effects of cessation from cigarette smoking on the lipid and lipoprotein profiles: a meta-analysis. Preventive medicine 2003; 37(4):283-290

This study approaches the benefits but not the smoking cessation methods.

Tingle LR, DeSimone M, Covington B. A meta-evaluation of 11 school-based smoking prevention programmes. The Journal of school health 2003; 73(2):64-67

This review evaluates only the programmes but not their outcomes.

Polanska K, Hanke W, Sobala W. Meta-analysis of prenatal smoking cessation interventions. Przeglad Epidemiologiczny 2003; 57(4):683-692

The article was written in Polish, there was no international language translation available.

Huibers MJH, Beurskens AJHM, Bleijenberg G, Schayck CP. Psychosocial interventions delivered by general practitioners: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2003; Issue 2

Review to evaluate the efficacy of psychosocial interventions by the family doctor in a wide range of disturbances, including only 2 trials on smoking cessation, one of which was of low quality. The existence of other works with scientific evidence of excellent quality that have evaluated directly this counselling, determined the exclusion.

Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2003; Issue 4

This study approaches the benefits but not the smoking cessation methods.

Lee PN, Sanders E. Does increased cigarette consumption nullify any reduction in lung cancer risk associated with low-tar filter cigarettes? Inhalation toxicology 2004; 16(13):817-833

This study approaches the benefits but not the smoking cessation methods.

Mooney M, White T, Hatsukami D. The blind spot in the nicotine replacement therapy literature: assessment of the double-blind in clinical trials. Addictive behaviours 2004; 29(4):673-684

This study focuses the methodology of selection of papers on nicotine replacement therapy, but does not mention other smoking cessation methods.

Park EW, Tudiver F, Schultz JK, Campbell T. Does enhancing partner support and interaction improve smoking cessation? A meta-analysis. Annals of family medicine 2004; 2(2):170-174

The existence of a systematic review, with scientific evidence of excellent quality, published in Cochrane Library, including the same authors and more recently published studies, has determined the exclusion.

Rice VH, Stead LF. Nursing interventions for smoking cessation: Cochrane Systematic Review. Cochrane Database of Systematic Reviews 2004; Issue 1

The existence of an updated version of this systematic review, included in the present CPG, has determined the exclusion.

Woodward M, Lam TH, arzi F et al. Smoking, quitting, and the risk of cardiovascular disease among women and men in the Asia-Pacific region. Int J Epidemiol 2005; 34(5):1045-1046

This study approaches the benefits but not the smoking cessation methods.

White A, Moody R. The effects of auricular acupuncture on smoking cessation may not depend on the point chosen--an exploratory meta-analysis. Acupuncture in medicine 2006; 24(4):149-156.

This meta-analysis was developed based on controlled non-randomized trials. Given the existence of a systemic review, exclusively based in RCTs, on the same subject, we chose to exclude this article.

Stead LF, Lancaster T. Nicobrevin for smoking cessation: Cochrane Systematic
Review. Cochrane Database of Systematic Reviews 2006; Issue 2

This drug is not available in Portugal.

Green JP, Jay Lynn S, Montgomery GH. A meta-analysis of gender, smoking cessation, and hypnosis: a brief communication. The International journal of clinical and experimental hypnosis 2006; 54(2):224-233

Excluded study as it approaches the gender role in the hypnoses success and not the hypnoses technique role per si in smoking cessation.

13. Practical interventions

13.1 Pharmacological interventions

As previously discussed, tobacco is a risk factor for several diseases, and smoking cessation is a challenge, both to smokers and health professionals who guide and stimulate their attempts to stop smoking. Presently there are several pharmacological therapies available to smokers aiming to reduce the smoking craving and decrease abstinence symptoms.

13.1.1 Nicotine replacement therapy (NRT)

Nicotine replacement therapy is largely used to replace the nicotine levels smokers acquire by inhaling tobacco smoke. The NRT efficacy in smoking eviction was proven in many studies.

In the West and Shiffman[26] review, published in 2001, 12 clinical trials were included, evaluating the NRT effects in abstinence symptoms and in smoking craving. Based on the results, the authors concluded that there is strong evidence that NRT reduces discomfort (6 out of 7 trials), irritability (9 out of 9 trials) and anxiety (3 out of 4 studies) and some evidence of a beneficial effect in decreasing depressive humour and smoking craving (in the latter, nicotine gums were not so effective). Nevertheless, they underline the need for trials with better methodological quality and more comprehensive descriptions.

According to the analysis conducted by Etter and Stapleton[27], including 12 RCTs with placebo, a unique course of NRT for a period varying between 2 to 8 years has also shown benefit in smoking cessation, without evidence that this effect varies according to the duration of the initial therapy or the follow-up periods. The global relapse rate after 12 months was 30%, drawing attention to the possibility of an over estimate of the benefit and cost-effectiveness of the replacement treatment, when we only evaluate quit rates at 6 and 12 months. Most relapses after the first 12 months have occurred during the first or the second year, and were not detectable later. Nevertheless, and in spite of the exceptions related to the bias induced by short follow-up periods (6 and 12 months), smoking cessation benefits were confirmed by a systematic review, published in 2006 by Wu et al[28], that compared different smoking cessation therapies (NRT, bupoprion, varenicline) at 12 months. In 70 RCTs, comparing NRT to a control group, a significant benefit with NRT was found, confirmed by the advantage of NRT versus placebo in 49 RCTs.

As there are several pharmaceutical forms of nicotine replacement therapies, Silagy[29] evaluated, in 2004, 103 RCTs demonstrating that all

marketed pharmaceutical forms are effective in smoking cessation and that there is no evidence, by indirect comparison, of a significant difference between the different forms, namely in transdermal patches or gums. These results seem to be independent of the duration or context in which the therapy is applied and the intensity of additional support provided to the patient. Also according to this publication, the association of different forms of NRT recommended by the *U.S. Department of Health and Human Services* CPG[30], was proven to be beneficial, although this evidence is presented with some reserve, due to the heterogeneity of the available studies. The combination of nicotine patches with a self-administered form of NRT may be recommended to smokers who are not successful with a single type of 1st line pharmacotherapy. In highly dependent smokers (Fagerström score ≥7) a significant benefit was found with the use of 4 mg gums, instead of 2 mg, and, in this group, there was a low quality evidence supporting the combination of different forms of NRT. Only one clinical trial compared NRT with other pharmacological treatments, showing higher rates of smoking cessation when bupoprion was associated to a placebo patch comparatively to the use of nicotine patches plus a placebo tablet. More studies are needed to evaluate the association of NRT with other drugs.

Assuming that the efficacy of NRT is independent of the association with non-pharmacological therapies, Hughes et al[31] published in 2003 the results of a meta-analysis of 4 RCTs which proved NRT over the counter (OTC) efficacy versus placebo. This review included two randomized studies and two non-randomized trials, comparing NRT subject and non-subject to medical prescription, which presented non-homogenous results, but that, when combined via random effects mode, have produced a OR higher that 1 (1.4, CI 95%, 0.6 to 3.3); the authors could therefore conclude that OTC NRT was as effective as NRT subject to medical prescription.

Comparing the efficacy of this therapy in men and women, Cepeda-Benito[32] evaluated 21 double blind, randomized trials versus placebo, showing that NRT, together with non intensive non-pharmacological support, is more effective than placebo in men at 3, 6 and 12 months. In women, the benefit was only found at 3 and 6 months, so it was concluded that in this group the association of intensive pharmacological support is even more important.

13.1.2 Antidepressants

The idea that smoking cessation may induce depression and that nicotine itself may have an antidepressant effect has promoted the use of bupoprion and nortriptyline in smoking cessation attempts.

We have identified four systematic reviews discussing this issue. In the first one, a meta-analysis of 12 RCTs published by Scharf and Shiffman[33] in 2004 in the journal *Addiction*, the differences between genders in smoking cessation were analyzed with or without bupoprion; in the second one, published in 2005, also in *Addiction* by Wagena[34], 5 RCTs were analyzed, comparing nortriptyline with bupoprion or placebo; the third one, published in 2006 by Wu et al[28], compared the result of different smoking cessation therapies (nicotine replacement therapy, bupoprion, varenicline) at 12 months; the fourth one was published in Cochrane Library in 2007, by Hughes et al[35], studying the efficacy of antidepressant therapy in smoking cessation, and it included 53 trials (40 of which on bupoprion and 8 on nortriptyline).

So, when used isolated, and according to Scharf[33] and Hughes[35] reviews, bupoprion presents an effective aid effect to smoking cessation comparatively to placebo. The first study has demonstrated that the benefit of this drug is equal in men and women; however, there was evidence that women presented a lower success rate regardless of the treatment used.

Also in Hughes and Wagena studies, nortriptyline has shown benefit compared to placebo in the smoking abstinence rate evaluated at 6 and 12 months. The second study certified this difference as higher in the first months of treatment, and the number of abstinent people increased faster in smokers taking nortriptyline. Both studies showed that bupoprion achieved greater abstinence rates comparing to nortriptyline, but the difference was not statistically significant.

When compared to NRT, bupoprion and nortriptyline seem to have a similar efficacy, and there is no evidence that adding these antidepressants to NRT increases long term cessation (Hughes et al.). Through a direct and indirect comparison, Wu et al did not demonstrate as well a statistically significant advantage of bupoprion versus NRT.

These two antidepressants are effective regardless of the present or former history of depression, and the adverse effects are rarely serious or causing the treatment withdrawl, if the usual recommended dosage to smoking cessation is respected.

There was no evidence of a significant benefit, in the long term, of the prolonged use of bupoprion to prevent relapses[35].

In what concerns selective inhibitors of serotonin recapture, there was no significant benefit in smoking cessation > 12 months, with this class of drugs[35].

13.1.3 Partial agonists of nicotine receptors

Partial nicotine agonists aim at reduction of smoking abstinence symptoms and the pleasure gained by tobacco smoke, and varenicline is the only molecule of this group available in the Portuguese market.

In 2007, Cahill et al[36], published in Cochrane Library a systematic review evaluating the efficacy and tolerability of partial agonists of nicotine receptors, including 5 RCTs. The authors have identified a significant increase in smoking cessation rates in the long term (12 months), in patients treated with varenicline compared to placebo or bupoprion.

Likewise, in the reviews by Hughes et al[35] and Wu et al[28], quoted above, varenicline proved to be, by direct comparison, superior to bupoprion. In the last trial it was also seen a greater efficacy of varenicline face to NRT by indirect comparison, versus placebo and all the control groups.

In spite of the evidence of varenicline efficacy in smoking cessation, several authors consider it necessary to conduct comparative trials between varenicline and NRT and more trials versus bupoprion, as well as more trials to evaluate its efficacy in the treatment of relapses.

13.1.4 Anxiolytics

Anxiety may be an important component in the failure of smoking cessation attempts, so several authors have pondered the use of anxiolytics as helper in smoking cessation.

In a systematic review published in 2000 in Cochrane Library, Hughes, Stead and Lancaster[37], reviewed 6 RCTs studying different anxiolytics (diazepam, meprobamate, motoprolol, oxprenolol and buspirone) but none of the trials has shown evidence of a beneficial effect from any of these drugs. Nevertheless, the confidence intervals were wide, so the exclusion of a possible favourable effect can not be definitive. More trials are required in order to clarify the real role of this class of drugs.

13.1.5 Other pharmacological classes

13.1.5.1 Clonidine

Clonidine belongs to the central alfa-2 agonists class, used primarily as anti-hypertensive therapy and the treatment of opioid abstinence; its use has been recently proposed for smoking cessation.

Gourlay e Stead[38] evaluated the use of clonidine in smoking cessation therapy, after 12 months of follow-up, through 6 RCTs that included potential bias sources, and the benefit of this therapy was statistically significant versus placebo. Nevertheless, adverse effects such as xerostomia or sedation were very frequent. According to these authors,

transdermal clonidine may be indicated as a 2nd line drug, and its sedative effect may be useful in specific patients. It requires a careful vigilance in order to adjust the dose and monitor potential serious adverse effects.

13.1.5.2 Opioid antagonists

Assuming the role of the opioid system in the pleasure of smoking, David et al[39], conducted a systematic review to evaluate the role of the opioid antagonists in smoking cessation. They did not identify studies with long term follow-up of therapies with naloxone or buprenofine. Based on the data of only 4 RCTs, there was no significant difference between naltrexone and placebo in quit or long term abstinence rates (OR 1.26 CI 95%, 0.80 to 2.01). Nevertheless, since the confidence interval is very wide, evidence does not allow the exclusion of some efficacy of this drug, and so it is necessary to conduct larger clinical trials in order to make practical recommendations.

13.2 Non-pharmacological interventions

13.2.1 Complementary therapies

13.2.1.1 Acupuncture

White et al[40] review, exclusively based in RCTs, has shown that there is no consistent evidence that acupuncture and related techniques (digit pressure, laser therapy and electro stimulation) are effective interventions in smoking cessation, since it is not possible to prove that the effect of these techniques is a placebo effect. Nevertheless, the selected studies are heterogeneous and present several methodological flaws, thus justifying the need for further trials in order to draw firm conclusions.

13.2.1.2 Hypnotherapy

The systematic review by Abbot et al[41], published by Cochrane Library, has not shown a superior effect of hypnotherapy in smoking quit rates at six months versus another interventions, or the absence of treatment. Nevertheless, some consideration has to be made relating to the evaluation of this technique. Firstly, in order to identify a positive effect of hypnotherapy in smoking cessation, versus the absence of treatment, we should exclude the non-specific effects conditioned by the presence of a therapist. This verification is made difficult by the non-existence of a suitable placebo. Secondly, since it was not possible to prove the efficacy of other behavioural interventions, the comparison of the latter with hypnotherapy becomes a problem.

