

Application for Inclusion of Nicotine Replacement Therapy(NRT)
in the WHO Model List of Essential Medicines

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Proposal for Inclusion of Nicotine Replacement Therapy in the WHO Model List of Essential Medicines

Tobacco Free Initiative



**World Health
Organization**

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Summary

Tobacco smoking is one of the leading causes of death throughout the world, accounting for approximately 5.4 million deaths per year currently but for a predicted 8 million deaths per year within 20 years. Tobacco use is also a barrier to economic development in low-income countries due to morbidity-associated impairment of productivity and health-care costs (World Bank, 1999). More than 1 billion adults are smokers, of whom 82% live in low-income countries, and worldwide consumption of tobacco is rising. The World Health Organization (WHO) facilitated negotiation of the world's first public health treaty, the WHO Framework Convention on Tobacco Control (FCTC), which has codified the most important strategies for reducing tobacco use, including management and treatment of tobacco dependence.

Nicotine replacement therapy (NRT) is a class of nicotine delivering medicines which help people to stop smoking by acting at brain nicotine receptors, thus reducing withdrawal symptoms. It is a 'clean' form for delivering nicotine, which is not accompanied by the main carcinogens and other toxic substances found in tobacco products and produced by their combustion. There are two systems for delivering medicinal nicotine: the transdermal patch, which delivers a relatively steady level of nicotine during the time it is worn, and several acute dosing systems, including chewing-gum, inhalers, sprays, tablets and lozenges. Although use according to the approved labelling is important to optimize benefits and safety, the wide availability of NRT in many countries has shown that they can be used safely and beneficially with little supervision.

NRT has been available in many high-income countries for about 25 years and has been studied intensively for its effectiveness, safety, adverse effects, cost and cost-effectiveness. There is strong, consistent evidence that use of NRT increases the rate of success in quitting smoking and is cost-effective. It delivers nicotine 'cleanly', unaccompanied by the major carcinogens and other toxic substances in tobacco and its combustion products.

At least 46 systematic reviews have been conducted on the effectiveness of NRT, which showed a statistically significant benefit for smoking cessation in populations of smokers that differ by sex, age, ethnic background, country and economic status. The Cochrane Library contains systematic reviews conducted since 1994 on the effectiveness of NRT for the general population. The seventh update, released in 2008, was a review of 111 randomized or quasi-randomized trials with at least 6 months of follow-up (Stead et al., 2008). It found that people taking NRT had a pooled risk ratio for quitting smoking of 1.58 (95% confidence interval [CI], 1.50–1.66) when compared with controls. The authors concluded that all commercially available forms of NRT can increase people's chances of stopping smoking.

The World Bank (1999) estimated that 25% coverage with NRT would cost only US\$ 276–297 per disability life year saved in low-income countries, which is much lower than the costs of other already accepted treatments. It is reasonable to predict that the cost-benefit ratio, the accessibility and the affordability of NRT would be improved by its listing as an essential medicine, because the manufacture of generic brands of products that are now off patent would be stimulated, particularly in developing countries.

Several products other than nicotine have been shown to be effective in helping people to stop smoking, and two (bupropion and varenicline) are approved by many drug regulatory authorities (WHO, 2003; Fiore et al., 2008). Applications have not been entered to make these drugs essential medicines because they are prescription drugs with a broader range of safety concerns and generally higher costs, which would be barriers to widespread access and use in

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low-income countries and regions. In contrast, the most widely used NRT products (nicotine chewing-gum, patches and lozenges) are available without prescription in most countries, and there are several makers of ‘private label’ nicotine chewing-gum (United States Food and Drug Administration, 2008).

Many factors are important in stimulating attempts to quit smoking and increasing the probability that cessation will last. Tobacco control policies and social factors are particularly important and will be strengthened by implementation of the WHO FCTC. For example, attempts to stop smoking are more likely to be successful for a smoker who is in a social context with other smokers who are quitting, when smoking is prohibited in the workplace and when smokers are properly informed of the health consequences of smoking and receive cessation tips, through either health warnings or educational campaigns targeted to the cessation and treatment of tobacco dependence. The number of national tobacco control initiatives has augmented since ratification of the WHO FCTC, increasing the numbers of people who want to stop. Between 35% and 50% of smokers in high-income countries attempt to stop annually; the rates are lower in low-income countries. Unassisted cessation by healthy smokers is generally considered to result in a long-term sustained rate of of less than 10%, with wide variation across studies. Unfortunately, for many tobacco users, social support and national policies are no match for the biological pressures of dependence and withdrawal, and lasting cessation is extremely unlikely without treatment. This leads many smokers to divert their limited financial resources to purchase cigarettes rather than food and other necessities for their families. Some low-income countries do not have strategies to treat tobacco dependence, impeding their economic development due to rising burdens of disease, lost productivity and diversion of personal resources to buy cigarettes (World Bank, 1999; WHO, 2004a).

