Background Paper 6.17
Tobacco use cessation therapies

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# Executive summary

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# Major changes in the area of smoking cessation between 2004 and 2012

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Executive summary

Smoking is considered the single most important cause of preventable morbidity and premature mortality worldwide. Tobacco addiction caused about 100 million deaths during the 20th century, each year 5.4 million people die from this cause, and if resolute and urgent action is not taken by 2030 the epidemic will cause between 8 and 10 million deaths each year, of which over 80% occur in low- and middle-income countries (LMIC).

Stopping smoking is very difficult; often require repeated intervention and/or multiple attempts to quit. Nowadays, there are numerous effective medications available for tobacco dependence. In general, seven first-line medications (five nicotine and two non-nicotine) are recommended and reliably increase long-term smoking abstinence rates. Based on this evidence, clinicians should encourage their use in patients attempting to quit smoking except when medical contraindication exists or with specific populations (i.e. pregnant women, smokeless tobacco users, light smokers, and adolescents) for which there is insufficient evidence of effectiveness.

The research currently available suggests that abstinence rates can be increased by combining different forms of nicotine replacement therapy (NRT) or simultaneous administration of NRT and non-nicotinic compounds. However, more research is needed in this area, as well as a better definition of the criteria which need to be fulfilled to use some of the therapeutic modalities in combination. Additionally, evidence suggests that smokers who relapse sometimes during their cessation attempt are at high risk of future relapses, so that rescue interventions for smokers are necessary.

More research is needed on the cost-effectiveness of pharmacotherapy for smoking cessation in LMIC to inform decision makers about the need for the development of lower costs therapeutic options for their countries.
Major changes in the area of smoking cessation between 2004 and 2012

a) Strategies and guidelines of international organizations such as World Health Organization (WHO)
   - MPOWER initiative was launched as a tool for countries to successfully implement the Framework Convention on Tobacco Control (FCTC).
   - The WHO Model List of Essential Medicines application and granting of NRT for smoking cessation and the management of tobacco dependence in adult smokers.
   - Definition of "best buy" interventions by WHO including four key elements of the FCTC (increase the tax on tobacco products, comprehensive legal framework to ensure tobacco smoke free public places, information and warning about the harms of tobacco, and the ban on advertising, promotion and sponsorship)
   - In 2009, NRT products were included in the WHO Model List of Essential Medicines.

b) Newly available treatment options for smoking cessation
   - Introduction of new treatment alternatives to the market as selective partial agonists of nicotinic receptors (varenicline) and nicotinic antagonist (mecamylamine).
   - Medicines obtained new indication for their use in the treatment for tobacco addiction: antidepressants (bupropion, nortriptyline), antihypertensives (clonidine), opioid antagonists (naltrexone).
   - New definition of a first-line treatment for the management of patients who wish to stop smoking (NRT, bupropion or varenicline) and second-line treatment (clonidine and nortriptyline).
   - Start of using different treatment options in combination (i.e., patches with other forms of NRT). Additionally, further research is required about other combinations as nortriptyline and NRT, varenicline and bupropion, varenicline and NRT, etc.).
   - New clinical trials conducted in specific populations such as pregnant women and adolescents. More research is needed in this area.

c) Evidence on the cost-effectiveness of interventions
   - Increasing number for pharmacoeconomic studies that comparatively evaluate different treatment options, particularly in low income countries.
   - Most studies were carried out in high-income and upper middle income countries. There is a lack of studies of the cost-effectiveness of treatment options including combinations of pharmacotherapy, individual and group counseling in low middle income and low income countries.

d) Research and development of new treatments
   - Negative NicVAX vaccine study outcomes in two phase III clinical trials conducted by Nabi Biopharmaceuticals.
   - Numerous treatments are currently in development: vaccine (TA-NIC, NIC002, Niccine), antidepressants (EVT 302), partial agonists selective nicotinic
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receptors (cytisine), opioid antagonists (nalmefene), selective antagonists of the cannabinoid receptor type 1 (taranabant).
1. Introduction

Smoking is one of the public health problems with the greatest impact on morbidity and mortality globally. Estimates projecting future consequences of using tobacco products show a worrying picture especially for developing countries with the highest proportion of deaths related to tobacco consumption in the coming years coming from these countries. However, high income countries also face serious challenges in relation to the control of the tobacco epidemic. For the European Region, these challenges include the high prevalence of tobacco consumption among women, much higher than those in other regions such as Asia, Africa and the Middle East. The growing trend of women consuming tobacco products has narrowed the gap between the genders, which could be interpreted as a “feminization” of the addiction to tobacco in these countries.

The World Health Organization (WHO) has targeted priority areas to combat the tobacco epidemic, one of which is to support the smoker in their attempt to quit smoking. The cessation support covers a broad spectrum of actions or interventions offered to smokers who want to make a serious attempt to quit ranging from medical advice (offered in any health services received by the smoker, regardless of reason that leads to seeking care) to comprehensive treatment, multicomponent and multidisciplinary service in a clinic specializing in the treatment of addiction to tobacco products.

According to international scientific evidence, about 70% of smokers want to quit, 30% have made a previous cessation attempt and 8% of them have used any medications for smoking cessation. A recent study reported estimations about individual cessation assistance in 15 middle and high income countries (five of them in Europe) participating in the International Tobacco Control (ITC) policy evaluation surveys. Results show that recent quitting activity varied considerably by country whereby reports of ever having tried to quit varied from around 60% in New Zealand, Mexico and China, to over 80% in most of the other countries. Prevalence of quit attempts in the last year varied from under 20% to over 50% across countries. The study also shows much higher use of quit smoking medications among those who made quit attempts in the previous year in western countries (over 40% in Australia, Canada, United Kingdom & USA) than in middle-income countries. Additionally, it is known that less than 3% of smokers quitting the habit have done this on their own (only with their own will power), while medication support may double or triple the probability of successful cessation long-term compared to unsupported attempts. Evidence shows that individual attempts to quit have low success rates: of those who try without the assistance of cessation programs, about 98% will have started again within a year. Offering support to smokers in the form of medication, facilitating access to those interventions through reimbursement and thereby increasing the probability of success seems desirable, so that every smoker who wants to quit smoking, has access to safe, effective and affordable medications to meet their needs.

The aim of this study is to review the current status of the tobacco epidemic globally and the different interventions to combat addiction with a particular focus on pharmacotherapeutic options. We also discuss whether there is a therapeutic gap in offering treatment for tobacco addiction currently and whether and where investment in research is desirable from a public health perspective.
1.1 What is the size and nature of the disease burden?

Smoking is considered the single most important cause of preventable morbidity and premature mortality worldwide due to the effects it has on numerous causes of illness and death.\textsuperscript{12,14} The regular consumption of tobacco is responsible for numerous diseases that cause premature death and/or disability in smokers and people exposed routinely to tobacco smoke in the environment. Since the 1950s when it was first documented that cigarette smoking was a major causal factor in the development of lung cancer,\textsuperscript{15} numerous studies described the health consequences resulting from the regular consumption of tobacco, both for smokers and for those who are affected due to passive smoking. For the last four decades the Surgeon General’s Reports in the United States have summarized and analyzed evidence about the negative health effects of the consumption of tobacco.\textsuperscript{14,16}

Addiction to tobacco caused about 100 million deaths during the 20th century, each year 5.4 million people die from this cause, and – if resolute and urgent action is not taken- by 2030 the epidemic will cause between 8 and 10 million deaths each year, of which over 80% will occur in low and middle income countries (LMIC).\textsuperscript{4,17,18} Additionally, in the 21st century it is estimated that, based on current patterns in the prevalence of smoking in the world, approximately between 500 million and one billion people will die as a result of the consumption of tobacco and of these, half will be between the ages of 35-69 years.\textsuperscript{1,19,20} The only way to reverse these estimates is to adopt effective strategies, efficient (with evidence of cost effectiveness) and affordable to the people in all the countries affected. Estimates from The World Bank show that 25% coverage with NRT would cost only US$ 276-US$ 297 per disability life year saved in low-income countries, values comparable to many health interventions financed by governments in these countries.\textsuperscript{9}

In the European Region in 2011, about 32% of the adult population were smoking on a regular basis. Data from the Global Adult Tobacco Survey 2009 (GATS 2009) show that the prevalence of smoking at country level is highly variable, with countries like the Russian Federation and other Eastern European countries with a higher prevalence (39.1% in the Russian Federation\textsuperscript{21}, 30.3% in Poland\textsuperscript{22} and 28.8% in Ukraine\textsuperscript{23}) than the rest of Europe (21% in Israel, 24% in United Kingdom, Republic of Moldova, Portugal, Kazakhstan and Iceland and 25% in Finland).\textsuperscript{24} Tobacco was the main risk factor associated with premature mortality in the region, causing about 1.6 million deaths.\textsuperscript{5} Currently, Europe, along with the Region of the Americas, shows the highest proportion of deaths attributable to tobacco (16%). Contrastingly, the proportion in Africa and the Eastern Mediterranean attributable to tobacco is 3% and 7%, respectively, with a global average of 12%.\textsuperscript{2,3} Overall, more men than women die from causes related to the consumption of tobacco. However, in the WHO European Region, at present, this difference is greater than the global average (5:1).\textsuperscript{2,3}