In future trials, the investigators should consider the definition and description of the type of hypnotherapy used and the comparison with active interventions (preferably with an equivalent duration of contact with the therapist).

13.2.2 Behavioural interventions

All the studies published within this area agreeon the methodological difficulties associated with the evaluation of different behavioural interventions.

The evaluation of efficacy of behavioural therapy is more difficult than the pharmacological therapy. This fact is related to the difficulty in defining an adequate control and keeping the necessary conditions for a double blind trial (the smoker and the therapist usually know the group which they belong to). The standardization of the health care providers' attitude is a complex process, and many times it is accepted that the same method, applied by different professionals, may lead to different results. Whenever the therapeutic method is known by those who apply it and there is a formed opinion on the efficacy of each one of the interventions being studied, a performance bias may be induced. This is also possible whenever the same therapists apply different methods.

The design of trials of behavioural interventions, usually with multiple treatment arms to identify the effective therapeutic element, makes it difficult to explicitly predefine control groups. Nevertheless, and in opposition to what is seen when evaluating pharmacological interventions, the choice of an adequate control for a behavioural intervention poses serious problems, since it will hardly be equivalent to the non-specific effects of the study method.

13.2.2.1 Self-help

There is evidence, in a small dimension, of the systematic review of Lancaster e Stead[42] in Cochrane Library, that self-help materials for smoking cessation can increase the number of individuals who stop smoking, comparatively to the absence of treatment. These materials were defined as leaflets, audiovisual media or computer programmes, which may be used by smokers as adjuvant factors in the attempt of quitting smoking without the help of a health care provider, therapist or therapy group.

Personalized self-help materials seem to be the most effective. They can produce a superior effect relatively to the non-personalized ones, being more attractive and easier to read, and they can be used by a higher number of people. Nevertheless, it is difficult not to confuse this type of materials with the ones that require additional contacts. On the other hand, it was seen that help advices to smoking cessation are

currently widely spread among the entire population. This "contamination" may complicate the demonstration of the standard self-help programmes, since the control group and the experimental one may have suffered similar interventions.

The necessary evidence to determine which are the theoretical models and the most important elements to the individualization of the materials is insufficient. All studies suggest that the supply of self-help materials, together with health care providers counselling, does not improve the results. Likewise, there is small evidence of the effect of adding self-help materials to nicotine replacement therapy.

There were no studies with direct comparison between self-help materials and minimal counselling interventions.

The authors consider that self-help interventions are probably most suitable to smokers who are not in contact with the health system (since individualized interventions depend on the capacity to obtain baseline data). All smokers who seek help will probably benefit more from a brief counselling or personalized materials. Internet may be an important vehicle to provide smokers access to individualized resources.

13.2.2.2 Group therapy

Stead e Lancaster[43] analyzed group therapy as an aid to smoking cessation, in the systematic review published by the Cochrane Library. They enumerate several particularities that hinder the evaluation of the role of group therapy in smoking cessation, namely the difficulty to explicitly define experimental groups (different approaches are tested in one single study), the non-existence of an adequate control group and variations in the characteristics of the groups. There is not sufficient evidence to identify which elements in group therapy are the most important to the success of smoking cessation.

In spite of these interventions having at first glance a more favourable cost-effectiveness relatio than one individual one, there are no trials to consubstantiate a comparative efficacy between the two approaches.

On the other hand, to attend a therapy group the smoker must have not only the will to quit smoking, but also the time and effort needed to participate in the sessions.

The comparison between a therapy group and another with no intervention supports the conclusion that the group programmes may help smoking cessation, in spite of not providing evidence on the specific benefit of this therapy.

There is reasonable evidence that group therapy is superior to self-help in smoking cessation, but there is no evidence that the meeting with

other smokers, alone, is superior to brief or intensive individual counselling, and that its association with NRT is superior to its use alone.

One can assume that behavioural and pharmacological interventions contribute in an independent way, to the success of smoking cessation. As such, group therapy may be considered as one of the constituents to include in a multifactorial intervention.

13.2.2.3 Telephone counselling

Three systematic reviews were identified, studying the role of telephone counselling in smoking cessation. A rigorous evaluation of reactive services, such as aid telephone lines, has been made difficult since it is not possible to develop randomized trials in which the adequate support is denied to some individuals who contact those services, preventing the formation of a comparative group.

In the systematic review from Cochrane Library, conducted by Stead et al[44] the role of telephone counselling was evaluated, whether pro-active (initiated by the health care provider) or reactive (initiated by the smoker, through aid lines); there was a slight benefit in adding telephone counselling to pharmacotherapy. It provides smokers with a route of access to smoking cessation support and the call-back counselling increases their utility. Within this counselling there is a dose-response relationship, that is, the accomplishment of three or more telephone calls increases the odds of quitting, comparatively to a minimal intervention (self-help material, counselling minimal intervention, isolated pharmacotherapy).

The meta-analysis, conducted by Pan[45], evaluated 22 trials and the pro-active telephone counselling role as adjuvant to minimal intervention to smoking cessation. It was seen that this type of intervention is effective in younger males who smoke <10 cigarettes per day.

Solomon et al[46] review concluded that pro-active telephone counselling, when added to transdermal patches of NRT provided at no cost, has a favourable effect on the short term abstinence rates. There was no long term significant result.

13.2.2.4 Individual counselling

The systematic review by Lancaster et al[47] studied the role of individual counselling to smoking cessation. Individual counselling was defined as a face-to-face meeting between a smoker and a therapist with trained competencies to help him stop smoking. Different types of behavioural approaches were accepted and all the interventions initiated by professionals within their usual practice context were excluded, in order to avoid a possible confounding bias. Individual counselling (lasting over ten minutes) was more effective than the control with a minimum contact

(lasting less than ten minutes) with the therapist. There was no evidence of a dose-response effect with the increase in counselling intensity over the 10 minutes period (in spite of, statistically, not being possible to exclude the possibility of a clinically useful effect).

There was no significant additional benefit when individual counselling was provided to smokers under NRT. This fact can only indicate that, in this context, additional relative benefit is small, since quit rates in control groups were increased by the use of effective pharmacotherapy.

It is concluded that interventions such as individual counselling, given by smoking cessation trained professionals, outside the scope of usual clinical practice and lasting over 10 minutes, help smokers in smoking cessation.

13.2.2.5 Stage based behavioural intervention

The stage based intervention is a type of behavioural intervention in which individuals are classified in five stadiums: pre-contemplation, contemplation, preparation, action, maintenance. This type of intervention is based on the hypothesis that the actions that consider the stage of the behavioural change process where the individual is will be more effective and efficient than an identical intervention in all stages.

In the trials selected for the systematic review by Riemsma et al[48], the efficacy of stage based behavioural interventions showed a heterogeneous methodological quality of the trials; few referred the validation of the scale used to determine the change stage; there was no homogeneity in the type of intervention defined for each of the stages; and the description of the interventions was sometimes very limited and not sufficient to draw conclusions on the adequacy to the defined stage.

13.2.2.6 Prevention of relapse

Different strategies to prevent relapses after a well succeeded smoking cessation process were evaluated. It should be noted that there is no clear distinction between treatments to prevent relapses and prolonged treatments for smoking cessation. Nevertheless, we consider interventions to prevent relapses, those that explicitly seek to reduce relapse rates after the end of an initial well succeeded treatment phase, or after the date of abandon of a self motto attempt.

The behavioural and cognitive strategies to the development of competencies related to the identification of high risk situations for relapsing are the most common studies.

In the systematic review by Hajek et al[49], there was no evidence to support the use of any type of strategies to avoid relapses in abstinent smokers, nevertheless, there were methodological and contents

limitations that may have contributed to this result. This conclusion is related, particularly, with the traditional treatments based on identifying and attempting to solve the problems with minimal interventions.

Currently, and until the release of further data, it seems more efficient to concentrate efforts in attempts of early smoking cessation.

13.2.3 Aversion therapy

Hajek and Stead[50] review evaluated the aversion therapy role in smoking cessation. This technique is based on classical animal conditioning experiments and it consists of adding unpleasant stimuli to the smoking action, in an attempt to extinguish it.

The authors found a large number of published articles on this subject, but most papers had several methodological flaws that could origin false-positive results. As such, it was concluded that the available evidence is insufficient to determine the efficacy of the "rapid smoke" (aversion therapeutic method which requires several smoke inhalations within a few seconds) or the existence of a dose-response to the aversion stimulation. Other aversion methods (lighter forms of the "rapid smoke" method) do not seem to present any specific efficacy. It is justified, nevertheless, to conduct a larger number of trials with adequate methodology in order to achieve a correct evaluation of this type of approach.

13.3 Special populations

It is important to consider the particularities of some specific populations, in which the harmful effects of tobacco may have more serious consequences (such as pregnant women or cardiovascular patients), or that may represent a more favourable context for smoking cessation. On the other hand, the groups where the efficacy of the interventions generally used may be questioned deserve a more careful approach, and/or the pertinence of the use of different methodologies should also be more carefully evaluated.

13.3.1 Cardiovascular patients

There are three systematic reviews published relating to smoking cessation as a strategy to secondary prevention in smokers with cardiovascular disease.

Only the work by Wiggers et al[51], published in 2003, refers cardiovascular disease in general, and does not show evidence of benefit in most interventions (nicotine replacement therapy or other pharmacological therapy, self-help materials, individual group or telephone counselling) in these patients. There was just limited evidence

of efficacy of medical or the nursing team counselling. The number of studies available then in cardiovascular patients was small and the effects very limited (only 5 of the 12 analyzed trials showed significant results).

More recently, two systematic reviews were performed, focusing on smokers with coronary heart disease. The review of 33 randomized double-blind clinical trials, included in the review by Ludvig et all[52], demonstrated that each of the smoking cessation aids (nicotine in its several forms, bupoprion and behavioural therapy) increases modestly the abstinence rates at 12 months in coronary patients, comparatively to placebo. There is no evidence showing a significant difference in the efficacy of several aids. The meta-analysis by Barth et al[53], published in 2006, states that psychosocial interventions (behavioural approaches, telephone support, self-help material) have a positive effect in smoking cessation in patients with ischemic disease, versus the usual treatment, if applied for a minimum period of 1 month. The analyzed studies were randomized heterogeneous trials, using the model of random effects.

In what concerns adverse effects of smoking cessation drugs in patients with cardiovascular disease, several RCTs were analyzed individually in the review by Ludvig and the work of Silagy et al[29], already mentioned in the pharmacotherapy chapter. It was seen that high levels of nicotine may be a risk factor to cardiac events. Nevertheless, the risk from nicotine within the replacement drugs currently marketed is probably not superior to the risk of smoking per se. The transdermal patch, through its slow release and reduced nicotine concentrations, was safe in patients with stable coronary disease, and it did not increase the number of events, being considered therefore as a viable option in patients following an acute myocardial infarction (after 2 weeks).

There was no available evidence of quality relating to the safety of gums and inhalers but, considering that they are immediatly released, they should not be recommended to high risk cardiac patients. Bupoprion was considered safe in coronary disease patients.

13.3.2 Pregnancy

Considering the serious risks associated to smoking in pregnant women, several studies were conducted in order to evaluate the efficacy of smoking cessation interventions, when integrated in pre-natal care.

Polanska et al[54] meta-analysis, published in 2003, confirms that the interventions in prenatal smoking significantly increase the smoking cessation rates at the end of pregnancy, and they refer a greater efficacy in interventions including specific material to pregnant women.

In the systematic review by Lumley et al[55], published in 2004, the analysis of 48 randomized and non randomized clinical trials, having significant statistical heterogeneity, has shown that the application of

smoking cessation programmes lead to a reduction of the proportion of women who keep on smoking at the end of their pregnancy. All 16 trials that included information on prenatal outcomes, with demonstrated homogeneity, have revealed a reduction in the occurrence of low weight at birth and pre-term labour. The analysis relating to the occurrence of very low weight at birth, still born babies and peri or neonatal death did not present an adequate statistical power. This review also included 5 trials relating to relapses prevention (800 women) that did not show a significant reduction of relapses.

Concern of use of NRT in pregnant, puerperal or breast feeding women, is centered on the fear of adverse effects on the foetus. In the above mentioned review, NRT did not present a significant advantage over other types of intervention to smoking cessation during pregnancy. On the other hand, the number of trials conducted to date evaluating the drug safety in pregnancy is very small.

Also, there are no published articles on the use of bupoprion as smoking cessation drug during pregnancy.

We might possibly consider the use of pharmacotherapy in smoking pregnant or breast feeding women who cannot cease smoking only with psychosocial interventions, after considering the risks and the fact that its efficacy is not known, opposing to the risks of keeping on smoking. If this is the case, the lower dose of the established therapeutic interval should be used[30].

13.3.3 Psychiatric disease

The results of a meta-analysis with 15 clinical trials, published in 2003 by Hitsman et al[56], suggest that the existence of personal history of major depression is not an independent risk factor to cessation failures in the short or long term in a smoking cessation programme. Consequently, these patients should be offered the interventions identified as effective in this CPG. Considering that slow release bupoprion and nortriptyline – effective treatments to smoking cessation in the general population – are also effective to treat depression, these drugs should be specially considered to the treatment of tobacco dependency in smokers with current or previous history of depressive syndromes.