WHO has estimated that better access to intervention with NRT would help more people to decide and attempt to stop smoking. Many people, particularly in low-income countries, face substantial barriers to obtaining NRT, which could be removed if NRT was an essential medicine. Article 14 of the WHO FCTC requires Parties to implement measures for the management and treatment of tobacco dependence by collaborating with other countries to facilitate access to and the affordability of treatment for tobacco dependence, including pharmaceutical products. Inclusion of NRT in the WHO Model List of Essential Medicines will motivate countries to discharge this duty and improve access to treatment for tobacco dependence.

The accumulated evidence has led every major public health organization that has examined the issue to recommend better access and use of evidence-based treatment to reduce the prevalence of tobacco use and the associated premature morbidity and mortality. Conservative estimates indicate that provision of NRTs to all smokers with an effectiveness of 0.5% is predicted to result in 6 million people giving up smoking in one year of which 1 million would avoid dying from smoking-attributable causes over their lifetime (Ranson K et al, 2000). A NRT effectiveness of 1% would result in the avoidance of 3.5 million smoking attributable deaths. At an effectiveness level of 5%, NRT would avert 17.4 million tobacco related deaths from the smokers that quit in one year. 80% of quitters and averted deaths would be in low-income and middle-income countries (Jha P et al, 2006).

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1. Summary statement of proposal for inclusion, change or deletion

Nicotine replacement therapy (NRT) for smoking cessation is proposed for inclusion in the WHO Model List of Essential Medicines for the management of tobacco dependence in adult smokers.

2. Focal point in WHO for application

Dr Douglas Bettcher, Tobacco Free Initiative

3. International Nonproprietary Name (generic name)

Nicotine replacement therapy

4. Formulations proposed for inclusion

Commercially available nicotine replacement devices for smoking cessation in the form of chewing-gum, transdermal patches, inhalers, nasal sprays, sublingual tablets and lozenges

5. International availability

According to the records of Euromonitor 2006, 60 countries had data on sales of at least one type of NRT in 2005. According to the survey reported in the *WHO report on the global tobacco epidemic, 2008* (WHO, 2008), some type of nicotine replacement device is available in 136 Member States.

6. Request for listing as an individual medicine or as an example of a therapeutic group

Listing is requested in the WHO Model List of Essential Medicines as an example of a therapeutic group under the heading ‘nicotine (systemic) for smoking cessation’.

7. Evidence for public health relevance

7.1 *Epidemiology of tobacco smoking*

7.1.1 *Prevalence*

Currently, more than 1 billion people, or approximately one third of the world’s adults, smoke tobacco. The estimated overall prevalence of smoking among men and women aged 15 years and over is 38.4% and 19.9% in high-income countries and 44.9% and 5.2% in low- and middle-income countries, respectively (WHO, 2008). About 82% of the world’s smokers live in low-income countries (Jha et al., 2006). The prevalence of tobacco smoking has increased dramatically in Africa, Asia and the Middle East over the past 30 years (Guindon, Boisclair, 2003), and the most recent figures indicate that almost half of the world’s smokers are Chinese, Indian, Indonesian or Russian men (WHO, 2008). Most women smokers still live in rich countries, but high rates are found in some low- and middle-income countries, such as Chile, Montenegro and Serbia (Mackay, Eriksen, Shafey, 2006). Approximately

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9.5% of adolescents aged 13–15 years smoke, with wide variation among countries (Warren et al., 2008).

In 2006, 5.76 trillion cigarettes were sold (Altria Group, 2007). Consumption rates are increasing in both low- and middle-income countries and have decreased only slightly in high-income countries (Food and Agriculture Organization of the United Nations, 2003).

Use of tobacco is a complicated issue, as its causes and its cure are rooted in social behaviour and regulation of the forces that encourage its use, as well as the physical pathogenesis of the dependence and withdrawal disorders that develop in most long-term tobacco users (Royal College of Physicians, 2001; WHO, 2001; da Costa e Silva, David, 2003; WHO, 2004b; Royal College of Physicians, 2007). Despite the large body of evidence on the health damage caused by tobacco, people continue to take up or maintain smoking. Tobacco is a psychoactive substance that creates dependence, tipping the hierarchy of choices towards continued use, even when information about health risks is available (American Psychiatric Association, 1994). Nicotine is known to be addictive. Pharmacologically, it is a nicotine receptor stimulant, with various other psycho-pharmacological properties that can include anxiolytic and anti-depressant effects, depending on the dose, the the individual and other factors (Balfour et al., 2000). The nicotine in inhaled tobacco smoke activates the brain reward system by increasing dopamine release (Peters, Morgan, 2002). This is a transient effect, and, as the nicotine level in the blood decreases, withdrawal symptoms emerge, frequently accompanied by mental impairment, a sense of physical and psychological deprivation and a powerful urge to resume tobacco smoking. This is the cycle that underpins continued use, which is reinforced by the setting, the situation, the emotional context, sensory cues and behavioural rituals (WHO, 2004c). Withdrawal from tobacco use can be stressful and uncomfortable. Tobacco dependence is reinforced in its users and is a major factor in not stopping smoking or in relapsing after a cessation attempt (Aveyard, West, 2008).