In 2010 in the WHO European region, 22% of women smoke which is high when comparing with Africa, Asia and the Middle East (3.5%). While the use of tobacco products was formerly largely a male phenomenon, the gap in use between male and female adults is now smaller in countries like Austria, Denmark, Ireland, Norway and the United Kingdom. In Sweden and Norway today, the prevalence of daily consumption of tobacco is higher in women. Also more girls than young boys use tobacco in Bulgaria, Croatia, Poland and Slovenia.\textsuperscript{2,3} A recently study in 1.3 million United Kingdom women shows that 20% were current smokers, 28% were ex-smokers, and 52% were never-smokers. Two-thirds of all
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deads of smokers in their 50s, 60s and 70s are caused by tobacco use. Woman smokers lose at least 10 years of life.25

The WHO data base shows the age standardized prevalence rate use of any tobacco product in 2009 (Figure 6.17.1). Data suggests that tobacco use prevalence often differs across countries and by gender, indicating social inequity.5 The currently available evidence is very consistent in showing that smoking is a major cause of inequality in health between socioeconomic groups and (so far) between men and women. Mortality rates of smoking-related diseases (such as lung cancer and COPD), on average, are two to three times higher in low-income population groups compared to high income groups and, in addition, more men than women die from smoking-related diseases 2,3

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Source: WHO Global Report 2012. Mortality attributable to tobacco.2

Tobacco addiction is a chronic medical condition and is treatable. The cessation of smoking produces immediate and substantial health benefits and reduces much of the risk from smoking within the first years after cessation.5,26,27 Smokers who manage to quit cigarette smoking before developing a smoking-related disease, avoid most of the risk of morbidity and mortality associated with the consumption of tobacco in a few years after overcoming their addiction, so that effective strategies to increase cessation rates (abandonment of addiction) may prevent millions of deaths associated with smoking in the next 50 years.10,28

Interventions for smoking cessation have been shown to be effective and cost-effective in a variety of settings compared with other interventions within the health system.4 Providing smoking cessation strategies within the benefit packages of all medical insurances or public health plans promotes access to these interventions to all smokers who seek help in their cessation attempt.


1.2 What is the control strategy?

Reducing demand

The World Health Organization (WHO) in 2004 adopted the Framework Convention on Tobacco Control (FCTC), a global treaty to combat smoking, which took effect from February 2005. According to the WHO, until April 2012, 174 of the 194 WHO member countries have ratified the FCTC. To support countries to implement the FCTC, in 2008, the WHO introduced the initiative called "MPOWER" which brings together a series of cost-effectiveness measures and policies that act synergistically to combat smoking. These are:

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**Figure 6.17.1: Current smoking of any tobacco product (age-standardized rate (%)). European Region 2009**

Source: Own production based on World Health Organization data [http://apps.who.int/gho/data/#](http://apps.who.int/gho/data/#). Note: Data were not available for Cyprus, Ireland, Luxembourg, Monaco, Montenegro, San Marino, Sweden, Tajikistan, The former Yugoslav Republic of Macedonia and Turkmenistan.
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- Monitoring (Monitor the consumption of tobacco and prevention measures);
- Protecting (Protect the population from tobacco smoke exposure);
- Offering (Offer help to quit tobacco consumption);
- Warning (Warn about the dangers of tobacco);
- Enforcing (Enforce bans on tobacco advertising, promotion and sponsorship) and;
- Raising (Raise taxes on tobacco).

The MPOWER strategy - along with implementation guidelines of Article 14 of the FCTC - have provided practical assistance to implement effectively policies to reduce demand for tobacco products at the country level. This MPOWER strategy has focused particularly on demand reduction, although the WHO has recognized the importance of implementing measures on the supply side that are contained in the FCTC.

Specific measures recommended to reduce the consumption of tobacco, and considered as one of the most powerful and cost-effective, are those related to fiscal and tax policy related to tobacco products. Other important measures to reduce the tobacco consumption are related to information (ban on advertising in certain places, including warnings about the health risks of smoking), prohibiting the consumption of tobacco in certain public places and some specific medical interventions. Those medical interventions include the medical advice provided by health care providers to patients on an individual basis, patient support groups which often involve psychologists, and medication for cessation support.

Recently the WHO has recommended a series of interventions as "best buy" for countries to control noncommunicable diseases (NCDs). The interventions can generate significant financial savings and improve health. They have low implementation costs as well as the feasibility of being scaled up, particularly in resource-constrained settings. Within this group of interventions are four key elements of the FCTC (increase the tax on tobacco products, comprehensive legal framework to ensure banning smoking from public places, information and warning about the harms of tobacco and the ban on advertising, promotion and sponsorship).

It has been estimated that these interventions alone could prevent more than five million deaths in 23 LMIC during the period 2006-2015. The evidence provided by these estimates indicate that the cost of implementing the four interventions could cost less than 0.40 US dollars per person per year in LMIC, while in high-income countries the cost would be between 0.5-1.0 US dollars per person per year.

**Pharmacotherapeutic interventions**

A recent systematic review published in 2012 shows that medication and behavioral therapies in the treatment of smoking cessation are cost-effective and even cost-saving for health systems in the long-term, generating substantial savings by avoiding costs associated with morbidity and mortality.

However, it is noteworthy that, although individualized interventions for smoking cessation such as medication have proven to be effective and, for many settings, to be cost-effective compared with other interventions within the health system, these individual interventions were not included in the group of "best buy" interventions recommended by WHO. The reason is concern about their currently low cost-effectiveness in LMIC. For example, a cost...
effectiveness study conducted in 2011 in Viet Nam, a lower middle income country, compared a brief counseling intervention for smoking cessation and pharmacological therapies. The cost-effectiveness result of physician brief advice was 1 742 000 Vietnamese Dong (VND) per DALY averted (international dollars 543), which was considered as ‘very cost-effective’. Authors reported that varenicline dominated bupropion and nicotine-replacement therapies, although it did not fall within the range of being ‘cost-effective’ under different scenarios. The study concluded that the brief counseling intervention is cost-effective and should be included in the list of priorities within the tobacco control policies in the country, meanwhile, pharmacological treatments would not be recommended in this context, unless the same are locally produced at a significantly lower cost in the future.36

The currently available evidence is very consistent in showing that smoking cessation provides an important window of opportunity in combating the epidemic. Most smokers know the damage of tobacco products and want to stop smoking; however, quitting without help is hard because nicotine delivered in tobacco smoke is a highly addictive substance. 4, 5, 26

Three types of treatments should be included in any individual smoking cessation effort: a) Medical counseling: brief advice offered by service providers in primary care units, 26 b) Support lines on smoking cessation: cessation advice may also be offered from free helplines (internet or phone).26 c) Medication: Currently, there are several options to offer medication to those who try to quit smoking. (Annex 6.17.1).

The medication belongs mainly to two distinctive groups: (1) replacement therapy or nicotine replacement (NRT), mainly patches, gum and nicotine inhalers and (2) non-nicotinic compounds as bupropion hydrochloride, nortriptyline and more recently, varenicline tartrate and cytisine.8,37 Varenicline and cytisine are selective nicotinic receptor partial agonists, which block the action of nicotine, decreasing the urgency of smoking and withdrawal symptoms. In addition, it also decreases the rewarding effect of nicotine. 8,38,39,40,41

The Public Health Service-sponsored Clinical Practice Guideline (a product of the Tobacco Use and Dependence Guideline Panel consortium representatives, consultants, and staff) had recommended NRT (nicotine gum, nicotine inhaler, nicotine lozenges, nicotine nasal spray and nicotine patches), bupropion and varenicline as first line drug therapy, while recommending the use of clonidine and nortriptyline as second-line treatments. 42 The clinical selection among first-line treatments will depend on practical considerations such as patient preference, time and cost of treatments. For patients who do not show successful results with first-line treatments, administered individually or combined, or when there are contraindications to its use, the use of second line medication therapy for smoking cessation is recommended.42,43

Other medicines primarily used for a variety of indications other than smoking cessation have been evaluated as potential candidates for smoking cessation support demonstrating varying degrees of effectiveness (Annex 6.17.1). However side effects are common and this may reduce the widespread use of these products.

Similarly, there have been numerous studies documenting the utility of psychological interventions as a smoking cessation aid. This group of interventions includes besides the brief advice provided by health professionals, self-help materials and intensive individual or
group counseling. Evidence suggests that these interventions increase the probability of success varying in their magnitude. Motivational therapy, for example, has shown a modest but significant increase in risk ratios (RR) of success compared with brief advice (RR 1.27, 95% CI 1.14-1.42), results improve when conducting motivational interventions of longer duration (more than 20 minutes per session), showing a RR of 1.31 (95% CI 1.16-1.49).\(^4\) Compared with short counseling and behavioral self-support the probability of individual and group therapy results was RR 1.39 (95% CI 1.24 to 1.57) and RR 1.98 (95% CI 1.60 to 2.46), respectively.\(^45,46\)

2. Why does the disease burden persist?

As argued by many organizations, smoking cessation is primarily a responsibility of the health systems of the countries.\(^5,26\) The available evidence suggests that smoking cessation services are more effective when they are part of a coordinated programme of tobacco control.\(^5,26\) The costs of these treatments change between countries and very few European nations offer reimbursement for providing these services. (Annex 6.17.2).