Prochaska et al[57] meta-analysis indicates that there is a strong evidence that all smoking cessation interventions in individuals involved in treatment programmes for other forms of dependency are effective in the short term, both for patients undergoing treatment as for patients in recovery; however, they are not effective in the long run. These interventions seem to promote as well the long term abstinence of alcohol or illicit drugs.

13.3.4 Young people (adolescents)

Considering the young population, Sussman et al[58] meta-analysis, published in 2006 and including 48 clinical trials, led to the conclusion that young people included in smoking cessation programmes present higher abandon rates in short and long term. It was also seen that these rates are relatively higher in programmes lasting longer than 5 sessions, those that include a motivational component, cognitive behavioural techniques, social influence approaches, or programmes conducted in scholar clinics and within their school class.

Grimshaw and Santon[58] published in the same year in the Cochrane Library a systematic review of 15 randomized and non randomized clinical trials, to evaluate the efficacy of smoking cessation strategies in young people under 20, with an average of at least one cigarette per week (defined as regular smokers). No intervention has shown an increase in smoking cessation rates up to six months, nevertheless the so-called complex interventions (including multiple components – psychological, social, cognitive behavioural), with some persistence of abstinence (30 days or occasional abstinence prevalence at 6 months), and particularly the ones that included elements of the "change stages" model, had some success.

The evidence currently available does not permit to consider that the efficacy, effectiveness and neuropharmacological safety would be different in young people relatively to other smoking groups; however, the only two trials that studied pharmacological interventions (nicotine replacement therapy isolated or combined with bupoprion) in this group of individuals, were small in size and did not present a statistically significant benefit in smoking cessation rates.

13.3.5 Elderly patients

As with younger smokers, smoking cessation in the elderly may reduce the risk of acute myocardial infarction, death due to coronary disease and pulmonary neoplasia[30]. It can also enable faster recoveries from diseases exacerbated by smoking and improve the brain circulation.

The recommended interventions to the general population have also proved beneficial to the elderly; however, due to some individuals' difficulties of mobility and transportation, the pro-active telephone counselling is especially indicated in this population.

13.3.6 Hospitalized smokers

In the particular context of hospitalized patients, it was seen that smoking cessation treatments are effective.

The publication in 2002 of the Rigotti et al[59] meta-analysis, analyzing 17 randomized and randomized clinical trials to interventions in hospitalized patients, showed that behavioural interventions which include contact during hospitalization and at least one month of follow-up are effective in promoting smoking cessation in hospitalized patients. Nicotine replacement therapy increased smoking abandon rates.

13.3.7 Preoperative patients

Moller et al[60], identified 4 statistically heterogeneous clinical trials related to preoperative smoking cessation, and their analysis, as a systematic review, concluded that the preoperative interventions to smoking cessation are only effective in the perioperative period, without a long term significant effect. The available data on the smoking cessation effect in postoperative complications are contradictory, and we need more research in order to issue a valid opinion.

13.3.8 Chronic obstructive pulmonary disease (COPD) patients

Smoking cessation is presently considered the most important therapy of COPD smokers; therefore, it is pertinent to know the efficacy of the different interventions to smoking cessation in this particular group of patients.

In a systematic review, published in 2001, 5 RCTs analyzing smoking cessation in patients with COPD were included; two of them were of high quality. The authors concluded that the combination of pharmacological and psychosocial therapy was superior than the isolated use of psychosocial therapy or the absence of therapy in these patients. Nevertheless, there is no satisfactory level of evidence proving that isolated psychosocial therapy increases the success rate of smoking cessation in patients with COPD[61].

13.3.9 Ethnic and racial groups

Certain ethnic and racial groups present susceptibilities to some diseases susceptible to tobacco use (cardiovascular disease, neoplasias, among others).

According to Fiore et al[30] CPG, these individuals usually have little access to health care and they are not aware of the harms caused by tobacco. Studies have demonstrated that the strategies used in general populations, may be adapted, considering the language and cultural differences.

13.4 Role of health care providers

All health care providers are potential agents for smoking cessation. Over the last several years many reviews have been done on the efficacy of the intervention of several types of health professionals.

The meta-analysis from Gorin e al[62], has shown that counselling from health care providers leads to a small increase in smoking cessation rates. Within the promotion of smoking cessation, the doctors have shown to be the most effective, when compared to multidisciplinary teams, dentists and nurses; nurses seem to be the less effective, although the tendency is not statistically significant; and there was no significant difference between dentists and multidisciplinary teams, although the number of studies involving dentists is rather small. There was also a statistical tendency towards a higher smoking cessation with a larger number of health care providers involved.

Mojica[63] meta-analysis, published in 2005, also involving several types of health care providers, showed that the interventions performed by psychologists, doctors or nurses are effective in smoking cessation.

Lancaster et al[64] systematic review, published in 2004, studied 39 RCTs (31.000 smokers) relating to the medical counselling role in promoting smoking cessation. It was demonstrated, through the analysis of 17 RCTs, that a brief counselling from the doctor, when compared to the absence of counselling, has a small but significant effect in smoking cessation rates. There was no sufficient evidence, from indirect comparisons, to establish a significant difference in the efficacy of medical counselling related to the interventions intensity, the amount of follow-up given or the use of support materials. The direct comparison between intensive and minimum counselling suggested a small advantage from the first one, but the results presented some degree of heterogeneity. Direct comparison also showed evidence of a small but significant benefit of follow-up visits.

The 2006 update of the Rice et al[65] meta-analysis, initially published in 2004 by Cochrane Library, identified 34 randomized clinical trials relative to interventions of nurse professionals in smoking cessation. It was shown that a structured intervention from this class (including counselling, and/or behavioural therapy) in hospital or in clinic, increases the probability of smoking cessation, comparatively to the usual health care. Counselling during tracing or multifactorial secondary prevention programmes has proven to be the less effective. The results of the several trials were heterogeneous, but using a random effects model, there was no change in the estimate of a statistically significant effect.

The role of pharmacists in smoking cessation was analyzed in the systematic review by Sinclair et al[66], comparing a counselling and support programme with data registration, provided by previously trained professional in a communitarian pharmacy, with the support usually given

at the pharmacy. The small number of studies and the significant statistical heterogeneity of results only allowed the conclusion that there is limited evidence that the referred interventions in community pharmacies may have a positive effect in smoking cessation rates.

Carr and Ebbert[67] have published a systematic review of 6 clinical trials, to evaluate the efficacy of interventions by dentists in their practice or in the context of school health. The available evidence suggests that behavioural interventions provided by oral health professionals, along with an oral/dental evaluation component, may increase the smoking abstinence rates among users of non-smoked tobacco. Only one of the analyzed studies included smokers, so there was not enough evidence to conclude on the efficacy of these interventions in that group.

13.5 Special topics

13.5.1 Communitarian interventions

The systematic review by Secker-Walker et al[68], which included only controlled trials, studied community interventions regarding the promotion of smoking cessation. It was shown that, comparing communities with smoking cessation intervention programmes and control communities, there is no impact of those initiatives in the smokers' prevalence.

The community approach will remain an important part of the health promotion activities, but we should consider the limited effect of these initiatives when planning the magnitude of projects and resources to use.

13.5.2 Workplace interventions

"Smoke free" environments and more specifically "smoke free" workplaces, protect non-smokers from the increasingly known harmful effects of passive smoking and may create an environment that encourages active smokers to cease or reduce consumption. The efficacy of interventions for smoking cessation and the effects of smoking restrictions in the workplace, were recently studied in 3 systematic reviews.

The work by Fichtenberg et al[69], published in 2002, studied the differences in consuming and prevalence before and after a workplace becoming "smoke free", or between comparable samples with and without smoke restrictions. The analysis of the 26 selected trials (cohort, cross sectional and population trials) has shown that workplaces totally smoke free are associated to reductions in smoking prevalence of 3.8% and less 3.1 cigarettes smoked per day by working people who keep on smoking.

Smedslund et al[70] meta-analysis, published in 2004, and involving 19 controlled clinical trials, has shown that interventions to smoking cessation in the workplace are effective in the short run (6 months). However, the effect seems to diminish with time, disappearing after 12 months. The effect described was found in both trial groups (randomized and non-randomized), that presented adequate statistical homogeneity. The data found were also consistent with the results of Fisher 1990 meta-analysis, the only one previously conducted on the effects of workplace smoking cessation programmes.

Recently, in 2005, Moher[71] group confirmed some of the main conclusions of the previous work, showing that interventions directed to the smoker, already proven efficient (group therapy, individual counselling and nicotine replacement therapy) are likewise effective when provided in the workplace. Only the self-help methods seem to be less effective. The authors also found limited evidence that the use of incentives and competitions increased the participation in smoking cessation programmes. These results were found only in randomized, but highly heterogeneous, trials. This study also concluded that prohibitions and smoking restrictions reduce smoke incidence in the workplace, but it was not clear that they reduce the prevalence of active smoking or the total smoking load of the working people. This last conclusion opposes the results of Fitchenberg et al, which showed a reduction in the prevalence and daily consumption of cigarettes.

Thus, as it decreases the smoke incidence in the workplace (and consequently passive smoking) and possibly the smoking prevalence and the total smoking load of smokers, we would strongly advise transforming workplaces in "smoke free" environments.

The incentives to smoking cessation may be given in different forms: economical, competitions and financing systems to smoking cessation programmes.

Hey and Perra[72] systematic review, included 15 RCTs and proved that economical incentives and competitions provided within the community context, health service and workplace, do not increase long term smoking cessation rates. Nevertheless, they may increase recruitment rates for a smoking cessation attempt, and indirectly, the number of individuals who successfully quit smoking. Given the impossibility of showing the efficacy of these interventions, it simply is not possible to estimate the respective cost-efficacy relationship. Specifically, regarding contests as *Quit and Win* (created in 1980 by Minnesota Cardiovascular Health Programme and conducted since 1994 twice a year as an international contest) it was shown, in a second systematic review by the same investigators[73], that local and regional proofs seem to increase

smoking cessation rates in spite of the reduced impact in the population smoking prevalence. The international level contests may become an effective intervention to smoking cessation, but it is not possible to draw safe conclusions from the currently available data.

Relating to the financing programmes for smoking cessation programmes (which eliminate costs to the patient), a systematic review by Kaper et al[74] concluded that total financing of smoking cessation programmes increased the number of ex-smokers, the number of participants trying to quit and the use of low cost smoking cessation treatments, comparatively to the partial financial beneficial or the absence of financial intervention; the methodological quality of these trials was low, and there was also some heterogeneity between contexts, interventions and selected participants, which represent some limitative factors, so the results should be interpreted with caution.

13.5.3 Biomedical risk determination

Calculating biomedical risk consists of measuring physiological parameters (e.g. respiratory function tests, measurement of exhaled carbon monoxide, etc.) aiming to supply smokers with a measure of the harmful effects of smoking.

According to the results of the systematic review by Bize et al[75], based in 8 RCTs, there is no quality evidence allowing to draw conclusions on the efficacy of the biomedical risk determination as an incentive to smoking cessation.

13.5.4 Partner support

The systematic review by Park et al[76], of 9 RCTs studied the role of the partner in smoking cessation strategies. It was shown that in interventions for gaining partner's support in smoking cessation programmes did not increase long term cessation rates. Nevertheless, we cannot draw conclusions on the impact of this strategy, since that interventions capable of successfully changing the support given by partners to smokers who wanted to quit smoking are lacking.

13.5.5 Physical exercise

In Ussher[77] systematic review, only one of the eleven selected trials has shown a positive effect of exercise as an auxiliary for long term smoking cessation. Thus, there is no sufficient evidence to recommend physical exercise as a specific auxiliary to smoking cessation. Nevertheless, all trials that did not shown a significant effect presented limitations, namely insufficient sample size to exclude an effect of the interventions, methodological flaws, inadequate interventions (e.g. the exercise level was not sufficiently intense to produce the necessary changes).

There is some evidence that points to the recommendation of physical exercise as a specific auxiliary to reduce symptoms of smoking abstinence and smoking craving. More trials are needed to exclude the psychophisiological basis of this effect.

13.5.6 Training of health care providers

Since the efficacy of the interventions of health care providers in increasing smoking cessation rats is established, it seems coherent to increase the number and the quality of the mentioned interventions, especially if we consider the reduced number of smokers who presently receive counselling from this professional group. The training of health professionals in smoking cessation may become a means to attain that purpose and was studied in two well elaborated systematic reviews.

The results of the Lancaster et al[78] review, published in 2002, concluded that trained professionals have a greater probability of identifying smoking patients and consequently to propose smoking cessation strategies. However, there was no significant evidence that this training actually changes the smoking habits of their patients.

Andeerson et al[79] systematic review, published in 2004, complements the previous one, showing that interventions on increasing primary health care professional involvement are effective, both in increasing smoking cessation rates in patients, as in tracing and professional counselling rates. Training programmes were more effective to training doctors than to more differentiated doctors. It was also concluded that, to training professionals, educational programmes are the most effective ones, and that for established doctors, educational interventions and combined practices are the ones that achieve the better results.

13.5.7 Passive smoking

Currently, there is no evidence to draw conclusions on the most effective intervention to reduce parental smoking, within pediatric health practice, and we cannot extrapolate the usually successfull brief medical counselling used for the adult health context. This information is based on the results of a systematic review designed by Roseby et al[76], and published in 2002, that studied 18 RCTs on several mechanisms eventually involved in the prevention of environmental smoking exposure in children, including paediatricians (0-12 years).

In spite of the information mentioned above, and the fact that there is not currently sufficient evidence of its effectiveness, it makes sense in the context of the paediatric appointment to provide counselling to smoking cessation directed to parents, in order to limit their children exposure to passive smoking.