7.1.2 Disease burden

Illnesses caused by tobacco smoking

The broad categories of disease caused by active smoking (inhaled mainstream smoke) are numerous cancers, cardiovascular disease, respiratory disease and reproductive effects (United States Department of Health and Human Services, 2004; Table 1). Smoking and exposure to tobacco smoke causally increase the risk for tuberculosis (Slama et al., 2007), and evidence is accumulating that tobacco use exacerbates other infectious diseases and their outcomes (Arcavi, Benowitz, 2004).

Exposure to secondhand smoke (sidestream smoke from burning cigarettes and from exhaled smoke) also increases the risks for many diseases in these categories, most notably lung cancer and coronary heart disease in adults, respiratory disease in young people and fetal damage (United States Department of Health and Human Services, 2006).

Mortality attributed to smoking

It is estimated that about 5.4 million people die every year from diseases caused by smoking (WHO, 2008), and the number of deaths is predicted to increase to 8 million per year by 2030 if current consumption rates continue (Mathers, Loncar, 2006). If current patterns do not change, up to 1 billion people could die from smoking tobacco this century.

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Table 1. Diseases caused by smoking

Disease category	Disease type or site
CancersCancer	Bladder
	Cervix
	EsophagusOesophagus
	Renal cell and renal pelvis (kidney)
	Larynx
	Acute myeloid leukemialeukaemia
	Lung cancer
	Oral cavity and pharynx
	Pancreas
	Stomach (gastric cancers)
Cardiovascular diseases	Abdominal aortic aneurysm
	Subclinical atherosclerosis
	Stroke
	Coronary heart disease
Respiratory diseases	Chronic obstructive pulmonary disease
	Pneumonia and other acute respiratory illnessesdisease
	Respiratory effects in utero
	Impaired lung growth in childhood and adolescence
	Asthma-related symptoms in childhood and adolescence
	Accelerated age-related decline in lung function
Reproductive effects	Respiratory symptoms and poor asthma control in adults
	Fetal death and stillbirth
	Reduced fertility
	Low birth weight
Other effects	Pregnancy complications: placenta previa, placental abruption, preterm delivery
	Nuclear cataract
	Diminished health status, manifested byas increased absenteeism, increased use of health - care services
	Adverse surgical outcomes and respiratory complications
	Hip fractures
	LowDecreased bone density
	Peptic ulcer disease

Source: US Surgeon General, United States Department of Health and Human Services (2004)

Risk reduction after cessation

Stopping smoking reduces the risk for developing a smoking-related disease (United States Department of Health and Human Services, 1990), the degree of risk reduction depending on the duration and intensity of smoking. The risk for cardiovascular disease can be reduced within 5 years (Bakhru, Erlinger, 2005), while that for lung cancer is generally reduced by half within about 20 years (Burns, 2000). Although lung function cannot be restored, smoking cessation can decrease the speed of decline (Fletcher & Peto, 1977). An analysis of the survival of smokers and former smokers between the ages of 40 and 70 demonstrated that the excess mortality of female and male former smokers was 25% and 31% higher than that of people who had never smoked, while the mortality rate of smokers was more than doubled

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(Vollset, Tverdal, Gjessing, 2006). A World Bank study confirmed that smoking cessation is cost-effective (Ronckers, Ament, 2003).

Contribution to poverty and impaired economic development

Tobacco and poverty create a vicious circle. In most countries, especially those in development, tobacco use tends to be higher among the poor, so that poor families spend a larger proportion of their income on tobacco. Money spent on tobacco cannot be spent on basic human needs, such as food, shelter, education and health care. Another way in which tobacco use exacerbates poverty among users and their families is the effects of tobacco on health with a much higher risk for falling ill and dying prematurely of cancer, a heart attack, respiratory disease or other tobacco-related diseases, depriving families of much-needed income and imposing additional costs for health care (WHO, 2004a).

7.2 Current use of nicotine replacement therapy

The role of nicotine in the pharmacological effects of addiction led to the development of nicotine replacement devices, which help smokers by providing a low dose of nicotine to nicotinic receptors, thus reducing physical withdrawal symptoms and giving the quitting smoker a more comfortable phase of transition during behaviour change and self-definition. Two core assumptions in the development of NRT, which have been substantiated over decades of study, are relevant to both its safety and its efficacy. The first is that, although nicotine is the primary pharmacological driver of tobacco use, the main causes of disease and premature mortality in tobacco users are the numerous toxicants in tobacco and smoke. Secondly, most tobacco users are accustomed to substantial nicotine intake and readily tolerate the generally lower levels and slower absorption of nicotine from NRT (Royal College of Physicians, 2001; United States Department of Health and Human Services, 1988; Royal College of Physicians, 2007).