The offer of adequate insurance coverage for these treatments, including reimbursement for both patients and health providers; have been shown to be effective increasing quit rates.\(^47\) The available evidence shows that paying for tobacco use cessation treatments is the single most cost-effective health insurance benefit for adults that can be provided to employees.\(^48,49\) Coverage of tobacco-use cessation treatment increases both use of effective treatment and the number of successful quit attempts.\(^48,49\) However, the attempts of governments to provide broad coverage of these services to their populations are diverse and still insufficient. According to WHO estimates, between 2008 and 2010, only one additional country (Turkey) began offering comprehensive treatment for dependency to tobacco which includes phone support line, reimbursement for NRT and at least some of the additional individual cessation services. This brings the number of high income countries providing comprehensive treatment for smoking cessation services to 19, which have covered in 2011 up to 980 million people (about 14% of the world population), an increase from 76 million since 2008.\(^5\) In general, in the European Region only a few number of countries offer total or partial reimbursement of pharmacotherapy support of smoking cessation. (Annex 6.17.2)

Despite these successes in combating tobacco addiction only 30% of high-income countries are fully reimbursing smoking cessation services even though they are more likely to be able to fund cessation services than occurs in LMIC. Both high-and middle-income countries show progress in offering at least some coverage of costs for treatment of dependence to tobacco: 80% of high-income countries and about 40% of middle-income countries reimbursed some individual smoking cessation services in 2011. Only one of eight of the low-income countries provided reimbursement for currently available cessation services in 2011.\(^5\)

In relation to research funding in the area of tobacco control, many international and national organizations have funded projects. Also the European Union has funded a number of research projects related to it. One example is the project "Pricing Policies and Control of Tobacco in Europe (PPACTE)", partly funded by the European Commission’s Seventh
3. What can be learnt from past/current research into pharmaceutical interventions for this condition?

3.1 Current pharmacotherapeutic interventions

More than half of all regular smokers have the desire to quit smoking. 51 Motivation of the smoker to quit is crucial for successful cessation. However, at the same time it is known that the sheer force of will is often not enough to result in quitting smoking. Only 1 to 5% of smokers attempting to quit succeed with a high relapse rate of 93% after 10 months of follow up.51 Hence, it is particularly important to support smoking cessation with comprehensive and effective treatment options. A recent study analyzing individual cessation assistance in 15 high and middle income countries7 shows much higher use of quit smoking medications among those who made quit attempts in the previous year in high income countries (over 40%) than in middle-income countries,7 which the authors attributed to the increased coverage for smoking cessation treatments in high income countries compared to middle income countries. They recommend insurers and purchasers to ensure that all insurance plans include the counseling and medication.7

3.1.1 Pharmacological intervention with nicotine

When a smoker starts smoking cessation treatment, they experience the so-called "withdrawal", due to the sudden removal of nicotine. Based on this principle, pharmacological treatment with replacement products or nicotine substitutes have been recommended. These replacement products have a lower addictive power because the plasma levels obtained are significantly lower than when inhaling cigarette smoke. In this way, smokers avoid the negative effects caused by smoke toxicity.52,53 Among the compounds nicotinic or nicotine replacement therapy (NRT) are indicated as follows: (1) polacrilex gum (gum or nicotine gum), (2) nicotine patches, and (3) nicotine inhalers. Additionally, it identifies other nicotinic compounds as oral tablets and nasal spray.52,53 In general there is consensus that all forms of NRT are effective in the treatment of smoking cessation. (See Annex 6.17.1) 54,55,56,57

A systematic review 58 reported a risk ratio (RR) of abstinence for any form of NRT of 1.60 (95% CI: 1.53-1.68) compared to no medication for smoking cessation. When gum was used the RR was 1.49 (95% CI 1.40-1.60). For patches, the RR was 1.64 (95% CI: 1.52-1.78) and for the inhalation device, the RR of achieving abstinence was 1.90 (95% CI: 1.36-2.67). Finally, a RR of 1.95 (95% CI 1.61-2.36) for oral tablets/lozenges, and 2.02 (95% CI: 1.49-2.73) for the nasal spray was also reported. 58 One trial of oral spray had an RR of 2.48 (95% CI 1.24 to 4.94). These all reported RR are not absolute rate of success. These medications increase the long term successful rates by approximately 50% to 70% regardless of setting.58
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The most common side effects of these treatments are generally of mild intensity and are often related to effects on the site of action and/or application. For example, hiccups, gastrointestinal problems, jaw pain and orodental problems were reported in the case of nicotine gum; increased sensitivity of the skin and mucous membrane irritation with light intensity that rarely lead to the suspension of treatment in the case of patches, burns for inhalers and nasal spray and smarting sensation in the mouth, throat pain, cough and sores dry mouth and lips in the case of oral nicotine tablets. 55

The basal rate of success in which smokers quit with their own willpower is estimated to be 3-5% after 6-12 months of follow-up, it is expected that with the use of NRT increases cessation rates by 2-3% with a number needed to treat between 33 and 50 (NNT). (NNT is used to express how many patients need to be treated to have one patient with the desired outcome; in this case it means that 33 to 50 would need to be treated to have one patient quitting smoking). However, if termination rates are estimated to be 15% because of receiving in addition intensive behavioral support, then one would expect an additional 8% probability of success with NRT resulting in a NNT of around 12 (meaning 12 people would need to receive NRT in addition to intensive behavioral support to quit smoking). 55 Another study reported that assuming a cessation rate of 7.5% with behavioral therapy, the NNT with any type of NRT would be of 23 (95% CI 20 to 27). 8

The evidence suggests that all of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. 58

Pharmacological treatment without nicotine

Within the group of pharmacological treatment without nicotine are the antidepressants such as bupropion and nortriptyline, selective partial agonists of nicotinic receptors such as varenicline tartrate and others treatments including antihypertensives, opioid antagonists, silver acetate and anxiolytics.

3.1.2 Antidepressants

At least two arguments have been reported in the literature that justify the use of antidepressants in the treatment of smoking cessation: 53,59 (1) nicotine withdrawal may produce depressive symptoms or trigger an episode of major depression and (2) nicotine may have some type of antidepressive effect that drive smokers to continue consuming it, so the use of antidepressant drugs can be a substitute for this kind of effect. Additionally, it is noted that some antidepressants may specifically act on neurotransmission pathways involved in the mechanisms of nicotine addiction, such as blocking nicotine receptors, independently of their antidepressive effects. 53,59

Out of all antidepressants bupropion and nortriptyline have shown the best results in smoking cessation in clinical practice so far.

1. Bupropion: Originally, bupropion was marketed as an antidepressant; however, once it proved its utility as an adjunctive treatment for tobacco addiction it gained international acceptance as smoking cessation treatment. In North America, Australia and Europe, slow or
prolonged release bupropion, under the name Zyban, is licensed for smoking cessation. \textsuperscript{59} Compared to placebo it is twice as effective with a success rate of 35\% at six months, and 30\% at 12 months compared to 19 and 16\% of placebo at the same intervals. \textsuperscript{53} Godfrey et al.\textsuperscript{60} reported that bupropion is the more cost-effective therapy for smoking cessation in USA and Europe. Additionally, Hughes et al.\textsuperscript{59} in a systematic review documented that the use of bupropion is associated with increased abstinence rates at one year (OR 1.94, 95\% CI 1.72-2.19). Assuming a cessation rate of 7.5\% for behavioral therapy, the NNT to obtain additional benefits with bupropion is 20 (95\% CI 16 to 26).\textsuperscript{8}

However, the administration of bupropion has been associated with adverse events. (Annex 6.17.1) As an example: insomnia (30-40\%), dry mouth (10\%) and seizures (15\%), among others, with a dropout rate between 7 and 12\%.\textsuperscript{59}

2. Nortriptyline: The mechanism of action by which nortriptyline act as smoking cessation support is not yet clearly known.\textsuperscript{59} It seems that it achieves effects similar to those obtained with the use of bupropion. The recommended dose for smoking cessation is 25 mg every eight hours for 12 weeks, starting with 25 mg the first three days, continuing with 50 mg for four days and finally, for the remaining time with 75 mg per day. Nortriptyline has proved capable of doubling smoking abstinence rates, both in patients with and without depression.\textsuperscript{59, 61, 62} The use of nortriptyline is accompanied by an increase in abstinence rates a year with an OR of 2.34 (95\% CI: 1.61-3.41).\textsuperscript{53} A recent systematic review documented a RR of 2.03 (95\% CI: 1.48-2.78) versus placebo and a non-significant RR of 1.29 (95\% CI: 0.97-1.72) for the association of nortriptyline and NRT versus NRT alone.\textsuperscript{59}

Dropout rates within the recommended dosing of nortriptyline range from 4 to 12\%. The only serious adverse event in patients treated with nortriptyline was the association of collapse and palpitations. However, this treatment has not been officially approved for smoking cessation treatment in any country, so there are no post-marketing surveillance studies for this indication as this is in off-label use.\textsuperscript{59}

Other antidepressants as the selective serotonin reuptake inhibitors (SSRIs) (fluoxetine, paroxetine and sertraline) have been tested for treatment of smoking cessation, however, the evidence available so far does not appear to support the use of other antidepressants than bupropion and nortriptyline. Other antidepressants such as fluoxetine have shown negative results.