13.5.8 Weight gain after smoking cessation[30]

Weight gain after smoking cessation is an important concern for many smokers and this may lead to intervention failure. Most ex-smokers gain less than 4.5 kg, but around 10% gain around 13.5 kg or more.

Some evidence suggests that rigorous dieting during the beginning of smoking cessation may later induce failure. There are also data which permits to state that a moderate increase in physical activities may slow the weight gain.

Bupoprion therapy or the use of NRT delays weight gain. However, after finishing the therapy, ex-smokers gain approximately the same weight they would gain if they had not used the therapy. There is also evidence that after a relapse, smokers have tendency to loose the weight gained during the abstinence period. As such, and according to Fiore et al[30], the health care provider should not deny the possibility of a weight gain, nor minimize the importance of that fact to the patient; he should prepare the patient to this eventuality; the greater benefit of smoking cessation should also be stressed out in face of the weight gain; during the smoking cessation attempt it should be stressed the importance of not taking any rigorous measures to avoid weight gain, since the latter can make smoking cessation even more difficult, and, finally, the health care provider should offer to help the patient to loose weight, after an effective smoking abstinence.

13.5.9 Other tobacco products[30]

As tobacco smoke, the use of chewing tobacco or other forms of tobacco (cigar, cigarillo, pipe) increases the risk of stomach, cardiovascular, pulmonary and neoplasic disease.

The available evidence is limited, but it shows benefit of using the described therapies for smoking cessation in smokers of other forms of tobacco. Since the majority of studies focused smoked tobacco in the form of a cigarette, the benefit of pharmacological therapies in smokers of other forms of tobacco it is not precisely known.

14. Outcomes

The outcome is the long term cessation of tobacco use.

15. Implementation strategy

This CPG does not describe, or recommend, a specific implementation strategy.

The users of this document are the agents who naturally will implement the respective recommendations. Nevertheless, in the present CPG appendices, the GLIA (Guideline Implementability Appraisal)[80] instrument is described, and it may be used as a basis to practical implementation schemes.

16. Main recommendations

16.1 Pharmacological interventions

- **Nicotine replacement therapy** (NRT) should be recommended to patients who wish stop smoking (Recommendation level: A)
  - All the available forms of nicotine can be recommended, since they all are equally effective in smoking cessation (Recommendation level: A)
  - The choice of NRT type should consider the patient needs, tolerance and cost (Recommendation level: D)
  - In highly dependent smokers (Fagerström score ≥7) the 4 mg gums should be administered instead of the 2 mg gums (Recommendation level: A)
  - In women, it is more important to associate to NRT an intensive non-pharmacological support. (Recommendation level: B)
  - The combination of transdermal patches with a self-administered NRT form may be recommended in patients who cannot abandon tobacco with a single type of 1st line pharmacotherapy (Recommendation level : B)
- **Bupoprion** is an effective drug and should be recommended to patients who want to stop smoking (Recommendation level A)
- **Nortriptyline** is an effective drug and should be recommended to patients who want to stop smoking (Recommendation level: A)
- **Varenicline** is an effective drug and should be recommended to patients to want to stop smoking (Recommendation level: A)
- **Nicotine replacement therapy, varenicline, bupoprion and nortriptyline** should all be considered as **first line drugs**, to use separately (Recommendation level A); considering, in the drug choice, the needs of the patient, tolerance and cost. (Recommendation level: D)
- **Clonidine** is an effective drug and should be prescribed, under medical supervision, as a **second line drug**, to patients who want to stop smoking (Recommendation level: A). It's sedative effect may be useful in specific patients (Recommendation level: D)

16.2 Non-pharmacological interventions

- **Self-help** materials should be supplied to smokers who are not receiving other type of interventions for smoking cessation. It is more useful to supply brief counselling or individualized self-help materials to smokers who seek help (Recommendation level A)
- The smoker who is motivated to abandon smoking should have the possibility of attending **therapy groups** (Recommendation level: A)
- Pro-active **telephone counselling** should be given to smokers interested in quitting smoking, as there is a dose-response relationship. The response telephone call with counselling increases the usefulness of support telephone lines (Recommendation level: A)
- **Individual counselling** should be supplied by smoking cessation trained professionals outside the clinical practice environment and lasting over 10 minutes (Recommendation level: A)
- **Physical exercise** may be recommended to individuals with greater intolerance to abstinence symptoms and craving. (Recommendation level: D).

16.3 Role of health care providers

- Any health care provider (doctor, nurse, psychologist or multidisciplinary professional teams) should cooperate to smoking cessation with smokers they usually have contact with (Recommendation level: A). Dentists should also perform these interventions whenever possible. (Recommendation level: B).
- Doctors, as the most effective professionals in smoking cessation, should be the priority elements in the application of interventions to this purpose. (Recommendation level: A)
- All doctors should offer their patients counselling regarding smoking cessation (Recommendation level: A), and perform, if possible, at least one follow-up appointment (Recommendation level: B)
- Nurses should, whenever possible, provide smokers, hospitalized or not, with a structured intervention to smoking cessation, including counselling and/or behavioural therapy (Recommendation level: A)
- All health professionals working in community pharmacies should, whenever possible (and after previous training), provide their smoking patients counselling to smoking cessation. This counselling should, if possible, be accompanied by a support programme with data registration. (Recommendation level: B)

16.4 Special populations

16.4.1 Cardiovascular patients

- The methods of smoking cessation considered in this CPG should be recommended to patients with cardiovascular disease who smoke (Recommendation level: A)
- Patients with worsening cardiac disease or acute myocardial infarction should only make behavioural therapy and/or bupoprion (Recommendation level: B)
- Patients with coronary disease or stable cardiac disease should take bupoprion, nicotine patches and/or behavioural therapy, and abstain from inhaled nicotine or nicotine gums. (Recommendation level: B)

16.4.2 Pregnancy

- Behavioural evaluation and smoking cessation programmes should be implemented in every context of pre-natal care, and the pregnant women should be offered all interventions that exceed minimal counselling (Recommendation level: A)
- The use of pharmacotherapy in pregnant or breast feeding women can be considered whenever the smoking cessation is not achieved with only psychosocial interventions, and when the probability of cessation and the associated potential benefits overcome the risks. In this case, the lowest dose of the established therapeutic interval should be used (Recommendation level: D).

16.4.3 Psychiatric disease

- In presence of a previous history of major depression, all the interventions identified as effective in this CPG should be used, including counselling and pharmacotherapy. (Recommendation level: A)
- Slow release bupoprion and nortriptyline should be specially considered in treating tobacco dependence in smokers with current or previous history of depressive syndromes (Recommendation level: D)
- The smoking cessation interventions considered effective in the present CPG, including counselling and pharmacotherapy, should be offered to smokers being treated or recovering from other dependencies (Recommendation level: A).

16.4.4 Young people

- All counselling and behavioural interventions to smoking cessation considered effective to the adult population in the present CPG may also be applied to teenage smokers. The programmes should include multiple components, namely motivational, cognitive-behavioural techniques, social influence approaches and/or interventions within the school/class environment. (Recommendation level: B).

16.4.5 Elderly

- All smoking cessation treatments were proven effective in elderly adults. Thus, these should receive the smoking cessation treatments considered effective in the present CPG. (Recommendation level: A).

16.4.6 Hospitalized smokers

- The hospitalized patients should be offered smoking cessation behavioural interventions including contact during the internal periods and at least one month of follow-up (Recommendation level: A). If possible, all other types of strategies considered valid in the present CPG can be used as well.

16.4.7 Preoperative patients

- Preoperative patients should be offered the smoking cessation interventions considered valid in the present CPG (Recommendation level: B).

16.4.8 Chronic obstructive pulmonary disease (COPD) patients

- COPD patients should receive combined pharmacological and psychosocial therapy to smoking cessation (Recommendation level: A).

16.4.9 Ethnic and racial groups

- All smoking cessation treatments have been effective in different racial and ethnic groups, so all treatments considered effective in the present CPG should be supplied to these patients (Recommendation level: A)[81]
- The tobacco dependency treatments should be, whenever possible, changed or adapted to become appropriate to the specific racial and ethnic population to whom they are supplied (Recommendation level: D)[81].

16.5 Special topics

16.5.1 Workplace interventions

- All workplaces should be smoke free. (Recommendation level: A)
- The smoking cessation interventions considered effective in this CPG should, if possible, be offered in workplaces. (Recommendation level: A)
- Incentives and competitions can be used to increase smoking cessation programmes adherence in workplaces (Recommendation level: B).

16.5.2 Training of health care providers

- Smoking cessation training programmes should be provided to primary health care providers who can have an active role in this area. (Recommendation level: A)
- Training programmes for doctors in training should include preferably an educational component; the programmes to differentiated doctors should include combined interventions with a practical and educational component. (Recommendation level: A).

16.5.3 Passive smoking

- The paediatricians should offer parents smoking cessation counselling to limit their children's exposure to passive smoking (Recommendation level: D).

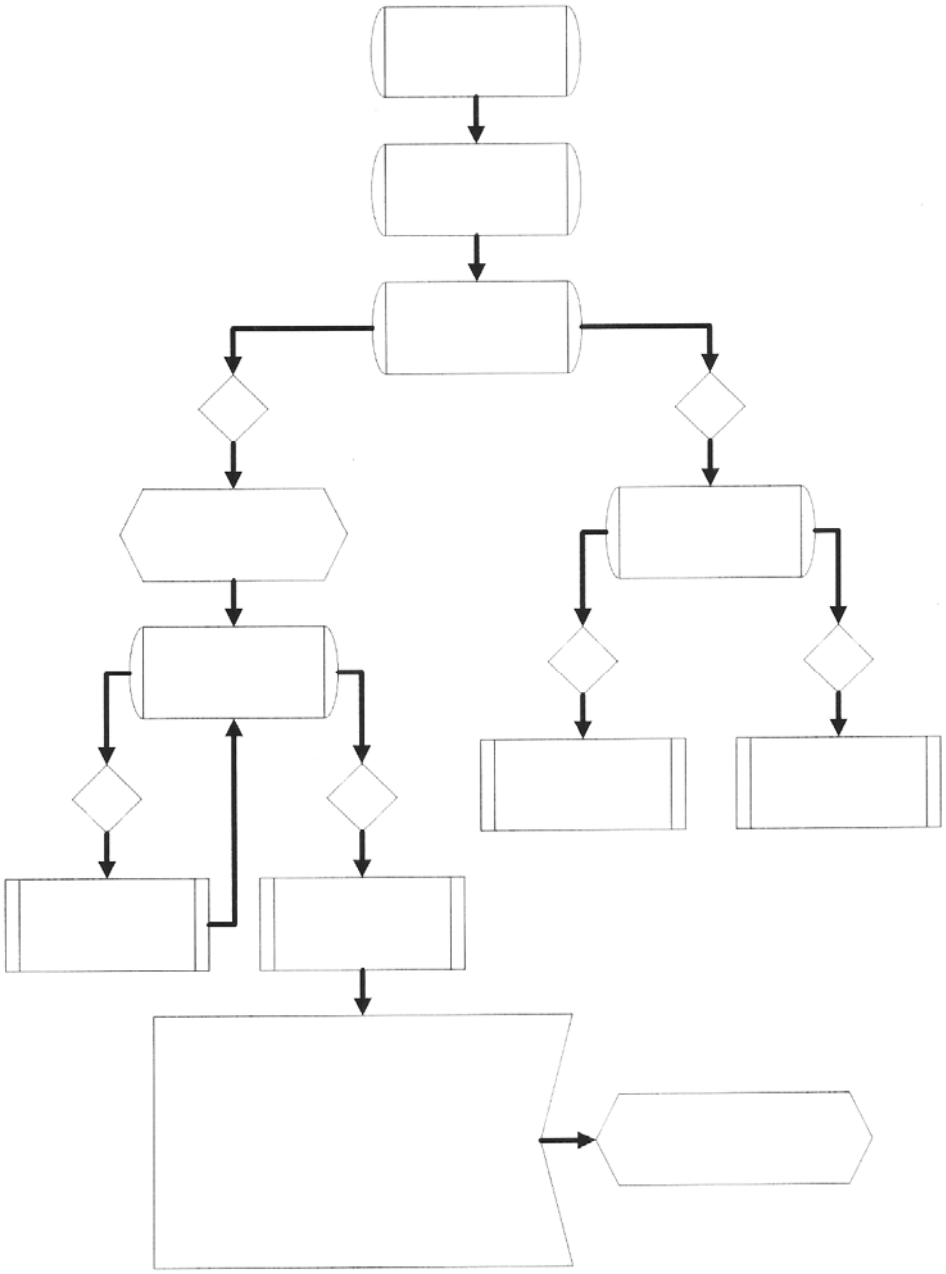
16.5.4 Weight gain after smoking cessation

- The health professional should recognize that smoking cessation is frequently followed by weight gain. Additionally, he should: a) underline that the health risks related to weight gain are small, comparing to the risks associated to the persistence of smoking; b) recommend physical activity and a healthy diet; c) recommend that patients should focus primarily in smoking cessation and not weight control, until ex-smokers become confident on their abstinence (Recommendation level: D)
- In case of smokers highly concerned with weight gain, it may be appropriate to prescribe or recommend slow release bupoprion or nicotine replacement therapy, especially chewing gums, which proved to delay the weight gain after cessation. (Recommendation level: B).