Data from Euromonitor 2006 show a global market turnover of US\$ 965 838 000 for NRT in 2005. In the United States in 1998, NRT and Zyban (bupropion) were estimated to account for 150 million prescriptions, corresponding to an estimated 6 million attempts to quit with NRT (Centers for Disease Control and Prevention, 2000). In a more recent estimate, 2 million smokers used NRT in the United Kingdom in 2005 (cited by West, Zhou, 2007). NRT is used most frequently in high-income countries, but its use has been registered in at least 30 low-income countries (Euromonitor, 2006).

7.3 Target population

The target population that stands to benefit in the near term is current adult cigarette smokers, because, if they continue to smoke, they face an overall risk for premature mortality of approximately 50%; smoking cessation reduces these risks (United States Department of Health and Human Services, 2000; da Costa e Silva, David, 2003). The best rate by which smoking has been reduced is 3% per year, as in Canada (Health Canada, 2006), indicating that the smokers who quit or die are not fully replaced by new smokers. Success in smoking cessation is more likely for a smoker who is in a social context where other smokers are also quitting (Christakis, Fowler, 2008). The number of national tobacco control initiatives has increased with ratification of the WHO Framework Convention on Tobacco Control (FCTC) (WHO, 2005), the world's first public health treaty, and more and more people appear to want to stop smoking (Yang et al., 2007). Currently, the percentage of smokers who make an

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attempt to stop is between 35% and 50% in high-income countries and much lower in low-income countries (Aveyard, West, 2008). The long-term sustained rate of unassisted cessation is generally considered to be 2–3% for healthy smokers (Stead, Bergson, Lancaster, 2008) and up to 10% for patients with cardiac disease or hospitalized patients (Rigotti, Munafo', Stead, 2007). These are similar to the rates for healthy patients who receive non-pharmaceutical counselling (Valery et al., 2008). WHO has estimated that greater access to NRT would help more people to stop smoking and also help more people to decide and attempt to stop smoking (WHO, 2004b).

The WHO FCTC stipulates in Article 14 that treatment modalities, including pharmaceutical aids for cessation, should be made available to populations:

“Article 14

“Demand reduction measures concerning tobacco dependence and cessation

“1. Each party shall develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices, taking into account national circumstances and priorities, and shall take effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence.

“2. Towards this end, each Party shall endeavour to:

“(a) design and implement effective programmes aimed at promoting the cessation of tobacco use, in such locations as educational institutions, health care facilities, workplaces and sporting environment;

“(b) include diagnosis and treatment of tobacco dependence and counseling services on cessation of tobacco use in national health and educations programmes, plans and strategies, with the participation of health workers, community workers and social workers as appropriate;

“(c) establish in health care facilities and rehabilitation centres programmes for diagnosing, counselling, prevention and treating tobacco dependence; and

“(d) collaborate with other Parties to facilitate accessibility and affordability for treatment of tobacco dependence including pharmaceutical products pursuant to Article 22*. Such products and their constituents may include medicines, products used to administer medicines and diagnostics when appropriate.”

*Article 22 relates to cooperation in the scientific, technical, and legal fields and provision of related expertise

8. Treatment

8.1 Indications for use and mode of action

NRT is intended for use by people who are regular smokers and are aged 18 or older, to replace tobacco products with the goal of smoking cessation. Caution should be exercised by people with acute symptoms of cardiovascular disease (serious arrhythmia or serious or worsening angina pectoris) or recent cardiac events (the 2-week post-myocardial infarction period), who should use NRT only on the advice of a health professional. Pregnant women should attempt cessation with non-pharmacological modalities before using NRT. There is no evidence for the effectiveness of NRT in occasional (non-daily) smokers, and it should not be used by nonsmokers.

Nicotine polacrilex medicated chewing-gum

Nicotine chewing-gum should be chewed intermittently and held in the mouth for over 30 min in response to a craving to smoke. It exists in 2- and 4-mg forms, which release about 50% of their nicotine over 15–30 min. Chewing-gum results in relatively slow absorption. Food and acidic drinks should be avoided 15 min before and during use.

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Nicotine transdermal patches

Patches comes in doses of 5, 10 or 15 mg for application during 16 h and doses of 7, 14 or 21 mg for application over 24 h. The patch is the easiest form of NRT to use, and compliance appears to be better than with other nicotine replacement devices. One nicotine transdermal patch is applied in the morning upon rising and removed either at bedtime or in the morning before applying another patch, to a non-hairy, non-broken area of skin on the chest, hip or upper arm. Application sites on the skin should be alternated to minimize skin irritation. Patches are contraindicated in people with generalized skin disease.