3.1.3 Selective partial agonist of nicotinic receptors

Partial agonists of nicotinic receptors (cytisine, dianicline, varenicline) can help patients quit smoking through a combination of two effects: firstly, they help maintain moderate levels of dopamine related reducing withdrawal symptoms and nicotine reward (acting as agonists) and, moreover, reducing the feeling of satisfaction when smoking (acting as antagonists).\textsuperscript{8}

1. Cytisine: A systematic review found two trials reporting a RR in individuals treated with cytisine of 3.98 (95\% CI: 2.01-7.87).\textsuperscript{8}

2. Dianicline: For the case of dianicline, the only reported clinical trial does not show enough evidence that this drug is effective in the treatment of smoking cessation (RR 1.20, 95\% CI: 0.82-1.75).\textsuperscript{8}
3. Varenicline: The same systematic review of 50 clinical trials evaluating varenicline reported a RR of 2.27 compared to placebo for continuous abstinence at six months (95% CI: 2.02-2.55). A lower dose of varenicline was also be effective with a RR of 2.09 (95% CI: 1.56-2.78). The RR for varenicline versus bupropion at one year follow-up was 1.52 (95% CI: 1.22-1.88). The RR for varenicline versus NRT for 24 weeks of follow-up was 1.13 (95% CI: 0.94-1.35). Two trials documenting the use of varenicline beyond 12 weeks with a standard regimen found that varenicline was well tolerated during use over long periods of time. Based on the fact that a clinical trial typically assumes a rate of 7.5% efficacy of behavioral therapy, the NNT of varenicline is 10 (95% CI: 8-12).

The main side effect of varenicline is mild to moderate nausea that usually disappears with time of use. A meta-analysis of serious adverse events occurring during or after active treatment, and not necessarily considered as treatment related, suggests an increase by a third of severe adverse events among people using varenicline (RR 1.36, 95% CI 1.04-1.79) compared to placebo but these findings need more study. It should be noted that post-marketing safety studies have raised the question about the possible association between varenicline and depression, anxiety, suicidal intentions and suicidal thoughts and behavior. As a warning or alarm mechanism for these potential adverse events, labeling of varenicline was amended in 2008, and manufacturers produced a Medication Guide to guide health professionals in their prescription. However, while the monitoring reports and secondary analyzes are inconclusive, the possibility of a link between varenicline and serious psychiatric or cardiovascular events cannot be excluded.

3.1.4 Antihypertensives

Clonidine was originally used for the treatment of hypertension. Additionally, this drug acts on the central nervous system and can reduce withdrawal symptoms in various addictive behaviors, including consumption of tobacco. The RR of success with clonidine versus placebo was 1.63 (95% CI = 1.22-2.18). Others clinical controlled studies suggested that the success of the clonidine is higher (OR: 4.2) if it is associated with psychological and behavioral therapy, than without it (OR: 1.7). Likewise, the patches of clonidine seem to be more effective than the oral presentation (OR: 3.2 versus 2.2). Other studies demonstrate an OR of 1.89 (95 % CI: 1.30-2.74). Nevertheless, there was a high incidence of dose-related adverse effects, including dry mouth, sedation, dizziness and symptomatic postural hypotension. The authors concluded, based on a small number of clinical trials, that clonidine is effective in promoting smoking cessation. However, significant adverse effects limit its consumption.

3.1.5 Additional pharmacological treatments for smoking cessation

Silver acetate

Silver acetate produces an unpleasant taste when combining with cigarettes. It has been suggested that it reduces the urge to smoke and to associate smoking with an unpleasant stimulus. Products containing silver acetate have been marketed in different presentation forms (gum, spray, etc). Its usefulness is questionable and it has only been tested in smokers with low nicotine dependence. A systematic review on pharmacological treatment for smoking cessation identified two long-term studies of patients randomized to either silver
acetate or placebo. The RR of ceasing after administration silver acetate versus placebo was 1.04 (95% CI: 0.69-1.57). The authors concluded that the existing clinical trials show little evidence of a specific effect of silver acetate in promoting smoking cessation. However, the absence of silver acetate effect may also be due to poor adherence to treatment.

**Opioid antagonists**

It has been documented that smokers experience a number of positive effects such as pleasure, increased alertness or relaxation, when consuming cigarettes. In this sense, the use of opioid antagonists or narcotics agents may be useful in smoking cessation because of the potential to mitigate the positive effects that smokers experience during tobacco consumption. However, the use of opioid antagonists such as naltrexone or naloxone which might create similar effects failed to demonstrate the utility of these drugs in the treatment of this addiction. All four clinical trials identified in a systematic review conclude that it is possible to detect a difference in cessation rates between naltrexone and placebo. However, no significant effect was found on long-term abstinence (OR 1.26, 95% CI 0.80-2.01). None of the trials of naloxone reported long-term monitoring. The authors concluded that, based on limited data from four clinical trials there is insufficient evidence on the effect size that naltrexone is effective as a smoking cessation support. Confidence intervals are compatible with both the ability to offer significant clinical benefits and the possibility of negative effects. Information from larger clinical trials would be needed to evaluate the potential role of naltrexone in smoking cessation.

**Anxiolytics**

There are two reasons to believe that anxiolytics may aid in smoking cessation. Anxiety can be a symptom of withdrawal and secondly, smoking itself can be seen as an attempt to self-medicate anxiety problems. However, there is no consistent evidence to support the conclusion that anxiolytics (diazepam, meprobamate, metoprolol, oxprenolol and buspirone) support smoking cessation, but the available evidence does not rule out or exclude a possible effect.

### 3.1.6 Combination pharmacotherapy for stopping smoking

Multiple combinations of medications have been shown to be effective. Some studies have shown therapeutic advantages of the combined use of different types of NRT and the use of combinations between NRT and other no nicotine smoking cessation treatments (bupropion, varenicline, nortriptyline, etc.). Combination therapy with different drugs provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action or therapeutic properties.

Table 6.17.2 shows examples of the two principal types of combination pharmacotherapy that have been used and evaluated. The first is the combination therapy with different forms of nicotine replacement therapy (NRT). Others examples are combinations between two medications that have different therapeutic targets.

A systematic review shows evidence that combining a nicotine patch with a rapid delivery form of NRT was more effective for long-term smoking cessation than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51). A combination of NRT and bupropion was more effective than bupropion alone (RR 1.24; 95% CI 1.06 to 1.45).
Table 6.17.2: Combination of pharmacotherapies for smoking cessation

<table>
<thead>
<tr>
<th>Combination Therapies</th>
<th>Estimated OR or RR</th>
<th>Estimated abstinence rate (%) at 3 or 6 months</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch + gum or spray</td>
<td>RR: 1.35 (95% CI: 1.11-1.63) 3.6 (2.5-5.2)</td>
<td>36.5 (95% CI: 28.6-45.3)</td>
<td>Stead et al. 200855</td>
</tr>
<tr>
<td>Patch + gum</td>
<td>RR: 1.75 (95% IC: 1.04-2.94) versus patch alone RR: 1.38 (95% IC: 0.88-2.17) versus gum alone</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Nasal spray + patch</td>
<td>RR: 2.48 (95% IC: 1.37-4.49) versus patch alone RR: 1.23 (95% IC: 0.85-1.78) versus either patch or spray alone</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Patch + inhaler</td>
<td>RR: 1.39 (95% IC: 0.89-2.17) versus inhaler alone RR: 0.51 (95% IC: 0.17-1.52) versus either patch or inhaler alone</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Patch + lozenge</td>
<td>RR: 1.27 (95% IC: 1.09-1.48) versus either patch or lozenge alone</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Patch + inhaler</td>
<td>OR: 2.2 (95% CI: 1.3-4.2)</td>
<td>25.8 (95% CI: 17.4-36.5)</td>
<td>Fiore et al. 200842</td>
</tr>
<tr>
<td>Patch + Bupropion SR</td>
<td>OR: 2.5 (95% CI: 1.9-3.4) RR: 1.22 (95% IC: 0.86-1.73) versus bupropion alone RR: 3.99 (95% IC: 2.03-7.85) versus placebo</td>
<td>28.9 (95% CI: 23.5-35.1)</td>
<td>Fiore et al. 200842 Stead et al. 201255</td>
</tr>
<tr>
<td>Gum + bupropion</td>
<td>RR: 1.10 (95% IC: 0.76-1.60) versus bupropion alone</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Lozenge + bupropion</td>
<td>RR: 1.30 (95% IC: 1.07-1.58) versus bupropion alone RR: 1.54 (95% IC: 0.81-2.90) versus placebo</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Bupropion + NRT</td>
<td>RR 2.61 (95% CI: 1.65-4.12) versus, placebo</td>
<td>Not available</td>
<td>Stead et al. 201255</td>
</tr>
<tr>
<td>Nortriptyline + NRT</td>
<td>OR: 1.29 (95% CI: 0.97-1.72) OR: 2.3 (95% CI: 1.3-4.2)</td>
<td>27.3 (95% CI: 17.2-40.4)</td>
<td>Hughes et al. 200759 Fiore et al. 200842</td>
</tr>
<tr>
<td>Patch + second</td>
<td>OR: 2.0 (95% CI: 1.2-3.4)</td>
<td>24.3 (95% CI: 16.1-35.0)</td>
<td>Fiore et al. 200842</td>
</tr>
<tr>
<td>generation</td>
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<tr>
<td>antidepressants</td>
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<tr>
<td>(paroxetine,</td>
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</tr>
<tr>
<td>venlafaxine)</td>
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<tr>
<td>Varenicline + Bupropion SR</td>
<td>Not available</td>
<td>71 (95% CI: 54-85) at 3 months and 58 (95% CI: 41-74) at 6 months</td>
<td>Ebbert et al. 200970</td>
</tr>
<tr>
<td>Varenicline + NRT</td>
<td>Not available</td>
<td>54; 95% CI= 44-64 (Not significant difference with usual-care patients (59; 95% CI = 50-66))</td>
<td>Ebbert et al. 200971</td>
</tr>
</tbody>
</table>
4. What is the current "pipeline" of products for smoking cessation? What is known, if anything, on the safety and efficacy of products in the pipeline?