16.5.5 Other tobacco products

- Cigar, pipe and other combustible forms of tobacco users should be identified and strongly advised to quit, and should get the same counselling interventions recommended to cigarette smokers. (Recommendation level: D)

17. Clinical algorithm



17.1 Screening and assessment of tobacco use

The first step to smoking cessation consists in identifying smokers[30, 81]. Doctors have a privileged position, since a large number of tobacco consumers go to the doctor at least once a year, and a large percentage of smokers – about 70% according to Fiore et al[30] – want to quit. In spite of smokers quoting medical intervention as an important stimulus to the cessation, most clinicians do not recognize them or do not advice and/or offer help to smoking cessation in a regular basis.

The awareness of doctors in identifying and giving support to smokers in their attempt to smoking cessation opens doors to interventions with potential success and guides the clinician to the type of intervention to supply each individual smoker. Thus, there are four types of responses that may be obtained within screening for tobacco use:

- The patient smokes and wishes to quit
- The patient smokes, but does not wish to quit for the moment
- The patient has smoked but he has already stopped
- The patient was never a regular consumer of tobacco.

According to the situation of the patient, there are different interventions that may be lead by the doctor and which we will describe in the next paragraphs.

17.2 Brief clinical interventions

The brief interventions[30,81] may be conducted by any health care provider, but are primarily directed to primary care doctors. They are an effective strategy in smoking cessation and have as a purpose to change the clinical culture and practice standards, in a way that each smoker is identified and offered treatment, at the same time that they consider the difficulties of managing the short time available for each patient's appointment. As such, it is essential that all tobacco users are subject to a brief intervention in each appointment, even if they are not available to intensive interventions.

This chapter describes the brief intervention according to the response obtained during the smoker's evaluation:

A. Smokers who wish to make and attempt to quit immediately
B. Smokers who do not wish to make an attempt to quit at this moment
C. Recent ex-smokers.

17.2.1 Smokers who wish to make an attempt to quit immediately

The five main steps (the "5 A's") of intervention in smoking cessation within the primary healthcare context are (see Table 31.2.1):

1. Approach the patient on tobacco consumption;
2. Advise the patient to stop smoking;
3. Assess the will to try to quit;
4. Assist the quitting attempt;
5. Accompany through follow-up appointments to prevent relapses.

These strategies were conceived to be brief. Pharmacological therapy should be provided to all smokers beyond counselling (see Tables 31.2.2 and 31.2.3), except in special circumstances, namely contraindications described above.

17.2.2 Smokers who do not wish to make an attempt to quit at the moment

The evaluation of tobacco use should be done as a routine. Smokers who do not wish to quit may not be aware of the damaging effects of tobacco, may have fears relating to the consequences of abstinence, may lack economical resources, or may be demoralized by previous relapses. These patients have the possibility of responding to a motivational intervention, designed to educate, reassure and motivate (see Table 31.2.4). The motivational interventions are more effective when the doctors have an emphatic posture, promote the patient autonomy (e.g. choice between different options), avoid arguments and support the patient individual performance (e.g. by identifying previous successes in behavioural changes).

17.2.3 Recent ex-smokers

Tobacco dependency should be seen as a chronic disease, and relapses have been identified mainly in the two first years after the beginning of smoking cessation (Wu et al[28]). According to Hajek et al[49] review, there was no consistent evidence of the benefit of prevention of relapse. Nevertheless, we may recommend minimal interventions based on the reinforcement of the importance of cessation and the availability of helping to solve obstacles that can make the maintenance of smoking cessation difficult. (see Table 31.2.5).

17.3 Intensive clinical interventions

In the systematic review by Lancaster et al[47] it was not possible to establish a statistical significant benefit of intensive clinical interventions. Nevertheless, it is not possible to exclude a dose-response relationship, so,

in motivated individuals may be beneficial to supply this type of interventions performed by professionals specialists in smoking cessation that have the necessary resources to intensive interventions[30]. In Table 31.2.6 the components of an intensive intervention are presented.

18. Qualitative reserves

We did not find hiatus of knowledge of significant dimension. The scientific evidence on which this CPG is based upon is of an excellent quality, since there are multiple systematic reviews (of Cochrane Collaboration amongst others), as well as randomized and controlled trials (RCTs) of good methodological quality, with consistent and relevant results.

19. Cost analysis

There was no cost analysis performed to determine the costs of the possible treatments to smoking cessation. The only economic information available is the daily average prices of the several therapeutic schemes.

20. General and subgroups potential benefits

To the population in general, the benefits that may be gained of the successful application of the present CPG recommendations regard the prevention of all diseases related to the use of tobacco (previously mentioned). Thus, all population – including the healthy individuals – may benefit from these measures.

The subgroups in which smoking cessation will present greater benefits include cardiac patients (especially coronary), vascular patients (specially the patients with peripheral arterial impairment), patients with pulmonary disease (namely COPD), the diabetics, the elderly, young people and pregnant women.

21. General and subgroups potential risks

There are no significant potential risks for any patient groups or smoking cessation patients. The benefits are universal.

22. Availability

This CPG text will be available as follows:

- Printed as a book/manual;
- Available on-line at the official site of CEMBE and others
- As a CD-ROM in Portuguese and English.

23. Attached documents

The decision algorithm will be available individually, in order to allow all potential users of the present CPG to have a fast and effective access to a synthesis of the recommendations of the present CPG.

24. Patients' resources

There are no resources specifically directed to patients who wish to quit smoking permanently available.

25. Supporters and subscribers

- COPPT
- IPPT
- Sociedade Portuguesa de Pneumologia
- Sociedade Portuguesa de Cardiologia
- Associação Portuguesa de Médicos de Clínica Geral
- Ordem dos Médicos
- Ordem dos Médicos Dentistas
- Ordem dos Farmacêuticos
- Faculdade de Medicina de Lisboa

26. Committees and responsible group

The entity responsability for the elaboration of the present CPG is from the Center for Evidence Based Medicine (CEMBE) at the University of Lisbon School of Medicine in Portugal.

The authors of the present CPG are part of the Clinical Practice Guidelines Department Group from CEMBE and they are: Inês Reis MD, Philip Fortuna MD, Raquel Ascenção MD, António Bugalho MD, João Costa MD and António Vaz Carneiro MD, PhD.

27. Funding sources

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28. Editorial independence

The present CPG is the intellectual property of the authors, who declare that they do not have any conflicts of interest on their part and and with their relationship with the sponsor, government, insurance companies, scientific and professional societies, patient associations or any other entity.

The expressed points of view and the final recommendations are the exclusive responsibility of CEMBE, and they were not influenced by any means by any institution or individuals not related to the authors.

29. Publication date

Completed in August 2007 and reviewed and published in October 2007.

30. Reviews

The present CPG will be reviewed, partially or globally, in 2012.

31. Appendices

31.1 Fagerström scale (evaluation of the dependency level)

Question to ask	Points
How soon after you wake up do you smoke your first cigarette?	
≤ 5 minutes	3
6-30 minutes	2
31-60 minutes	1
≥ 61 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden? (e.g. theatres, airplanes, hospitals)	
Yes	1
No	0
3. Which cigarette would you most hate to give up?	
First in the morning	1
Any other	0
4. How many cigarettes per day do you smoke?	
≤ 10 (less than half a pack)	0
11 - 20 (half to one pack)	1
21 - 30 (one pack to a pack and a half)	2

≥ 31 (more than one pack an a half)	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day? Yes No	 1 0
6. Do you smoke even if you are so ill that you are in bed most of the day? Yes No	 1 0

Scores:

- 7 - 10 = very high nicotine dependence
- 4 - 6 = medium nicotine dependence
- less than 4 = low nicotine dependence

31.2 Synoptic tables

31.2.1 Brief strategies to help the patient who wishes to quit smoking – "5 A's" Strategy

Action	Strategies for implementation
Step 1. Approach – systematically identify all tobacco users at each appointment	
Implement a system that assures that, for each patient in each appointment, tobacco use is investigated and documented	Add to the appointment notes a field relating to the use of tobacco
Step 2. Advise – incentive all tobacco users to quit with conviction	
In a clear, persuasive, strong and personalized way, encourage all tobacco users to quit	Counselling should be: • *Clear* – "I believe it is important for you to quit immediately and I can help you. To reduce only when you are ill is not enough." • *Strong* - "As your doctor I want you to know that stop smoking is the most important thing you can do to protect your health right now and in the future. I will be available to help you." • *Personalized* – Associate the use of tobacco to the present disease, and/or to its social and economic costs, level of motivation/availability to quit and/or the impact of tobacco use on the children and other members of the family
Step 3. Assess – determine if the patient wishes to try to quit	
Ask each tobacco user if he is willing to attempt to try to quit immediately (e.g.: within the following 30 days)	Assess the patient's will to quit: • If the patient wishes to make an attempt to quit immediately, provide the necessary assistance • If the patient wishes to participate in an intensive treatment, supply the treatment or refer the patient to

	intensive intervention • If the patient clearly states that he does not want, for the moment, to make an attempt to quit, supply a motivational intervention • If the patient is a member of a special population (teenager, pregnant women, racial/ethnic minority), consider supplying additional information
Step 4. Assist – assist the patient in his attempt to quit	
Elaborate, together with the patient, a plan to abandon the use of tobacco	Preparation of the patient to the abandon attempt: • Schedule a date: ideally, the abandon date should be within two weeks • Inform the family, friends and co-workers on the abandon attempt, and demand understanding and support • Anticipate difficulties that may arise during the abandon attempt. Particularly in the first weeks, the most critical ones. Among these, nicotine abstinence symptoms • Remove tobacco products from the environment before starting, avoid smoking in places where you spend a lot of time (workplace, home, car)
Supply practical counselling	• *Abstinence* – total abstinence is essential • *Experience of previous abandon attempts* – identify what helped and what went wrong in previous abandon attempts • *Anticipate problems or difficulties in the abandon attempt to be started* – discuss challenges / stimulus and how the patient can overcome them with success • *Alcohol* – the patient should consider to limit or abstain drinking alcohol, since its use may lead to relapses • *Other smokers at home* – abandon is more difficult when there are other smokers at home. Patients should encourage the people they live with to quit at the same time or not to smoke in their presence
Supply social support intra-treatment	Supply a supportive clinical environment when encouraging the patient in his attempt to quit "*We are available to help you*"
Help the patient to obtain social support extra-treatment	Help the patient to develop social support to his abandon attempt, in this environment, outside the treatment. "*Ask your family, friend and co-workers to help you in your attempt to quit*"
Recommend the use of approved pharmacotherapy, except in special circumstances	Recommend the use to effective pharmacotherapy. Explain how drugs increase the probability of success and reduce abstinence symptoms. 1st line drugs include: varenicline, bupoprion, nicotine replacements and nortriptyline.
Supply self-help materials	• *Type*: appropriate to the patient, relating to his culture, race, education, age and motivation • *Location*: readily accessible in each clinical practice

Step 5: Accompany – Schedule follow-up appointment	
Schedule follow-up appointment, either personally or by telephone	• *Date* – The follow-up appointment should be scheduled shortly after the abandon date, preferably during the 1st week. A second follow-up appointment is recommended in the 1st month. Schedule additional appointments as needed. • Actions during the follow-up appointment – Congratulate success; if tobacco has been used, review the circumstances and incentive new commitment with total abstinence; remind the patient that a lapse my be used as a learning experience; identify problems already found and anticipate difficulties in the immediate future; evaluate the use and problems of pharmacotherapy; consider the use or reference to a more intensive treatment.

Table adapted from Fiore MC, Bailey WC Cohen SJ, et al. Treating Tobacco Use and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000, pp 28-31.

31.2.2 General clinical practice guidelines to prescribe pharmacological therapy to smoking cessation

Who should receive pharmacological therapy to smoking cessation?	All patients in process of somoking cessation, except in the presence of special circumstances: clinical contraindications, pregnant and breast feeding women and teenagers
What are the 1st line pharmacological therapies?	Varenicline, slow release bupoprion chloridrate, nortriptyline and nicotine replacement therapies (chewing gums and transdermal patches)
What factors should be considered when choosing a 1st line pharmacological therapy?	Due to the non-existence of sufficient data to order these drugs, the choice of a specific 1st line pharmacological therapy should be guided by factors such as: • familiarity of the doctor with the drugs • contraindications to selected patients • preferences of the patient • previous experience of the patient with a specific drug (positive or negative) • characteristics of the patient (e.g.: history of depression, concerns with weight gain)
What are the recommended 2nd line pharmacological therapies?	Clonidine chloridrate

When should 2nd line agents be used to treat tobacco addiction?	In patients who cannot use 1st line drugs due to contraindications, or in patients in whom the 1st line drugs are not useful. Patients should be monitorized relating to clonidine adverse effects.
What are the pharmacological therapies most adequate to patients concerned with weight gain?	Slow release bupoprion chloride and nicotine replacement therapies, in particular nicotine chewing gums (that delay but do not prevent weight gain)
Are there pharmacological therapies that should be specially considered in patients with history of depression?	Slow release bupoprion chloride and nortriptyline chloride
Can pharmacological therapies for smoking cessation be used in patents with history of cardiovascular disease?	Yes. Patients with coronary disease or other stable cardiac diseases, should take bupoprion or nicotine patches, not inhaled nicotine or nicotine gums. Patients with worsening of the cardiac disease or recent acute myocardial infarction (< 2 weeks) should only use bupoprion.
Can smoking cessation pharmacological therapies be used in the long term (6 months or more?)	Yes. This approach can be useful in smokers who present persistent symptoms of abstinence during the course of the pharmacological therapy, or that want to use long term therapy. Nevertheless, it was verified that 8 weeks of therapy using the nicotine transdermal patch, is as effective as the longer regimens. The long term use of these drugs does not present a known health risk.
Can pharmacological therapies be combined?	Yes. There is limited evidence that combining nicotine transdermal patch with nicotine chewing gum increases the abstinence rates relatively to the use of each of these drugs individually.
	The chewing gums can be used in a fixed dosage regimen or in a free dose basis.