Nicotine inhalers

Originally called ‘vaporizers’, inhalers or inhalators consist of a mouthpiece and a plastic cartridge containing 10 mg of nicotine. The actual amount of nicotine delivered per ‘puff’ is about 0.05 mg, but the sensory stimulation produced by the nicotine that is absorbed provides relief for craving for tobacco (Henningfield et al., 2005). The cartridges are placed in the mouthpiece and the contents inhaled. Although they are called ‘inhalers’, most of the nicotine is delivered into the oral cavity (36%) and the oesophagus and stomach (36%); very little goes to the lung (4%) (da Costa e Silva, David, 2003). Food and acidic drinks should be avoided 15 min before and during use.

Nicotine nasal sprays

Nasal sprays offer faster delivery of nicotine than other forms of NRT. A multi-dose bottle with a pump mechanism fitted to a nozzle delivers 0.5 mg of nicotine per 50- μ l squirt. The nicotine is absorbed into the blood rapidly, like snuff or cigarettes. Nasal sprays should not be used by people with asthma, rhinitis, sinusitis or nasal polyps.

Nicotine sublingual tablets

Tablets and lozenges were created for people who cannot or prefer not to use chewing-gum. Sublingual tablets exist in 2- and 4-mg doses. The tablet is held under the tongue until it dissolves, delivering nicotine similarly to chewing-gum. Food and acidic drinks should be avoided 15 min before and during use.

Nicotine lozenges

Lozenges exists in 1-, 2- and 4-mg formulations and are used like nicotine chewing-gum, except that they are not chewed but held in the mouth while they dissolve (for about 30 min). A single lozenge delivers more nicotine than nicotine chewing-gum. Food and acidic drinks should be avoided 15 min before and during use.

8.2 Dosage, regimen and duration of treatment

The dosage varies according to the number of cigarettes smoked per day and the degree of craving and should be modified if unpleasant side-effects are experienced. The doses are envisaged to diminish gradually after 2–3 months. Some people may need even less NRT to maintain cessation.

Nicotine chewing-gum

Nicotine chewing-gum is available in 2-mg and 4-mg (per piece) doses and delivers about 50% of its nicotine to the user (Henningfield et al., 2005). The 2-mg dose is recommended for people who smoke fewer than 25 cigarettes per day, and the 4-mg dose is recommended for those who smoke 25 or more cigarettes per day. Smokers should use at least one piece every

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1–2 h for the first 6 weeks. Nicotine chewing-gum should be used for up to 12 weeks, with no more than 24 pieces per day.

Nicotine transdermal patches

Treatment of 8 weeks or less has been shown to be as effective as longer treatment. Patches containing different doses are sometimes available, and various dosing regimens have been recommended. The highest dose should be used at the beginning of treatment for 3–8 weeks, depending on the preparation, followed by a gradual reduction in the strength of the patch before completing treatment after 3 months. The 16-h patch should be used if the 24-h patch results in sleep disturbances, or, as the labelling on some 24-h patch brands recommends, they can be removed at bedtime. Clinicians should consider individualizing treatment on the basis of personal characteristics, such as previous experience with the patch, amount smoked and degree of dependence.

Nicotine inhalers

Each nicotine inhaler can be used for as long as needed and can be exchanged for a new inhaler if necessary. The recommended dosage is between 6 and 16 cartridges daily for up to 8 weeks, followed by half that dosage over 2 weeks and reduction to zero over the next 2 weeks. The rate of absorption is similar to that of chewing-gum.

Nicotine nasal sprays

The starting dose is one or two doses per hour, up to a maximum of 40 doses per day. Ten doses per day gives a nicotine plasma concentration of 8 ng/ml. The maximum period of use is 8 weeks, followed by a gradual reduction over the next 4 weeks.

Nicotine sublingual tablets

Smokers of 20 cigarettes or fewer per day should start by using 2-mg sublingual tablets. People who continue to have withdrawal symptoms or craving and heavier smokers can use the 4-mg dose. One nicotine sublingual tablet can be used hourly, as needed. The maximum recommended daily dose is 80 mg for 3 months, followed by a gradual reduction in use over the next 3 months for a treatment period of 6 months.

Nicotine lozenges

Nicotine lozenges are available in 2-mg and 4-mg (per piece) doses. The 2-mg lozenge is recommended for patients who smoke their first cigarette more than 30 min after waking, and the 4-mg lozenge is recommended for patients who smoke their first cigarette within 30 min of waking. Generally, smokers should use at least nine lozenges per day during the first 6 weeks. The lozenge should be used for up to 12 weeks, with no more than 20 lozenges to be used per day (Henningfield et al., 2005).