At present much research is done in the area of gene therapy. With respect to smoking cessation gene therapy is aiming at immunomodulation via vaccination with nicotine molecules in the form of a conjugate with an antigen associated protein, which activates the patient's immune system and stimulates the formation of antibodies. The presence of antibodies in the blood limits the amount of nicotine that enters the brain without causing side effects, thereby reducing psychopharmacological response to this substance. This is possible because the molecules are too large to cross the blood brain barrier. Thus, a nicotinic vaccine could reduce the amount of nicotine that reaches the brain when a person smokes cigarettes which may help people to stop smoking or to prevent future relapses in recent quitters. Even though the compounds studied so far show good tolerability and efficacy it seems unlikely that they can be used as first line therapy or prevention.

Currently there are no licensed vaccines for public use, but some are in development. The authors of a recent systematic review found four trials that met the inclusion criteria, three of them comparing NicVAX (developed by Nabi Biopharmaceuticals/GlaxoSmithKline (GSK) with placebo and one comparing NIC002 (NicQbeta developed by Cytos Biotechnology/Novartis) with placebo. All four clinical trials were conducted by pharmaceutical companies as part of the development process of these products and the authors of the review concluded that there were high risks of bias. Overall, 2642 smokers participated in the four studies; none found significant differences in long-term cessation. The RR for 12 months of cessation between the active group and the placebo group was 1.35 (95% CI: 0.82-2.22) in the trial of NIC002 (NicQbeta) and 1.74 (95% CI: 0.73-4.18) for NicVAX. Two phase III clinical trials of NicVAX, for which the full results were not available, reported similar cessation rates of approximately 11% in both groups. In both studies, with all available results, further analysis found high rates of cessation in participants with high levels of nicotine antibodies, but these results are not generalizable. The trials demonstrated that NicVAX is tolerated with most adverse events classified as mild or moderate. In the NIC002 study, participants who received the vaccine were more likely to report adverse events such as mild to moderate flu-like symptoms, whereas in the study of NicVAX no significant differences were reported between the two arms. Information on adverse events was not available for the Phase III NicVAX study. A preliminary assessment of both trial data - first and second NicVAX(R) Phase III clinical trials- showed that the primary end point was not met and there was no statistical difference between the NicVAX and Placebo groups.

The authors noted that further studies are required comparing vaccines with NRTs. Future studies also need to explore the potential of nicotinic vaccines in preventing relapses and adverse events and serious adverse events should continue need to be monitored and reported.

Additionally, another vaccine is currently in development which is called TA-NIC (Celtic Pharmaceuticals, Hamilton, Bermuda). Clinical research of this product includes clinical trials that have completed phase I/II and which have been found cessation rates at 12 months
of 19% and 38% in the groups treated with TA-NIC 250 mcg and 1000 mg, respectively, compared with those who received only placebo (8%).

Additionally, Independent Pharmaceutica AB (Sweden) is developing a new vaccine called Niccine. The multicenter clinical trial investigating the efficacy of this product is in phase II. The primary indication of the vaccine is the prevention of relapse in smokers who have recently quit smoking with the help of pharmacological treatment for smoking cessation.

The successful use of vaccines in the treatment of tobacco addiction could contribute to developing innovative ways to combat smoking. It has been noted that nicotinic vaccines may have the advantage of achieving a depot effect on the immune system, approximately six to 12 months after vaccination, which could reduce the relapse rate. Additionally, with the use of vaccines, it is not necessary to administer the full daily dose of smoking cessation medication. However, there are multiple challenges that still need to be overcome such as the need for multiple injections and the time to wait before they get an effective immune response. Finally, there are people who fail to reach antibody titers necessary for successful results which is a variation in efficacy which can still not be explained.

Other products are in development: they include new NRT (e.g. nicotine inhaled formulation ARD-1600, developed by Aradigm Corp.), cannabinoid 1 receptor antagonists (e.g. the inverse agonist CB1R taranabant Inc. of Merck & Co.), and antagonists of the dopamine D3 receptor (such as GSK598809 of GlaxoSmith Kline).

Finally, a new product is the battery-powered electronic delivery system (ENDS), with the appearance of a conventional cigarette, hence the colloquial names by which it is known such as "electronic cigarette", "e-cigarette ", "E-cigar "and" cigarette green", which is thought to allow aerosolized administration of nicotine in a more efficient way. However, these products have been brought onto the market against the principles of the WHO Framework Convention on Tobacco Control (FCTC). After reviewing the available evidence, the WHO recommended banning information suggesting that electronic nicotine vaporizers are an effective option in combating addiction to tobacco. This ban should be in effect until there is sufficient evidence to demonstrate health benefits. According to the WHO, the effectiveness of electronic cigarettes to quit smoking or health effects must be supported by reliable pharmacokinetic, safety and efficacy studies and appropriate certification by the regulating authorities.

5. What are the opportunities for research into new pharmaceutical interventions? What is the state-of-the-art science (basic and operational) for this disease and what does it offer? What is the current status of institutions and human resources available to address the disease?

The research currently available suggests that abstinence rates can be increased by combining different forms of nicotine replacement therapy or simultaneous administration of NRT and non-nicotinic compounds. However, more research is needed for a better
definition of the criteria that need to be fulfilled in or to combine different therapeutic modalities.

There is some evidence about the efficacy of smoking cessation medications in smokers uninterested in quitting. Carpenter et al 2004\textsuperscript{87}, reported results from a study in smokers unmotivated to quit showing that "a telephone intervention of smoking reduction plus nicotine replacement therapy and brief advice did not differ from motivational advice plus brief advice, but both were more effective than no treatment".\textsuperscript{87}

Another study reported results from a meta-analysis (five studies) showing estimated odds ratio (95% C.I.) of 2.5 (1.7–3.7), and estimated abstinence rate (95% C.I.) of 8.4 (5.9–12.0) for Nicotine replacement therapy (gum, inhaler, or patch) versus placebo in patients who are not currently willing to make a quit attempt but who state that they are willing to reduce their smoking.\textsuperscript{42} However, because of the selective participant inclusion criteria among other aspects the authors concluded that it is unclear whether the results would be relevant to a broader population of smokers not wanting to quitting.\textsuperscript{42}

More evidence is need in relation to the use of NRT to help smokers who are currently NOT willing to quit to reduce their tobacco use, effectiveness of prequit NRT use to increasing abstinence rates, use of NRT in ‘practice quit attempts’ and extended use of NRT to maintain abstinence.

Additionally, evidence suggests that smokers who relapse sometime during their cessation attempt are at high risk of future relapses, so that rescue interventions for those smokers are necessary. Although there have been studies that suggest that continuing use of nicotine patches after a relapse can be a prevention for future relapses, more research is needed to define what treatments would work best after relapse.\textsuperscript{88} Similarly, more research is needed to document the possibility of a link between varenicline and psychiatric or serious cardiovascular events. Additionally, there is a need for testing the efficacy of varenicline beyond 12 weeks.\textsuperscript{8} So far the number of clinical trials evaluating the efficacy and safety of cytisine are limited. Future clinical trials of cytisine may improve its efficacy when combined with other individual interventions.\textsuperscript{8}

Most of the evidence of cost-effectiveness of drug treatments comes from industrialized countries or upper middle income; however, more research is needed on the cost-effectiveness of pharmacotherapy for smoking cessation in low and middle income countries. This evidence is needed to inform decision makers about the need for the development of medication at lower costs to their countries.