What are the most appropriate dosages for nicotine replacement therapies?	Highly dependent smokers or the ones who failed with 2 mg chewing gum, should use the 4 mg gum. It is not been shown that the use of the nicotine transdermal patch in doses higher than 22mg/24h is more effective in achieving long term abstinence. There is no evidence that the gradual reduction of therapy is better than the abrupt suppression.

Table adapted from Fiore MC, Bailey WC Cohen SJ, et al. Treating Tobacco USE and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000, pp 26-27

31.2.3 Drugs available in Portugal with recognized efficacy in smoking cessation

	Drug	Pharmaceutical form	Dosage	Trade Mark®	Pack	Dosage	Recommendations	Adverse Reactions	Contra-indications
1st LINE	Nicotine	Gums/Chewing Gums	1,5mg	Nicopass	12, 36 or 96 units	• Initiate: 2 mg if habits < 20 cigarettes/day • Initiate: 4 mg if habits ≥ 20 cigarettes/day • Initially: 8-12 units/day • Maximum dosage: 50mg/day • Tt duration: 8-12 weeks	• Initiate tt on the stipulated day for cessation • Do not smoke concomitantly • Slow and cyclic chewing until obtaining a strong flavour; then promote contact with bucal mucosa • Average duration each unit ±30 min • No intake food or drinks (except water) 15 minutes before and during the chewing process	• Tempor-mandibular articulation pain • Unpleasant taste • Oral ulceration • Hiccups • Odinofagia • Nausea • Meteorism • Dyspepsia • Headaches	• Non smokers • Maintenance of smoking habits • AMY <4 weeks • Unstable angina • Serious arrhythmia • Stroke in evolution • Pregnancy • Breast feeding • <18 years • Oropharynx disease • Tempor-mandibular articulation disease • Dental changes • Dental protesis
			2mg	Nicorette	30 or 105 units				
				Nicotinell fruit Nicotinell mint	24 or 96 units				
				Niquitin	72 units				
			4mg	Nicorette	30 or 105 units				
				Nicotinell mint Nicotinell fruit	24 or 96 units				
				Niquitin	72 units				
		Transdermal system	21mg/24h	Nicotinell TTS 30	14 or 28 units	• Initiate: one patch of 21mg/24h or 15mg/16h during 4-6 weeks if habits ≥ 20 cigarettes/day • Initiate: one patch of 14mg/24h or 10mg/16h during 4-6 weeks if < 20 cigarettes/day	• Initiate tt on day stipulated to cessation • No concomitant smoking • Apply in the morning on healthy, clean and dry skin • Place preferably in the chest or any members proximal portion	• Skin irritation • Pruritus • Mialgia • Headache • Vertigo • Insomnia • Somnolence • Nausea • Vomit • Dyspepsia • Palpitations • Tachycardia •	• Non smokers • Maintenance of smoking habits • AMY <4 weeks • Unstable angina • Serious arrhythmia • Stroke in evolution • Pregnancy • Breast feeding • <18 years • Serious dermatological
				Niquitin clear	7 or 14 units				
			14mg/24h	Nicotinell TTS 20	14 or 28 units				
				Niquitin clear	7 or 14 units				
			7mg/24h	Nicotinell TTS 10	14 or 28 units				
				Niquitin clear	7 units				
			15mg/16h	Nicorette 15	14 or 28 units				

			10mg/16h	Nicorette 10	14 units	• Subsequent therapeutic periods of 2-4 weeks with gradual reduction to transdermal system with lower dose of nicotine release • Tt duration: 8-12 weeks	• Change local of application, avoiding panniculus adiposus, breasts and articular areas • Replace patch after 24h • If insomnia remove 24 h patch in the evening or choose the 16h ones	Precordialgia • Hypertension	disease
			5mg/16h	Nicorette 5	14 units				
1st LINE	Bupoprion	Slow release tablets	150mg	Zyban	60 units	• Initiate: 150 mg/day during 3 days • Day 4: increase to 150mg 12/12h • Maximum dosage: 450mg/day • Duration: 7-12 weeks (after cessation) • Maintained AE, renal or hepatic impairment, cardiopathy ischemia, diabetes mellitus, >65 years: maintenance dosage 150mg/day	• Initiate tt 2 weeks before the stipulated date for cessation. • Administrate with food • In case of insomnia, anticipate the 2nd daily dose to 8h after the first • In some patients tt can be maintained until a maximum of 6 months after cessation • It can be associated to NRT	• Insomnia • Xerostomia • Tremor • Weight loss • Headaches • Irritability • Anxiety • Nausea • Constipation • Hypertension	• Hypersensitivity • Epilepsy or convulsions • Anorexia or bulimia • Concomitant use of MAO inhibitors • Alcoholic or sedatives abstinence • Bipolar disorders • AMY <4 weeks • Pregnancy • Breast feeding

	Vareniclin e	Tablets	0,5mg	Champix	28 or 56 units	• Initiate: 0,5mg/day 3 days • 4th to 7th day: 0,5mg 12/12h • >7th day: 1mg 12/12h • Tt duration: 12 weeks (if tt effective after the 1st 3 months, consider 12 additional weeks with 1mg/day) • AE maintained or serious renal impairment: maintenance dose 0,5mg 12/12h	• Initiate tt 1-2 weeks before the stipulated date for cessation • Administrate with or without food	• Insomnia • Somnolence • Nightmares • Irritability • Headaches • Nausea • Fatigue • Increased appetite	• Hypersensitivity • Terminal renal impairment • <18 years • Pregnancy • Breast feeding
			0,5mg+1mg		11 units 0,5mg + 14 units 1,0mg				
			1mg		28 or 56 units				
	Nortriptylin e	Coated tablets	25mg	Norterol	10 or 60 units	• Initiate 25mg/day 3 days • 4th to 7th day: 50mg/day • >7th day: 75mg/day • Maximum dosage: 150mg/day • Tt duration: 8-12 weeks	• Initiate tt 10-14 days before the scheduled date to cessation • Sedation may influence driving ability • Overdose may lead to cardiotoxicity	• Somnolence • Xerostomia • Tremor • Urinary retention • Arrhythmia • Blurred vision • Hallucinations • Restlessness • Constipation	• Hypersensitivity • concomitant use of MAO inhibitors • AMY <4 weeks • Pregnancy
			50mg		60 units				

								• Nausea	
2nd LINE	Clonidine	Tablets	0,15mg	Catapresan	20 or 60 units	• Initiate: 0,15mg 12/12h • Growing titulation of 0,15mg/day each 7 days if necessary • Maximum dosage: 0,9mg/day • Tt duration: 3-10 weeks	• Initiate tt ≤3 days previous to the stipulated date to cessation • Therapy should not be stopped abruptly • Sedation may influence driving • Dose adjustment in renal impairment	• Xerostomia • Somnolence • Dizziness • Vertigo • Constipation • Depression • Hydrosaline retention • Orthostatic hypotension • Bradicardia sinusal • Atrioventricular block	• Sinusal knot disease • 2nd and 3rd degree atrioventricular block • Cerebral and peripheral hypoperfusion • Hypersensitivity • Concomitant use of β-bloquers • Syndrome of abstinence if sudden suspension • Pregnancy • Breast feeding

31.2.4 Increase the motivation to smoking cessation – "5 Rs" strategy

Relevance	Encourage the patient to describe in what measure is the abandon personally relevant, trying to be as specific as possible. The motivational information has a greater impact if it is relevant to the state of the disease or risk factors to the patient, family or social status (e.g. existence of children at home), health concern, age, sex and other important characteristics of the patient (e.g.: previous abandon experience, personal barriers to cessation).
Risks	The doctor should ask the patient to identify potential negative consequences of tobacco use. He may suggest and clarify the ones that seem more relevant to the patient. He should also stress that smoking low tar or light nicotine cigarettes or using other forms of tobacco (e.g.: free smoke tobacco, cigarillos, pipe) do not eliminate these risks. Some risk examples: • *Acute risks*: dyspnoea, asthma exacerbation, pregnancy hazard, impotence, increase of carbon monoxide levels in serum; • *Long term risks*: myocardial infarction, stroke, pulmonary neoplasias, other neoplasias (larynx, oral cavity, pharynx, oesophagus, pancreas, bladder, cervix uteri), chronic obstructive pulmonary diseases (chronic bronchitis and emphysema) long term disability and need to continuous care; • *Environmental risks*: higher risk to pulmonary neoplasia and cardiac disease in the partner; higher rates of smokers amongst children of tobacco users; higher risk of low birth weight, sudden infant death syndrome, asthma, disease of the medium ear, and respiratory infections, in smokers' children.
Rewards	The doctor should ask the patient to identify potential benefits of suspending tobacco use, and he can suggest and clarify the ones that seem more relevant to the patient. Examples of benefits: better condition, all food tastes better, improved sense of smell; reduction of expenses; feel better with one self; the house, the car, clothes and breath have a better smell; you do not have to worry about the cessation any more; it's a good example to your children; children are healthier; you feel in a better physical condition; better performance in physical activities; delays skin ageing.
Resistances	The doctor should ask the patient to identify barriers or obstacles to the cessation and indicate treatment forms (problem resolution, pharmacotherapy) addressed to their resolution. Examples of typical difficulties: abstinence symptoms; fear of failing; weight gain; lack of support; depression; having pleasure in tobacco.
Repetition	The motivational intervention should be repeated each time a non motivated patient comes to an appointment. Tobacco users who have failed in several previous attempts should be informed that many people make repeated attempts until attaining success.

Table adapted from Fiore MC, Bailey WC Cohen SJ, et al. Treating Tobacco USE and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000, pp 32-33.

31.2.5 Components of brief strategies to prevent tobacco use relapses

Minimal intervention	
These interventions should be part of all the appointments with a patient who has recently abandoned the use of tobacco	All ex-tobacco users should be congratulated for their achievement and strongly encouraged to remain abstinent. When faced with a recent ex-smoker, you should use open-ended questions with the purpose of promoting the resolution of problems by the patient himself (e.g.: in what manner was the suspension of tobacco use a benefit to you?). The doctor should encourage the active discussion by the patient of the following topics: • the benefits, including potential health benefits, that the patient my obtain from cessation • any success the patient might have had during the abandon process (e.g.: abstinence duration, decrease of abstinence symptoms) • The problems found or predicable difficulties in keeping abstinence(e.g.: depression, weight gain, alcohol, other tobacco users at home)
Directed prevention of relapses	
The components of the directed prevention of relapses are individualized according to the problems experienced by the patients when trying to keep abstinence. These more intensive interventions of relapse prevention may be applied during the scheduled follow-up appointment (in person or by telephone). Below we present a list of some specific problems that the patients may refer and some possible answers.	
Problems	**Responses**
Lack of support to cessation	Programme follow-up appointments or telephone calls with the patient. Help the patient to identify support sources in his environment. Reference the patient to appropriate organizations that offer counselling or support.
Negative humour or depression	If significant, give counselling, prescribe appropriate medication or reference the patient to a specialist.
Strong or prolonged abstinence symptoms	If the patient refers craving or other abstinence symptoms, consider to prolong the use of pharmacotherapy or add / combine drugs to reduce strong abstinence symptoms.
Weight gain	Recommend initiating or increasing physical activity; discourage strict diet. Stress the importance of a healthy diet. Reassure the patient that some weight gain after abandon is common and seems to be self-limited. Keep the patient with a pharmacotherapy that delays weight gain (e.g.: slow release bupoprion chloride and nicotine replacement therapies, particularly nicotine chewing gums). Reference the patient to a specialist or specialized programme.
Fall of motivation/feeling of loss	Reassure the patient that these feelings are common. Recommend compensating activities. Investigate to be sure that the patient does not use tobacco periodically, since that consumption increases the smoking stimulus, making the abandon more difficult.

Table adapted from Fiore MC, Bailey WC Cohen SJ, et al. Treating Tobacco USE and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000, pp 34-35

31.2.6 Components of an intensive intervention to abandon the habit of smoking

Component	Implementation strategy
Evaluation	The evaluation should assure that the tobacco users wish to make an abandon attempt using an intensive treatment programme. Other evaluations may supply useful information to counselling (e.g.: stress level, co morbidity presence)
Programme professionals	Multiple types of professionals are effective and should be used. A counselling strategy would be to place a doctor providing messages on risks and benefits to health and prescribing pharmacotherapy, and non-clinical professionals supplying additional psychosocial or behavioural interventions.
Programme intensity	Due to the evidence of a strong dose-response relation, the programme should consist of 4 or more sessions, being the longest session over 10 minutes (Total contact time= 30 minutes)
Programme format	Individual or group counselling can be used. Pro-active telephone counselling is also effective. The use of adjuvant self-help material is optional. Intervention processes should be used in follow-up evaluations.
Types of counselling and behavioural therapies	Counselling and behavioural therapies should include practical counselling (problems resolution / performance training) and social support intra and extra-treatment.
Pharmacotherapy	All smokers should be encouraged to use the pharmacotherapies mentioned in the present CPG, except in special circumstances. In selected populations (e.g.: pregnant women, teenagers) the use of pharmacotherapy should be subject to special considerations. The doctor should explain the patient the way these drugs increase the success rate of smoking cessation and reduce abstinence symptoms.
Population	The intensive intervention programmes can be used with all tobacco users who wish to participate

Table adapted from Fiore MC, Bailey WC Cohen SJ, et al. Treating Tobacco USE and Dependence, Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000, p. 39.