8.3 Existing clinical guidelines

NRT has been recommended as one means for assisting smoking cessation in the following WHO guidelines:

- da Costa e Silva V & David A, eds. *Policy recommendations for smoking cessation and treatment of tobacco dependence*. Geneva, World Health Organization, 2003.
- *Adherence to long-term therapies: evidence for action*. Geneva, World Health Organization, 2003.
- *Building blocks for tobacco control. A handbook*. Geneva, World Health Organization, 2004.

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- *WHO report on the global tobacco epidemic, 2008. The MPOWER package.* Geneva, World Health Organization, 2008.
- *A WHO/the Union monograph on TB and tobacco control: joining efforts to control two related global epidemics.* Geneva, World Health Organization, 2007.
- *Encouraging stopping smoking (Behavioural science learning modules).* Geneva, World Health Organization, 2001.

National guidelines for smoking cessation treatment have been drawn up in 31 countries. All recommend NRT as an appropriate, evidence-based therapy for smoking cessation (Raw, Slevin, 2007). The evidence base for effective smoking cessation treatment, including NRT, is also available on the public service website of the Society for Research on Nicotine and Tobacco at <http://www.treatobacco.net/en/index.html>.

8.4 Special diagnostic or treatment facilities and skills

While the evidence indicates that better results are obtained if NRT is used in association with other cessation strategies, use of NRT alone has been found in high-income countries to increase the chances of cessation. No evidence is available about the effectiveness of NRT alone in low-income countries, but, when used appropriately, NRT in combination with counselling or a brief intervention by the health services was associated with greater rates of successful cessation in Brazil (Otero et al., 2006), China (Lam et al., 2005) and Venezuela (Herrera et al., 1995).

9. Summary of effectiveness based on clinical evidence: review of systematic reviews

Since the introduction of nicotine chewing-gum, the patch and then other nicotine replacement devices, many randomized controlled trials and cohort studies have been conducted to compare the efficacy and effectiveness of NRT with placebo, other pharmaceutical aids to cessation, non-pharmaceutical interventions, alone or in combination, or no treatment and to compare the effectiveness of prescribed and over-the-counter NRT. Systematic reviews have proliferated in order to understand and synthesize these results. We looked at relevant systematic reviews of trials of the effectiveness or efficacy of NRT for smoking cessation.

9.1 Search strategy

PubMed and Google Scholar were consulted for systematic reviews of the effectiveness of NRT for smoking cessation that included meta-analyses of pooled results and effects ratios. We identified 46 published systematic reviews and meta-analyses, including several that had been updated, most notably the seven reviews in the Cochrane Library, in which all reviews follow a standardized methodology; they must be randomized or quasi-randomized, with at least 6-month cessation rates. The systematic reviews published before 2002 are summarized in a major review (Woolacott et al., 2002). Since that time, more attention has been paid to the quality of studies included in systematic reviews, to complement the analysis of Woolacott et al. Recent systematic reviews are presented in depth.

Between 2002 and 2008, 30 systematic reviews with meta-analyses were published. Thirteen addressed the general public and were included in this review of systematic reviews on the

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effectiveness of NRT for smoking cessation, including the most recent Cochrane review (Stead et al., 2008).

9.2 Summary of results

Overview of systematic reviews published 1987–2002

Woolacott et al. (2002) examined systematic reviews published up to 2001 and selected original randomized or quasi-randomized controlled studies from those reviews, as well as 13 new studies. The authors indicated that the most complete review was that of the Cochrane Library (Silagy et al., 2001). Table 2 gives the results of the meta-analysis by Woolacott and colleagues of 71 studies. The data indicate that NRT is more effective for smoking cessation than placebo, control or no treatment in most settings (community, smoking clinic, primary care, over-the-counter preparations). The Table gives the pooled odds ratios for each device and the results for any NRT at the 12-month follow-up.

Table 2. Pooled odds ratios (ORs) for abstinence from smoking measured at 12 months, by nicotine replacement therapy (NRT) delivery device (published studies)

Type of NRT	OR (95% CI)	No. of studies in meta-analysis
Chewing-gum	1.61 (1.45–1.78)	38
Patch	1.62 (1.42–1.84)	23
Inhaler	2.08 (1.43–3.04)	4
Nasal spray	2.27 (1.61–3.20)	4
Sublingual tablet or lozenge	1.73 (1.07–2.80)	2
Any	1.66 (1.54–1.79)	71

Adapted from Woolacott et al. (2002); CI, confidence interval

Woolacott et al. (2002) drew the following conclusions:

- In most of the studies, use of chewing-gum or patch was analysed, but there is sufficient evidence to conclude that the effectiveness of different delivery devices is similar.
- There is no evidence that the effects differ in different populations of smokers.
- Higher doses of NRT can be useful for heavily dependent smokers but not for the general population.
- The evidence that combinations of NRT types are effective is weak, and their effectiveness is similar to that of high doses of single types.
- No conclusion can be drawn about the relative effectiveness of different durations of NRT, fixed versus flexible dosing or gradual or abrupt weaning from NRT at the end of treatment.
- There is no evidence that a clinical setting is necessary for successful abstinence.