One area for future research is analyzing financing mechanisms of this type of intervention in different country settings. Currently, there is debate about whether these interventions should be totally covered by the public health systems or, on the contrary, it should take advantage of the ability and willingness to pay by some smokers to design innovative funding strategies. One possibility is the establishment of co-financing mechanisms for the latest technologies and high cost interventions, using international experiences.\textsuperscript{89,90,91,92}

Recent studies have explored the hypothesis that interventions to support the funding of cessation treatments on both the demand and supply increases success cessation rates. A recent systematic review\textsuperscript{95} demonstrates a beneficial effect (RR 2.45, 95% CI 1.17 to 5.12) in
financial support to smokers trying to quit smoking on success rates, however, more research is needed in this area.

6. What are the gaps between current research and potential research issues which could make a difference are affordable and could be carried out in a) five years or b) in the longer term?

Many pharmaceuticals which have been being tested for treatment of smoking cessation. In general, all seven first-line medications (five nicotine and two non-nicotine) are recommended and reliably increase long-term smoking abstinence rates. When combined with medical advice and psychological counseling for behavior change, most available treatments produce continuous abstinence rates around of 30%. However, these estimates come from randomized clinical trials involving smokers who are highly motivated and using rigorous monitoring methods, offering medical advice with high intensity, compared to what happens in real life scenarios.84,85 An issue has been raised about the effectiveness of NRT outside clinical trials. Many smokers in the “real world” may use the products sub-optimally leading to a lower level of effectiveness than the effectiveness reported in trials.96 However there is evidence that NRT use by smokers making self-initiated attempts to quit without formal behavioural support is associated with improved long-term abstinence rates [OR: 3.0 (95% CI 1.2 to 7.5)] comparing abstinence for six months in those smokers using and those not using NRT, adjusting for nicotine dependence.96

Clinicians should encourage the use of cessation medications in patients attempting to quit smoking except when medical contraindication exists or with specific populations (i.e. pregnant women, smokeless tobacco users, light smokers, and adolescents) for which there is insufficient evidence of effectiveness. However some areas need more research [e.g. effectiveness of OTC nicotine patch, gum, and lozenge, extent to which individuals use medications appropriately, extent to which the effectiveness of OTC medication is enhanced by other treatments (e.g. pharmacist counseling, telephone counseling, computer self-help resources, clinician interventions)].42

Annex 6.17.3 summarizes the objectives and future research areas. One solution is finding more effective medication for smoking cessation; other studies determine the most effective combination therapies and research on specific groups of smokers (teens, pregnant, cigar and pipe smokers, occasional smokers or light smokers, women, etc.) and its implications for the results of efficacy/effectiveness of pharmacotherapies. The effectiveness of smoking cessation therapies appears to be modulated by deep social inequities that need to be more clearly characterized and eliminated in order to reduce morbidity and mortality related to smoking in socially disadvantaged populations.95,97

Considering the lack of research focused on a large number of smokers who are not currently willing to quit, further studies are required to identify mechanisms to increase motivation to quit smoking in this population as was analyzed above.42,87 Alternatively, highly effective new treatments regardless of the intrinsic motivation of the smoker would be desirable, but it is unlikely that these advances will be available in the near future.95
Treatment costs can be an important barrier against effective uptake of smoking cessation treatment. Patients are more likely to use those treatment options that are free of costs to them or their costs may be reimbursed by their insurance company.\textsuperscript{96,99,100,101} Evidence on cost-effectiveness of these treatments, as well as findings from clinical studies show a significant increase in rates of abstinence followed by reimbursement of the cost of smoking cessation treatments. This supports the idea that during the development of those therapeutic options the reimbursement aspect needs to be included as one of the considerations of how the technology needs to be designed.\textsuperscript{95}

7. For which of these gaps are there opportunities for pharmaceutical research? Which issues can only realistically be addressed with increasing financial support or investment in human and institutional capacity? Which issues are best suited to the comparative advantage of the EU?

To date, pharmacological interventions for smoking cessation rates show moderate efficacy/effectiveness, so that more effective new treatment options are needed if one wants to substantially impact on morbidity and mortality associated with tobacco consumption. Regarding the cost-effectiveness evidence available today, many pharmacotherapeutic options for smoking cessation are cost-effective in high and upper middle income countries. However, in low and lower middle income countries, where the problem of consumption of tobacco and its impact on morbidity and mortality is very large and will continue to be very large, the limited evidence available indicates that smoking cessation treatments are not yet cost-effective, primarily due to the high cost of these products. It requires further research and development of low-cost products so that these countries have the opportunity to strengthen their programs to reduce tobacco consumption through interventions at individual level.

Additionally, future clinical research focused on medication already marketed or developed and which need to be tested in clinical trials should look for improvement in the quality of their design and analysis (e.g. analysis by group of smokers (age, gender, risk factors)) as well explicitly documenting the NNT, for each study. This would allow assessing more objectively the dimensions of health benefits that they report. Research on new low cost formulations of proven effective therapies would be worthy of support. This development might facilitate reimbursement or coverage by health insurance organizations.

To date, treatments for tobacco use (both medication and counseling) are not provided consistently as paid services for subscribers of health insurance packages.\textsuperscript{12,13,28,42} Without supportive systems, policies, insurance coverage, and environmental prompts, the individual clinician likely will not assess and treat tobacco use consistently.\textsuperscript{12}
References


Update on 2004 Background Paper, BP 6.17 Smoking Cessation


Update on 2004 Background Paper, BP 6.17 Smoking Cessation


Update on 2004 Background Paper, BP 6.17 Smoking Cessation


## Annex 6.17.1: Pharmacological treatments for smoking cessation

<table>
<thead>
<tr>
<th>Pharmacological intervention</th>
<th>Presentation/Brand/Manufacturer</th>
<th>Dose/ treatment duration</th>
<th>Efficacy (Risk ratios, abstinence rate or odds ratios)</th>
<th>Number needed to treat (NNT)</th>
<th>Adverse effects</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nicotine Products</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine Gum</td>
<td>2 mg, 4 mg (Nicorette, Pharmacia) (Nicotinell, Novartis Consumer Health) GUM, CHEWING; BUCCAL: EQ 2MG BASE ; EQ 4 MG BASE GLAXOSMITHKLINE (GSK)</td>
<td>2-4 mg during 2-3 months, fluctuating between 3-12 weeks</td>
<td>RR: 1.49 (95% CI 1.40 to 1.60) (versus placebo)</td>
<td>23 (95% CI 20 to 27)</td>
<td>Hiccoughs, gastrointestinal disturbances, jaw pain, and orodental problems</td>
<td>Stead et al. 2012 (Cochrane Review) Cahill K, et al. 2012. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>5 mg, 10 mg, 15 mg (Nicorette, Pharmacia) 7 mg, 14 mg, 21 mg per 24 hours (NICOTINELLE TTS 10, TTS 20 &amp;TTS 30 Novartis Consumer Health) 7 mg, 14 mg, 21 mg (NiQuitin CQ, GSK)</td>
<td>Daily maximum dose: 15 mg for 16 hours path 21 mg for 24 hours path During 2-3 months fluctuating between 3-12 weeks</td>
<td>RR: 1.64 (95% CI 1.52 to 1.78) (versus placebo)</td>
<td></td>
<td>Skin sensitivity and irritation</td>
<td>Stead et al. 2012 (Cochrane Review)</td>
</tr>
<tr>
<td>Nicotine Inhaler</td>
<td>10 mg (Nicorette, Pharmacia) INHALANT; ORAL: 4 MG/ CARTRIDGE PHARMACIA AND UPJOHN</td>
<td>4 MG/CARTRIDGE</td>
<td>RR: 1.90 (95% CI 1.36 to 2.67) (versus placebo)</td>
<td></td>
<td>Local irritation at the site of administration (mouth)</td>
<td>Stead et al. 2012 (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Nicotine lozenge and Nicotine Sublingual Tablet</td>
<td>1 mg (Nicotinell, Novartis Consumer Health) 2 mg and 4 mg (NiQuitin CQ, GSK)</td>
<td>Daily maximum dose 1 mg, 2 mg or 4 mg (depending of</td>
<td>RR: 1.95 (95% CI 1.61 to 2.36) (versus placebo)</td>
<td></td>
<td>Hiccoughs, burning and smarting sensation in the mouth</td>
<td>Stead et al. 2012 (Cochrane Review)</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.17 Smoking Cessation

### Nicotine Nasal Spray

<table>
<thead>
<tr>
<th>Nicotine Nasal Spray</th>
<th>Dosage</th>
<th>RR</th>
<th>CI</th>
<th>Additional Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicorette, Microtab, Pharmacia (sublingual tablet)</td>
<td>0.5 mg per puff metered nasal spray (Nicorette and Pharmacia)</td>
<td>0.5 mg</td>
<td>RR: 2.02 (95% CI 1.49 to 2.73)</td>
<td>Local irritation at the site of administration (nose)</td>
</tr>
</tbody>
</table>

### Antidepressants (there is an indication for smoking cessation for bupropion, whereas for the other anti-depressants, there is no indication for smoking cessation)