31.3 The Agree Instrument

PLEASE SEE ATTACHED FILE

31.4 The GLIA Instrument

PLEASE SEE ATTACHED FILE

31.5 Glossary

This glossary aims to standardize – as far as possible – the methodological and scientific concepts applied to the base studies of any CPG. If was initially published in *Revista Portuguesa de Cardiologia* (2001;20:99-103 and 2001;20:203-210) to whom we thank permission to publish.

31.5.1 TERMS USED IN THE DIAGNOSIS

		Results of the reference test	
		Existing disease a + c	Non existing disease b + d
Result of the diagnosis test	Positive test a + b	True positive A	False positive b
	c + d Negative test	C False negative	d True negative

- **Sensitivity** (a/a+c): proportion of patients with the target disease presenting a positive test.
- **Specificity** (d/b+d): proportion of patients without the target disease presenting a negative test.
- **Positive predictive value** (a/a+b): proportion of patients with a positive test with the target disease.
- **Negative predictive value** (d/c+d): proportion of patients with a negative test without the target disease.
- **Precision** (a+d)/(a+b+c+d): proportion of patients correctly classified through the test (true positive + true negative).
- **Pre-test probability (prevalence)** (a+c)/(a+b+c+d): proportion of patients who have the target disease, determined before the use of the diagnostic test.
- **Pre-test odds**: likelihood of the patient having the target disease before the use of diagnostic test. Calculation: prevalence/1- prevalence.
- **Post-test odds**: likelihood of the disease after the application of the diagnostic test. Calculation: pre-test odds x likelihood ratio.
- **Post-test probability** (post-test odds/1 + post-test odds): proportion of patients with a given result presenting the target disease.
- **Likelihood ratio** (LR): relationship between the probability of a given outcome in the population with the target disease and the likelihood of that outcome amongst non-patients. The LR can be a positive result (sensitivity/1 - specificity) or a negative result (1 – sensitivity / specificity).
  Calculation:

  LR+ = [a/(a+c)] / [b/(b+d)] LR- = [c/(a+c)] / [d/(b+d)]

31.5.2 TERMS USED IN THERAPY

	Event / final outcome		*Total*
	Yes	**No**	
Control group	a	b	a + b
Experimental group	c	d	c + d

- **Event rate**: is the proportion of subjects on which an event is observed. For example: if in 100 patients the event is observed 35 times, the event rate is 0.35.
- **Control Event Rate**: CER = a/a + b.
- **Experimental Event Rate**: EER = c/c + d

31.5.2.1 When the experimental treatment reduces the risk of an unfavourable event

- **Relative Risk Reduction - RRR**: proportional reduction in the rates of adverse events among patients in the therapeutic / experimental group (EER) and the ones in the control group (CER) in a clinical trial calculated using the formula (EER–CER/CER) with a confidence interval of 95%.
- **Absolute Risk Reduction - ARR**: absolute arithmetic difference between the rates in experimental and control groups (EER-CER).
- **Number Needed to Treat - NNT**: number of patients who need to be treated to achieve a favourable additional outcome; is the reverse of the ARR (1/ARR) and is rounded to the next whole number, with a confidence interval of 95%.

31.5.2.2 When the experimental treatment increases the likelihood of a favourable event

- **Relative Benefit Increase –RBI**: increase the rate of favourable events comparing the patients of the experimental group and the control group in a clinical trial (EER-CER/CER).
- **Absolute Benefit Increase – ABI**: absolute arithmetic difference between the event rates (EER-CER).
- **Number Needed to Treat - NNT**: number of patients who need to be treated to achieve a favourable additional outcome comparing to the control group; is the reverse of ABI (1/ABI) and is rounded to the next whole number, with a confidence interval of 95%.

31.5.2.3 When the experimental treatment increases the likelihood of an unfavourable event (iatrogeny)

- **Relative Risk Increase - RRI**: proportional increase in the rates of adverse events among patients in the therapeutic / experimental group (EER) and the patients in the control group (CER) in a clinical trial, calculated in a manner similar to the RBI (EER–CER/CER) with a confidence interval of 95%. It is also used in the evaluation of the effect of risk factors.
- **Absolute Risk Increase - ARI**: absolute arithmetic difference between the adverse events rates in the experimental and the control groups, whenever the treatment has more harmful effects. It is estimated in a manner similar to the ABI (EER-CER).
- **Number Needed to Harm - NNH**: number of patients that, if received the experimental treatment, would lead to an additional lesion in an experimental individual compared with the patients in the control group. It is the reverse of ARI (1/ARI) and is rounded to the next whole number, with a confidence interval of 95%.

31.5.3 TERMS USED IN RISK/IATROGENIA

		Adverse results	
		Present a + c	Absent b + d
Exposure	Yes a + b	a	b
	c + d No	c	d

- In a <u>randomized</u> or <u>prospective</u> trial: **Relative Risk** = RR = [a/(a+b)]/[c/(c+d)]
- In a <u>retrospective</u> trial: **Relative Odds** = RO = ad/bc
- **Patient Expected Event Rate** – PEER = susceptibility of the emergence of an adverse event in a given patient who does not receive treatment (experimental or conventional).
- To calculate the **Number Needed to Harm** - NNH – to a certain odds ratio and PEER:

$$NNH = [PEER\ (OR - 1) + 1]/[\ PEER\ (OR - 1) \times (1 - PEER)]$$

31.5.4 TERMS USED IN DIFFERENT CONTEXTS

- **Odds Ratio**: odd is a relationship between the probability of the occurrence with the non-occurrence of a particular event, that is, a relationship between the probability that something is really something and the probability that it may be nothing. For example, in 100 smokers, 80 develop chronic coughing and 20 do not, the odd of cough onset of this group is 80:20, that is, 4; in contrast, the probability that these smokers have to

develop chronic cough is 80/100, that is, 0,8 (80%). The odds ratio is the ration between the two odds thus described. Another example: if the odds (O) of the occurrence of an event (for example, a determined side effect) after the exposure to a drug A is called Oa, and if the odds of the occurrence of the same events after exposure to drug B is called Ob, the odds ratio is OR=Oa/Ob. If, hypothetically, the OR=6 then the probability of a patient presenting the side effect (event) with the drug A is six times higher than the probability that the event occurs with the drug B. Calculations (relating to the above table):

Event odds in the control group – **EOC** = a/b	Odds Ratio) – **OR**: (c/d) / (a/b)
Event odds in the experimental group – **EOE** = c/d	Relative Risk – **RR**: EER/CER

- **Confidence intervals (CI):** is the range within which it is hoped that the real value of a statistical measure is situated, is generally accompanied by a percentage (usually 95%), which defines the level of the respective confidence: in 95% of cases the value is within the limits defined.
- **Cost-benefit analysis**: evaluates whether the cost of an intervention is justified by the benefit obtained, using identical units of measuring the costs and benefits (usually monetary).
- **Cost-effectiveness analysis**: measures the real cost of a service and its outcomes – which are reported in the same unit of measure.
- **Cost-utility analysis**: converts the effects of an intervention in personal preferences of the patients (also known s utilities), indicating the cost of any additional quality (e.g. cost per QALY – quality-adjusted life year).
- **Decision analysis**: support technique for the clinical decision, used especially when it is accompanied by a high degree of uncertainty; includes the systematic description of all relevant information, quantifying the degree of uncertainty. The graphical form is a tree of decision.
- **Tests of N-1**: in this type of testing patients are tested in pairs of consecutive and alternate periods, in which in one of them is used an experimental treatment and in the other is used the usual treatment (or placebo); ideally, the details are concealed from patients and doctors in monitoring outcomes; this process is repeated the number of times necessary to establish the efficacy (or inefficacy) of the treatment in that individual patient.
- **Effectiveness**: measure of the effect of an intervention in normal clinical practice conditions. Tests for evaluating effectiveness are called management trials.

- **Efficacy**: measure of the effect of an intervention in ideal conditions – usually in randomized and controlled trials. Tests for evaluating efficacy are called explanatory trials.
- **Incidence**: number of new cases of a certain disease in a population, during a given period of time.
- **Prevalence**: number of cases of the disease existent in a population in a given point in time.
- **Phase I trials**: testing of a drug in normal volunteers (healthy), without the existence of a control group.
- **Phase II trials**: testing of a drug in normal volunteers (healthy), but sometimes as RCTs.
- **Phase III trials**: testing of a drug in patients usually compared to the standard therapy and as RCTs.
- **Phase IV trials**: post marketing pharmacovigilance.
- **Point estimate**: are the results of a sample of a study, to be used as the estimate closer to reality on the population from which it was selected; the confidence interval of a point estimate is a measure of the uncertainty (due to chance) associated with that estimate.
- **Sensitivity analysis**: is a process which re-estimates the results of a trial, changing certain parameters or perspectives, in order to investigate if the initial conclusions remain unchanged.

31.5.5 GENERAL TERMS FOR CLINICAL TRIALS

- **Evaluation of a study design**: in *lactu sensus*, the design is one of the most important characteristics of a trial, because it has a crucial importance in determining causality. A causal factor is defined as "… a factor which operation increases the frequency of an event…", this implies that: a) people affected by the causal factor present a higher frequency of a certain event or outcome; to test this hypothesis, we have to compare two groups, only one exposed to the putative factor – it is a cohort trial; and b) the individuals presenting a determined event or outcome, have had, in the past, a higher exposure to the causal factor than the individuals without that(those); to test this hypothesis, we have to compare two groups, one with the study event and the other without it – a case-control trial. In global terms, there are four main trial groups, which try to respond to different issues: *interventional trials* (…"what is the effect of this intervention?"…), *surveys* (…"is this condition/disease common?"… and … "is there some associations between certain conditions / diseases and certain exposures?"…), *cohort trials* (…"which are the effects cause by a certain exposure?"…) and *case-control trials* (…" What are the causes of this condition / disease?"…).

	Adverse event		
	Present (case)	**Absent**	**Totals**

			(control)	
Exposure to treatment	Yes (cohort)	a	b	a + b
	No (cohort)	c	d	c + d
	Totals	a + c	b + d	a + b + c + d

• **Randomized and controlled trials – RCTs**: start with a + b + c + d and randomize to (a + b) and (c + d)
• **Prospective (or cohort) trial**: select (a + b) and (c + d)
• **Crossed / analytical sectional trial**: select a + b + c + d
• **Case-control trial**: select (a + c) and (b + d)
• In a RCT or cohort trial, the **Relative Risk (RR)** = [a/(a+b)]/[c/(c+d)]
• In a case-control trial, the **Odds Ratio (OR)** = ad/bc

- **Clinical trial** (*clinical trial*, *therapeutic trial*, *intervention study*): is a trial that seeks to text the efficacy and safety of a drug, or an intervention. Clinical trials can be **randomized and controlled** or only **controlled**.
- **Randomized clinical trial – RCT**: a randomized and controlled clinical trial is an epidemiological experience in which the subject in study (sample) selected through explicit methods from a larger group (population), are randomly distributed between two groups: the experimental one, over which the treatment will occur (or preventive measure, or intervention) and the control group. The results are rigorously evaluated, comparing in both groups the disease, recovery, mortality, morbidity rates or any other outcome considered interesting. One can inclusively adapt a cross-over design in which patients and controls, after receiving treatment (or placebo, e.g.) are changed to the other group, that is, the initial experimental group changes to control group and vice-versa. The RCT design is considered the most valid to the testing of an intervention, so we consider it the gold-standard to the determination of the efficacy of a drug. *Advantages*: blinding of the distribution for treatment (blinding is easier), equal distribution of confounding factors and larger representativeness of statistical analysis. *Disadvantages*: expensive activity, possible volunteer bias (see below) and, sometimes, ethically problematic.
- **Controlled clinical trial**: trial that compares one or more experimental groups with one or more control groups. It can be non randomized (but all randomized trials are by definition controlled ones).
- **Prospective (or cohort) trial**: is a trial where the subjects are recruited and followed to that point in time forward, during a certain period. It is a particularly used design to the definition of risk and prognostic: for example, a group of health volunteers (cohort) can be recruited, subject to a risk factor (No. of cigarettes/day) to a certain disease (lung carcinoma), and follow the group for a certain period of time (years). The comparison, in the end of the follow-up period, of the disease incidence in certain subgroups (<10, 11-20, >20 cigarettes/day, e.g.) allows the establishment of the relation power between the risk factor and the respective disease. *Advantages*:

ethically safe, possibility of mating the subjects and establishing the temporality and direction of events, standardization of eligibility criteria and the evaluation of outcomes, easy to execute and nor very expensive. *Disadvantages*: difficult to identify controls, eventual impossibility to mate the subjects, difficulty in blinding, inexistence of randomization, need for large dimension samples to study rare diseases and highly expensive.