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Systematic reviews since 2002

Thirteen systematic reviews were found that comprised meta-analyses of pooled data for the general population of smokers. The overall quality of the reviews was good. They examined the general effectiveness of NRT (Woolacott et al, 2002; Wu et al., 2006; Myung et al., 2007; Eisenberg et al., 2008; Stead et al., 2008) or the effectiveness of NRT according to sex (Cepeda-Bonito, Reynoso, Erath, 2004; Munafo et al., 2004), provider (Mojica et al., 2004), the accompanying non-pharmaceutical strategy (Bala, Lesniak, Strzeszynski, 2008), industry or non-industry funding (Etter, Burri, Stapleton, 2007), over-the-counter versus non-over-the-counter NRT (Hughes et al., 2003), long-term (> 1 year sustained cessation) (Etter, Stapleton, 2006) and NRT versus placebo (Wang et al., 2008). All the systematic reviews found an increased probability of cessation with NRT, usually in combination with another cessation strategy.

The Cochrane review (Stead et al., 2008) represents the largest database on the effectiveness of NRT, with pooled data on over 40 000 people in 111 trials (1979–2007). The risk ratio for sustained cessation of 6 months or more with NRT was 1.58 (95% CI, 1.50–1.66) when compared with a control. The systematic reviews that sought to elucidate areas of bias or issues not examined in the Cochrane review (source of funding or results after more than 1 year) showed that NRT increased the chances of sustained abstinence, but the effect ratios were small. Two systematic reviews of differences in effectiveness by sex arrived at conflicting conclusions: a study by Munafo et al. (2004) found that transdermal patches had similar therapeutic efficacy in men and women, while Cepeda-Bonito, Reynoso and Erath (2004) found a significant but reduced long-term effect of NRT in men.

Table 3 presents the odds ratios and risk ratios derived from pooled data in the meta-analyses of the 13 systematic reviews on the effectiveness of NRT and the authors' conclusions. All the reviews found an added benefit for smokers who received NRT, except for an effect on long-term rates among women. The reports point out the modest results and the difficulty that all smokers have in maintaining long-term abstinence. Few studies included smokers of fewer than 10 cigarettes per day.

The systematic review by Bala, Lesniak and Strzeszynski (2008) comprised studies on the effectiveness of NRT in health policies in Poland. The research question was whether adding NRT to non-pharmacological cessation interventions could improve sustained 12-month cessation rates. The primary studies in the 2004 Cochrane review were randomized controlled trials with a non-pharmaceutical control. The review also investigated the effects of adding bupropion and varenicline to non-pharmaceutical cessation strategies, and found that adding any pharmacological method to simple advice, individual counselling or group therapy increased the probability of abstinence from smoking for 12 months.

Cepeda-Bonito, Reynoso and Erath (2004) looked at the effects of NRT in men and women over time, as previous systematic reviews had suggested that NRT was less effective for women. They found that the statistically significant increase in abstinence in the short term in both men and women dissipated over time, to reach nonsignificance among women in the long-term. The authors compared primary studies of the effectiveness of any NRT device plus high- or low-intensity support with placebo plus high- or low-intensity support. They detected a potential bias in the studies, in that the odds ratios in the papers that reported abstinence rates for men and women separately showed a sex differential, whereas the odds ratios of those that did not present separate data for men and women showed statistically significant results for both men and women at all follow-up times. The authors concluded, nevertheless, that the evidence showed a difference in effectiveness between men and women. They did not

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suggest that women should not receive NRT but considered that smokers should be armed with better skills and motivation to prevent relapse. They noted that investigations of the effectiveness of NRT should present rates for both men and women.

Eisenberg et al. (2008) analysed randomized controlled trials of bupropion, varenicline and NRT by device, including studies in which cessation was validated biochemically at 6 and 12 months. After adjustment for age, sex and daily consumption, bupropion, varenicline and five NRT devices were found to be more effective than placebo in promoting smoking cessation.

The review by Etter, Burri and Stapleton (2007) was initiated to test the possibility that funding by the pharmaceutical industry influenced the strength of the effect found in trials of their NRT products. The meta-analyses showed that industry-supported trials were more likely to have statistically significant results and larger odds ratios. This might be explained by publication bias: a funnel plot of industry-funded trials was highly asymmetrical, as the studies comprised fewer small or middle-sized trials with null or negative results than would be expected by chance. After adjustment for potential publication bias, the pooled treatment effects were similar in industry-supported and non-industry-supported trials. The pooled odds ratio (OR) for long-term effectiveness in the non-industry-supported trials was 1.61 (95% CI, 1.43–1.80), indicating that NRT increases long-term success rates by about 5%, which corresponds to a large number of people.