#### Bupropion (sustained release)

<table>
<thead>
<tr>
<th>Bupropion (sustained release)</th>
<th>Dosage</th>
<th>RR</th>
<th>CI</th>
<th>Additional Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zyban, tab 100 mg</td>
<td>150 mg once a day for three days increasing to 150 mg twice a day continued for at least seven weeks. There should be an interval of at least eight hours between successive doses. The maximum single dose should not exceed 150 mg and the total daily dose should not exceed 300 mg.</td>
<td>RR: 1.69 (95% CI: 1.53-1.85) (versus placebo)</td>
<td>20 (95% CI 16 to 26)</td>
<td>Insomnia, nausea, anorexia, seizures, changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide</td>
</tr>
<tr>
<td>Zyban, tab 150 mg, prolonged release tablets. GSK</td>
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<tr>
<td>Quomem, tab 150 mg, prolonged release tablets. GSK/Allen Pharmazeutika Gesellschaft</td>
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<tr>
<td>Corzen, tab 150 mg, prolonged release tablets. GSK</td>
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<tr>
<td>Zyntabac, tab 150 mg, prolonged release tablets. GSK</td>
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<td></td>
</tr>
</tbody>
</table>

#### Nortriptyline

<table>
<thead>
<tr>
<th>Nortriptyline</th>
<th>Dosage</th>
<th>RR</th>
<th>CI</th>
<th>Additional Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPSULE; ORAL: EQ 10 MG BASE</td>
<td>75 to 100 mg/day</td>
<td>RR: 2.03 (95% CI: 1.48-2.78)</td>
<td>Not available</td>
<td>Dry mouth,</td>
</tr>
</tbody>
</table>

### Smoking Cessation

- 2 mg (Nicorette, Microtab, Pharmacia) (sublingual tablet)
- 2 mg and 4 mg Nicorette lozenge
- 1.5 mg and 4 mg (outside of the United States) and
- 2 mg and 4 mg (inside the United States) NiQuitin mini lozenge

Additional effects include:
- Mouth, sore throat, coughing, dry lips and mouth ulcers
- Insomnia, nausea, anorexia, seizures, changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide
- RR: 0.66 (95% CI: 0.53-0.82) (versus varenicline)
## Smoking Cessation

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Route</th>
<th>Duration</th>
<th>Comparator</th>
<th>RR (95% CI)</th>
<th>Adverse Effects</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline + NRT</td>
<td>10 mg BASE/5 ML</td>
<td>400 mg/day began one week before quit day and continued for two months, reducing to 200 mg/day for a further month.</td>
<td>versus placebo</td>
<td>1.29 (0.97-1.72)</td>
<td>drowsiness, light-headedness and constipation</td>
<td>2011. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Not available</td>
<td>400 mg/day began one week before quit day and continued for two months, reducing to 200 mg/day for a further month.</td>
<td>Not available</td>
<td>Not available</td>
<td>Hughes JR, et al 2011. (Cochrane Review) EMEA</td>
<td></td>
</tr>
<tr>
<td>Selegiline</td>
<td>SELEGILINE HYDROCHLORIDE CAPSULE; ORAL: 5 MG TABLET; ORAL: 5 MG</td>
<td>10 mg/day for 9-26 weeks</td>
<td>versus placebo</td>
<td>1.45 (0.81 to 2.61)</td>
<td>Not available</td>
<td>Hughes JR, et al 2011. (Cochrane Review) FDA</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Not available</td>
<td>225 mg/day</td>
<td>versus placebo</td>
<td>1.22 (0.64 to 2.32)</td>
<td>Increase suicidal thoughts and behavior, and attempted suicide</td>
<td>Hughes JR, et al 2011. (Cochrane Review) EMEA</td>
</tr>
</tbody>
</table>

### Nicotine receptor partial agonists

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Route</th>
<th>Duration</th>
<th>Comparator</th>
<th>RR (95% CI)</th>
<th>Adverse Effects</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytisine</td>
<td>Tabex, tab 1.5 mg, Sopharma Pharmaceuticals</td>
<td>1.5 mg over 20 days or 25 days</td>
<td>versus placebo</td>
<td>3.98 (2.01 to 7.87)</td>
<td>Nausea, restlessness, insomnia, irritability, Dyspepsia, headache, gastrointestinal</td>
<td>Cahill K, et al 2012. (Cochrane Review)</td>
</tr>
</tbody>
</table>
### Update on 2004 Background Paper, BP 6.17 Smoking Cessation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Dose</th>
<th>Duration</th>
<th>RR (CI)</th>
<th>Adverse Events</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dianicline</strong>&lt;br&gt; (Averted by Sanofi-Aventis)</td>
<td>Tab 40 mg, Sanofi-Aventis</td>
<td>40 mg tablet twice a day for seven weeks</td>
<td>RR 1.20, 95% CI 0.82 to 1.75 (versus placebo)</td>
<td>Not available</td>
<td>Not available</td>
<td>Cahill K, et al 2012. (Cochrane Review)</td>
</tr>
<tr>
<td><strong>Varenicline</strong>&lt;br&gt; (Chantix, Champix)</td>
<td>Chantix, tab, 0.5 mg, 1 mg, Pfizer Inc (FDA)&lt;br&gt; Champix, tab, 0.5 mg, 1 mg, Pfizer Inc (EMEA)</td>
<td>1.0 mg twice a day for 9-12 weeks</td>
<td>RR: 2.27 (95% CI 2.02 to 2.55) (versus placebo, six months)&lt;br&gt; RR: 2.23, 95% CI 1.93 to 2.58 (versus placebo, 12 months)&lt;br&gt; RR: 2.32, 95% CI 2.08 to 2.58 (versus placebo, 24 weeks)&lt;br&gt; RR: 2.53 (95% CI 2.32 to 2.76) (versus placebo, 9-12 weeks)&lt;br&gt; RR: 1.52 (95% CI 1.22 to 1.88) (versus bupropion, 12 months)&lt;br&gt; RR: 1.13 (95% CI 0.94 to 1.35) (versus NRT, 24 weeks)&lt;br&gt; RR: 4.91 (95% CI 2.56-9.42) long term (52 weeks) use</td>
<td>10 (IC 95%: 8-12)&lt;br&gt; Nausea (feeling sick), insomnia (difficulty sleeping), abnormal dreams and headache cardiovascular adverse events psychiatric events</td>
<td>Cahill K, et al 2012. (Cochrane Review) FDA EMEA</td>
<td></td>
</tr>
</tbody>
</table>
## Antihypertensives agents

| **Clonidine** | Oral or transdermal clonidine  
TABLET; ORAL: 0.1 MG ; 0.2 MG ; 0.3 MG  
DAVA PHARMS INC/ VINTAGE/ IMPAX LABS/ UNICHEM/LUITPOLD/ALEMBIC PHARMS LTD/HIKMA FARMACEUTICA/APP PHARMS | Treatment with oral or transdermal clonidine with a maximum daily dosage of >=0.2 mg. The oral dosage varied from a maximum allowed of 0.15 mg per day to 0.45 mg per day. Transdermal dosages were 0.1 to 0.3 mg per day. | RR: 1.63 (95% CI: 1.22 to 2.18) (versus placebo) | Not available | Dry mouth and sedation  
dizziness | Not available  
Gourlay SG, et al 2008  
(Cochrane Review) |

| **Nicotine antagonists** | | | | | | |

| **Mecamylamine** | Capsule 2.5 mg | 2.5-20 mg/day  
2.5 mg twice daily  
two weeks before  
the quit date, and  
increased to 5mg  
twice daily,  
continued for three  
weeks after quitting | A combination of mecamylamine plus nicotine patch was more effective than nicotine patch alone  
(abstinence rate at one year 37.5% versus 4.2%). | Drowsiness,  
postural hypotension and constipation | Not available  
Lancaster T, et al. 2011  
(Cochrane Review) |

| **Opioid antagonists** | | | | | | |

| **Naltrexone** | NarpanTM, ReviaTM; half-life 240 min  
TABLET; ORAL: 100 MG ; 25 MG ; 50 MG | 50 mg per day during 8-12 weeks | OR: 1.34, 95% CI: 0.49 to 3.69 (versus placebo)  
OR: 1.24, 95% CI: 0.74 to 2.09 (Naltrexone +NRT versus placebo +NRT) | Not available | Not reported | David SP, et al. 2009  
(Cochrane Review)  
FDA |
## Selective type 1 cannabinoid (CB1) receptor antagonist (limited evidence available)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Duration</th>
<th>RR (95% CI)</th>
<th>Adverse Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rimonabant</td>
<td>5 mg or 20 mg during 10 weeks</td>
<td>RR 1.50 (95% CI 1.10 to 2.05)</td>
<td>Not available</td>
<td>Nausea (feeling sick), infections of the upper respiratory tract and serious harm</td>
<td>Cahill K, et al. 2009. (Cochrane Review) EMEA</td>
</tr>
<tr>
<td>Acomplia, 20 mg Sanofi-Aventis</td>
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<tr>
<td>Zimulti, 20 mg</td>
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</tbody>
</table>