- **Cross-sectional study**: also known as **prevalence trial**, is a trial whose aim is to observe a certain population in a specific point (or interval) of time, determining the exposure and outcome simultaneously. Advantages: ethically safe and with limited costs; Disadvantages: it only establishes association (not causality), susceptible to recall bias (see below), possibility of unequal distribution of confounding factors and possibility of unequal distribution of the groups dimension.
- **Retrospective (or case control) trial:** is a trial whose design permits to test the disease aetiology. This type of trial is based upon a concept which agrees that the clarification of the relationship between exposure to factors that may be a source of a particular disease (putative / causal factors), and the disease, can be achieved through data related to the individual characteristics of the study subjects, as well as the identification of events experienced by those in the past. The essential point is that some study subjects present the disease (or other interesting result) and others do not, therefore allowing comparing both groups in terms of past events. *Advantages*: ideal to rare diseases, need for few study subjects, quick and nor very expensive; *Disadvantages*: need to recur to remembrances of the subject or written processes, existence of confounding factors, difficulty in selecting the control group, potential remembrance and selection bias (see below).
- **Case Series**: an observational trial, non controlled, involving an intervention and a result in more than one patient.
- **Observational trial**: a trial with no intervention from the investigator, that is, he only collects data without influencing the course of the disease.
- **Sequential trial**: it is a trial in which the data are permanently analyzed according to the outcomes which are available for each individual patient. This process is kept until a clear benefit is detected in one of the experimental groups or it is verified that there will be no benefit; these trials are shorter and should only be used in situation where the outcome is shown relatively early.
- **Statistical power**: is the probability that the null hypothesis is rejected when in fact it is false; in a clinical trial, for example, it is the dimension of the certainty of the non existence of a false negative result (the drug is not effective when in fact it reveals efficacy); the statistical power of a trial depends on: 1) its dimension (No. of participants); 2) number of events in the

trial (e.g. acute myocardial infarctions); 3) the variation degree of a continuous outcome (e.g. weight); 4) which dimension of the effect between control and experimental groups is deemed important; and 5) which is the certainty we want to assure to avoid a false-positive result (the definition point of statistical significance).

- **Surrogate end-points**: measurements /factors related to the outcomes and that, although not practical relevant, are believed to reflect important aspects of the outcomes. The surrogate end-points are usually biochemical or physiological markers, that can be easily measured and may be used as predictive factors for important outcomes; for example, a determined cardiac biochemical value (troponin) can be a marker of the existence of coronary disease (AMY). The characteristics which a surrogate end-point should have are: 1) be reliable, reproducible, easy to measure and to obtain and present a relationship level / disease (i.e. the higher, the greatest possibility of disease); 2) it should be a real predictor of the disease (or its risk) and its relation to the disease should have a biological plausible explanation; 3) it should be sensitive (a positive result should detect most patients) and specific (a negative result should exclude most healthy individuals), and have a good predictive positive value (an abnormal value identifies patients at risk) and negative (a normal value identifies healthy individuals); 4) it should have a clear definition of what a normal value is; 5) the standardization of changes values should imply a response to therapy.
- **Importance of a trial**: it is a valorisation inference in terms of the outcomes impact of a trial / study in biomedical, epidemiological or research knowledge.
- **Bias of a clinical trial**: a bias is defined as a systematic deviation of the true value of a variable, factor or characteristic. A bias exists when the findings of a study are systematically away from the truth, due to problems with the collection, analysis, interpretation, publication or review of their data. There are several ways to introduce bias in a study: 1) systematic error in the measurement of data; 2) systematic error in the statistical calculations (medium, rates, measures of association, etc.); 3) methodological weaknesses of the study (in the collection, analysis, interpretation, publication or review of the data); 4) wrong analytical techniques applicable to the constituent factors of a test / clinical study; and 5) deviations caused by prejudices of the researchers. There are many bias described: 1) **publication bias**: it is a trend that the editors of medical journals have to publish more frequently studies that show "positive" results (especially if they are considered "news"), as opposed to studies with "negative" non significant results (especially if they confirm data already known in the literature). A major consequence of this bias is the potential to decrease the perception of the existence of an association between two factors (for

example a tumour marker with the original tumour) or the therapeutic efficacy of a new molecule (which seems more effective than in fact it is). A second major consequence is to be a source of problems in meta-analyses; 2) **volunteer bias**: the fact that the patients (or controls) that volunteer to participate in a clinical trial may have different characteristics, or respond to treatment differently from other groups selected at random; for example, there is evidence that patients who volunteer to studies on preventive measures may have, at the outset, a healthier lifestyle than most patients randomly selected from a non volunteer database; 3) **recall bias**: errors due to lack of sufficient information on retrospective studies, by difficulties of the subjects, when asked, to be able to remember precisely the relevant facts, for example, when questioned about the use of a particular drug, a patient experiencing a side effect with a particular drug, tends to recall more accurately that drug than a patient who never experienced a similar episode; 4) **selection bias**: errors due to the existence of systematic differences in the characteristics of the subjects selected for a study, versus those not selected; for example, volunteers selected as being in a certain place at a certain time (the emergency services during the night), forgetting the other potential candidates (patients going to the doctor during the day); 5) **ascertainment bias**: it is the systematic non inclusion of all potential classes or subgroups of patients supposedly representative in the formation of a sample; for example, select the population to study from hospital patients when the primary care are also important; 6) **detection bias**: systematic error in the verification, diagnosis and follow-up of patients in a trial; for example, to require analytical tests in patients in the hospital and forget the patients studied in clinic; 7) **bias of interpretation**: error from inferences and speculation (not considering all possible interpretations consistent for the facts, or ignoring the cases of exception); 8) **sampling bias**: systematic error in the study of a non-randomized sample of the population; 9) **attrition bias**: error in the comparison of results of patients in both groups of a RCT by differences in drop-outs or exclusion of those - for example due to side effects of the experimental drug.

- **Sample size**: the determination of the size of the sample is the mathematical process in which the decision is based, before the start of the trial, of how many patients will be studied. This decision is based on several factors: 1) incidence or prevalence of the condition that you want to study; 2) the strength of the relationship (real or putative) among the variables included in the trial; 3) the power that want the trial to have, that is, the ability to demonstrate a causal association (if any); 4) the extent permitted that the study may have in relation to the type I error (rejection of the null hypothesis when it is true, that is, saying that a treatment is effective when in fact it is

not); 5) the level of significance; 6) the existing confounding factors; 7) errors in the classification.

- **Criteria for inclusion and exclusion**: are the characteristics to be satisfied by the subjects to be included (criteria for inclusion) or excluded (criteria for exclusion) in a trial; these criteria are defined in advance and are crucial in defining the samples, and especially important in the implementation of the results of a clinical trial to the individual patient in the day-to-day (external validity). The transposition of the scientific evidence of a RCT to a therapeutic gesture involves a judgment on the applicability of that in the individual patient, and can be achieved by answering the following questions: 1) is my patient so different from the ones participating in the trial that its results can not be applied? 2) In the context in which we are, will the treatment be feasible? 3) What will be the benefits (and dangers) of treatment? 4) Will the values (moral, practical) of my patient influence the final decision?
- **Randomization**: is a method used for generation of a sequence of the random distribution of the participants in a RCT; usually, a correct randomization is achieved by using a table of random numbers or generated by computer, in which each subject is sequentially assigned a code that defines in what group he will be included. There are more sophisticated techniques of randomization for special cases: 1) stratification, where the groups are formed by having in common a confounding factor; 2) matching, in which the subjects of comparison are selected for their similarity – relating to confounding specific factors - with the studied subjects (which, in a retrospective study, present for example a given risk); and 3) techniques of multivariate regression, in which the analysis of a trial defines the outcome as the dependent variable of the equation, including in the latter the putative causal factor and the confounding factors.
- **Blinding or masking**: maintaining secrecy about which group the participants of a RCT were included in the initial randomization, the blinding can be **simple** (when patients do not know to which group they were distributed - experimental or control), **double** (besides the patient, also the investigator does not know what kind of treatment the patient is doing) and **triple** (the patient, the investigator and the statistician / investigator who analyzes the results do not know the groups in the study).
- **Concealment of allocation**: it is a process used to prevent the knowledge of the distribution of the subjects by the trial groups; is different from blinding and can be done, for example, by making the process of randomization to be done by an investigator who is not involved in recruitment of participants in the trial, or when the envelopes with the codes of randomization are opaque to light so that we can not know to which particular group will be assigned a certain patient.

- **Overall validity of the results of a trial**: is the degree of confidence that the results of a clinical trial - especially when you want to generalize them beyond the study population - transmit to whoever analyses them, based on the methodological analysis of the study, the representativeness of the sample and in the nature of the population from which this comes. There are two types of validity: 1) *internal validity*: the two studied groups - experimental and control - are selected and compared in such a way that any differences found in the variables can only be attributed to the effect under study (or possible sampling error) 2) *external validity (generalizability, applicability):* the results are applicable to other populations (not to the studied one).
- **Intention to treat analysis**: is the one that analysis all participants in a trial according to the intervention for which they had been randomized in the beginning, whether they have received it or not, for example, a patient in the experimental group will be analyzed at the end as having being treated, even if he has left the trial.
- **Factorial Design of a Test**: the participants of a trial with 2X2 factorial design are distributed to four groups: experimental I (with a particular treatment), experimental II (with a second different treatment), experimental III (both) and experimental IV (none). For example, in the prevention of an embolic stroke in patients with non-rheumatic arterial fibrillation, we could test a platelet anti-aggregant (aspirin), an anticoagulant (varfarin), both and none.

31.5.6 GENERAL TERMS FOR SYSTEMATIC REVIEWS AND META-ANALYSIS

- **Systematic review**: is a scientific literature review on a particular theme, executed so that the biases are reduced to a minimum. A key feature of a systematic review is the clear and not ambiguous explanation of the criteria used for the selection, critical evaluation and the inclusion of scientific evidence. Thus, a systematic review presents formal and precise objectives and criteria for inclusion (and exclusion) of the trials thoroughly explained. The systematic review is different from the usual reviews (also designated as narrative reviews):

Differences between systematic and narrative reviews

	Narrative review	**Systematic review**
Issue/theme	Usually broad and comprehensive	Usually focused and precise
Sources and research	Non specified (and therefore subject to bias)	Sources comprehensive and complete; explicit research strategy
Selection	Non specified (and therefore subject to bias)	Selection based in pre-defined criteria, uniformly applied
Evaluation	Variable	Rigorous and critical

Synthesis	Qualitative summary	Quantitative summary (if it includes statistical synthesis, it is a meta-analysis)
Inferences and recommendations	Sometimes based on scientific evidence	Always based on scientific evidence

- **Meta-analysis**: is a statistical technique that allows the combination of results of different clinical trials (usually RCTs) from a systematic review. The rationale of this approach is justified by the fact that most trials do not have enough power *per si* to respond effectively to the posed question. The meta-analyses have two kinds of structural components: 1) qualitative, with application of pre-defined methodological criteria of quality (absence of bias, degree of availability of data, e.g.) and 2) quantitative, which consist on the integration of numerical information. Usually, the meta-analyses have a typical graphic representation. A meta-analysis can be considered a systematic review with formal statistical information.
- **Heterogeneity of the trials for inclusion in a meta-analysis**: the heterogeneity of the trials can be detected up into three fields: the non-uniform effects of the treatment under analysis (statistical heterogeneity), the differences in the design of the studies (methodological heterogeneity) and in the groups of patients included in the trials (clinical heterogeneity); these differences should be systematically analyzed before the inclusion of clinical trials in meta-analysis, especially in situations where there are numerous clinical differences but only a small number of trials available for analysis.
- **Cumulative meta-analysis**: the trials are added one at a time by a particular order (publication date, e.g.), but the results are summarized with each new trial that is added.
- **Funnel plot**: is a graphical representation comparing the size of the samples with the size of the therapeutic effect, in clinical trials included in a meta-analysis; in certain circumstances, it can provide clues for determining the absence of trials.
- **Patient Expected Event Rate** - PEER: is the probability that the patient will demonstrate a particular event (e.g. sudden death) for a specific period of time. It is produced through prognostic studies, databases or personal experience.
- The importance of the results of a systematic review is based on the determination of NNTs, using odds ratios (OR) - especially when the results are binary - and the patient expected event rates (PEER); these calculations are different as the ORs are superior or inferior than 1 (see equation below). In the calculation of NNTs we may also use the following tables (which are based on the mentioned equations):

For an OR <1: NNT = 1 - [PEER x (1 - OR)] / (1 - PEER) x PEER x (1 - OR). The numbers of the table are the NNTs for the corresponding ORs in the expected level of events to the specific patient (PEER). This table applies whenever an adverse event is avoided by the therapy.

		Odds Ratios				
		0.90	0.80	0.70	0.60	0.50
Patient PEER	0.05	209	104	69	52	41
	0.10	110	54	36	27	21
	0.20	61	30	20	14	11
	0.30	46	22	14	10	8
	0.40	40	19	12	9	7
	0.50	***38***	***18***	***11***	***8***	***6***
	0.70	44	20	13	9	6
	0.90	101	46	27	18	12

Note: for a given OR the NNT is the lowest when PEER = 0.50

For an OR> 1: NNT = 1 + [PEER x (OR - 1)] / (1 - PEER) x PEER x (OR - 1). The numbers of the table are the NNTs for the corresponding ORs in the expected level of events to the specific patient (PEER). This table applies whenever a beneficial event is increased by therapy and when a side effect is caused by this.

		Odds Ratios				
		1.1	1.2	1.3	1.4	1.5
Patient PEER	0.05	212	106	71	54	43
	0.10	112	57	38	29	23
	0.20	64	33	22	17	14
	0.30	49	25	17	13	11
	0.40	43	23	16	12	10
	0.50‡	***42***	***22***	***15***	***12***	***10***
	0.70	51	27	19	15	13
	0.90	121	66	24	38	32

Note: for a given OR the NNT is the lowest when PEER = 0.50

The calculation of a NNT from the Relative Risk (RR) varies according to this being greater or less than 1:

For a RR <1: NNT = 1 / (1-RR) x PEER

For a RR> 1: NNT = 1 / (RR-1) x PEER

32. References

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