## Other treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>RR (95% CI)</th>
<th>Adverse Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver acetate</td>
<td></td>
<td>OR: 1.05 (95% CI: 0.63-1.73)</td>
<td>Not available</td>
<td>Not reported</td>
</tr>
<tr>
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<tr>
<td>NicQbeta, Cytos Biotechnology in Switzerland and Novartis</td>
<td>200 or 400 µg</td>
<td>RR: 1.35 (95% CI: 0.82 to 2.22) (NicQbeta vs placebo)</td>
<td>Not available</td>
<td>Flu-like symptoms, fever, myalgia, general discomfort/malaise, and headache</td>
</tr>
<tr>
<td>Niccine, Independent Pharmaceutica AB (Sweden).</td>
<td></td>
<td>RR: 1.74 (95% CI: 0.73 to 4.18) NicVAX vs placebo</td>
<td>Not available</td>
<td></td>
</tr>
<tr>
<td>NicVAX, Nabi Biopharmaceuticals (USA)*</td>
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<tr>
<td>TA-NIC, Xenova and Celtic Pharma (United Kingdom)</td>
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</tbody>
</table>

### Annex 6.17.2: Public coverage and three months complete treatments cost in some European countries

<table>
<thead>
<tr>
<th>European Country</th>
<th>Reimbursement of pharmacotherapies by public insurance</th>
<th>NRT</th>
<th>Bupropion</th>
<th>Varenicline</th>
<th>Currency/Year</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Gum</td>
<td>Patch</td>
<td>Spray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Not covered by compulsory insurance*</td>
<td>362</td>
<td>362</td>
<td>756</td>
<td>354</td>
<td>N/A</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Covered by public insurance*</td>
<td>254</td>
<td>321</td>
<td>649</td>
<td>193</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spain</td>
<td>Not covered by public insurance*</td>
<td>155</td>
<td>154</td>
<td>N/A</td>
<td>153</td>
<td>N/A</td>
</tr>
<tr>
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</tr>
<tr>
<td>France</td>
<td>Only NRT are covered. The rest of treatments are not covered by public insurance**</td>
<td>214</td>
<td>259</td>
<td>N/A</td>
<td>242</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>Not reported*</td>
<td>153</td>
<td>157</td>
<td>364</td>
<td>189</td>
<td>N/A</td>
</tr>
<tr>
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</table>


**Note: Public insurance not defined.
## Update on 2004 Background Paper, BP 6.17 Smoking Cessation

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>The Netherland</td>
<td>Not reported*</td>
<td>323.35</td>
<td>327.81</td>
<td>391.79</td>
<td>Vemer et al. 2010</td>
</tr>
<tr>
<td>Belgium</td>
<td>NRT and Bupropion are reimbursed under specific conditions**</td>
<td>311.05</td>
<td>277.42</td>
<td>391.78</td>
<td>Vemer et al. 2010</td>
</tr>
<tr>
<td>Germany</td>
<td>Not reported*</td>
<td>317.13</td>
<td>292.22</td>
<td>337.28</td>
<td>Vemer et al. 2010</td>
</tr>
</tbody>
</table>

*Data available in Cornuz et al. 2006 or Králíková et al. 2008

**PPRI Network Query: Smoking cessation (February 2009). Specific reimbursement conditions in Belgium: chronic obstructive pulmonary disease (GOLD classification stage II, III or IV); 35 years or older; test treatment of 18 days; maximum one package of 100 tablets (150 mg)/attempt to quit smoking; maximum three attempts/five years (at the least six months between two attempts); Co-payment of 8.90 euros (preferentially insured patients) or 13.50 euros (patients with “standard” insurance).
### Annex 6.17.3: Future research areas for smoking cessation

<table>
<thead>
<tr>
<th>Pharmacological intervention</th>
<th>Future research areas</th>
<th>Products under development</th>
<th>Source</th>
</tr>
</thead>
</table>
| **Nicotinic products**      | 1. Direct comparisons between the various forms of NRT and between different doses and durations of treatment.  
2. Use of combinations of different forms of NRT.  
3. Direct comparisons between NRT and newer pharmacotherapies including varenicline  
4. The effect of starting NRT use before the quit date.  
5. How best to overcome safety and efficacy misperceptions among smokers?  
6. Efficacy of extended use of NRT to maintain abstinence and determining which smokers are most likely to benefit from such a regimen. | 1. ARD-1600 (Aradigm Corporation) an inhaled aerosolized nicotine developed using AERx inhalation technology. (Phase I)  
2. Nicotine MDTS (Acrux) Metered dose skin spray delivery technology. (Phase I)  
3. NAL2771 (NAL Pharmaceuticals) a New nicotine 24 hour matrix patch (Phase I)  
4. NAL2762 (NAL Pharmaceuticals) developed as a nicotine orally dissolving film (ODF) for smoke cessation (Phase II) | Stead et al 2008 (Cochrane Review) Polosa et al 2011. |
| **Antidepressants**         | 1. Determine which antidepressants or classes of antidepressant are effective in smoking cessation.  
2. Determine the action mechanism of antidepressant efficacy and the biological factors controlling nicotine dependence and smoking.  
4. Research on the use of antidepressants in combination with nicotine replacement therapy, in smokers who have failed with NRT, and smokers with baseline dysphoria.  
5. Continued monitoring, given the numbers of | 1. EVT 302 (Evotec, MAO-B inhibitor) (Phase II)  
2. Selegiline (National Institute on Drug Abuse) (Phase II)  
3. GSK598809 (GlaxoSmithKline) (Phase I)  
### Update on 2004 Background Paper, BP 6.17 Smoking Cessation

Deaths and psychiatric disorders from antidepressants used for smoking cessation reported.

#### Nicotine receptor partial agonists
1. Compare the long term success of extended treatment with standard 12-week treatment
2. Monitoring the incidence of serious adverse events
3. Further exploration of safety issues, including psychiatric and cardiovascular adverse events
4. Additional trials of cytisine to explore variations in the drug regimen and in the level of behavioural support

<table>
<thead>
<tr>
<th>Tabex (Cytisine, Sopharma AD) a Nicotinic Receptor Partial Agonists) Phase III</th>
<th>Cahill K, et al., 2012. (Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polosa et al 2011</td>
<td></td>
</tr>
</tbody>
</table>

#### Antihypertensives agents
1. Determine whether the efficacy of drugs acting via these mechanisms can be dissociated from adverse effects.

<table>
<thead>
<tr>
<th>Not reported</th>
<th>Gourlay SG, et al. 2008 (Cochrane Review)</th>
</tr>
</thead>
</table>

#### Nicotine antagonists
1. Determine whether mecamylamine, combined with nicotine replacement, is more effective than nicotine alone.
2. Determine the best dose and timing if this therapy is used.
3. Whether mecamylamine is more effective when given prior to, or following, cessation
4. How it is best combined with nicotine replacement.

<table>
<thead>
<tr>
<th>Not reported</th>
<th>Lancaster T, et al. 2011 (Cochrane Review)</th>
</tr>
</thead>
</table>

#### Opioid antagonists
1. Determine whether naltrexone is efficacious for smoking cessation.
2. Investigate the efficacy of combining naltrexone with other smoking cessation medications (e.g., bupropion, nortriptyline, clonidine).

<table>
<thead>
<tr>
<th>Nalmefene (Somaxon Pharmaceuticals) (Phase II)</th>
<th>David SP, et al. 2009 (Cochrane Review)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone (University of Chicago) (Phase II)</td>
<td></td>
</tr>
<tr>
<td>Polosa et al 2011</td>
<td></td>
</tr>
</tbody>
</table>
### Selective type 1 cannabinoid (CB1) receptor antagonist

1. Compare Rimonabant with other pharmacotherapies, such as nicotine replacement therapy, bupropion and varenicline.
2. Consider the benefits of rimonabant for sub-groups of smokers (e.g. obese versus overweight versus healthy weight).
3. Rimonabant direct comparisons and interactions with nicotine replacement therapy, bupropion, exercise, etc.

1. MK0364 (Taranabant, Merck & Co) acts by reducing the food intake and increasing energy expenditure and fat oxidation (Phase II) — Cahill K, et al 2009. (Cochrane Review)

### Silver acetate

1. Further research on silver acetate for smoking cessation is unlikely to be helpful. — Not reported

### Vaccines

1. Compare vaccines with placebo for smoking cessation.
2. Explore the potential of nicotine vaccines as an aid to relapse prevention.
3. Adverse events and serious adverse events should continue to be carefully monitored and reported.
4. Report and categorize nicotine-specific antibody levels.
5. Specified the method used for antibody calculations.

1. TA-NIC (Celtic Pharmaceuticals) (Phase II) — Hartmann-Boyce J, et al. 2012 (Cochrane Review)
2. NIC002 (Cytos Biotechnology/Novartis) (Phase II)
3. Niccine (Independent Pharmaceutica) (Phase II)
4. NicVAX (GlaxoSmithKline/Nabi Biopharmaceuticals) (Phase III) — Polosa et al 2011