Etter and Stapleton (2006) conducted a systematic review of the effectiveness of NRT versus placebo among people who were followed up for longer than the usual 12 months after beginning treatment, the follow-up period in the 12 primary studies being 2–8 years (weighted mean, 4.3 years). All the interventions had included supportive advice or counselling, and all but one had excluded smokers of fewer than 10–15 cigarettes per day. In all but one of the studies, smoking status was validated at follow-up by biochemical verification of < 10 ppm carbon monoxide (10 studies) or of < 15 ng/ml cotinine (one study). About 30% of nonsmokers at the 12-month follow-up relapsed later. There appeared to be no difference in the rate of relapse after 12 months between NRT and control groups or between the nicotine replacement devices used. The duration of treatment (3–52 weeks) did not appear to influence long-term effectiveness. Despite heterogeneity in the effects among controls, the overall rate of long-term success was calculated to be 8.6%, and the improvement gained by adding NRT was another 7.2%. The substantial relapse led the authors to conclude that nicotine addiction should be viewed as a chronic recurring disease of the brain, necessitating long-term or prolonged treatment.

Hughes et al. (2003) conducted a meta-analysis of the efficacy of over-the-counter versus prescribed NRT, noting that studying cessation rates with over-the-counter NRT resulted in more contact between patients and investigators than would usually exist. Provision of placebos of over-the-counter NRT free of charge, for ethical reasons, might also have biased the results. Self-reported cessation was not validated in most of the studies; nonetheless, the authors considered that external conditions set the base rate of quitting and it was therefore possible to measure differences between active and placebo effectiveness (in this study called 'efficacy') correctly. The results were presented separately for comparisons of over-the-counter with placebo NRT (four studies) and over-the-counter with prescribed NRT (four studies). The comparisons with placebo showed a significantly better result with the active drug (pooled OR, 2.5; 95% CI, 1.8–3.6); one of the studies included anyone who smoked at least one cigarette per day. The comparisons with prescribed NRT showed no significant difference (pooled OR, 1.4; 95% CI, 0.6–3.3); two of the four studies were not randomized. The authors concluded that the average long-term quit rate with over-the-counter NRT is 7%.

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Table 3. Results of systematic reviews published since 2002 on the effectiveness of nicotine replacement therapy (NRT)

Reference, years of study	No. and types of studies	No. of people and setting	Follow-up criteria	Research question	NRT devices	Odds ratio or rate ratio (95% CI)		Study conclusions
						NRT vs control ¹	NRT vs placebo	
Bala, Lesniak, Strzeszynski (2008) 1987–2004	40 RCT from 2004 Cochrane review	Not given	12-month cessation rates	Effectiveness of adding NRT to (1) simple advice, (2) individual counselling, (3) group therapy	Chewing-gum, patch, tablet or lozenge	(1) OR, 1.64 (1.45–1.87) (2) OR, 1.52 (1.35–1.70) (3) OR, 1.63 (1.41–1.88)		NRT added to non-pharmacological methods increases the probability of smoking abstinence.
Cepeda-Bonito, Reynoso, Erath (2004) 1984–2002	90 effect sizes from 21 double-blind, placebo-controlled RCTs	10 159 men and women	3- and/or 6- and/or 12-month cessation rates	Effectiveness of NRT by sex	Chewing-gum, patch, tablet/lozenge, spray, inhaler		12-month results: NRT overall: OR, 1.47 (1.25–1.73) Men: OR, 1.75 (1.39–2.21) Women: OR, 1.24 (0.99–1.56)	Efficacy of NRT for both men and women declines over time, and at long-term follow-up is greater in men than in women.
Eisenberg et al. (2008) 1980–2006	69 placebo-controlled double-blind RCTs of pharmacotherapy for smoking cessation: 22 chewing-gum, 4 inhaler, 4 nasal spray, 30 patch, 6 tablet	32 908 men and women	Biochemically confirmed abstinence at 6 and/or 12 months	Effectiveness by device	Chewing-gum, patch, tablet, spray, inhaler		Chewing-gum: OR, 1.65 (1.37–2.01) Patch: OR, 1.88 (1.60–2.22) Tablet: OR, 2.06 (1.47–2.87) Spray: OR, 2.37 (1.57–3.60) Inhaler: OR, 2.18 (1.38–3.45)	NRT devices more effective than placebo in promoting smoking cessation; however, absolute abstinence rates were low.
Etter, Burri, Stapleton (2007) 1979–2003	41 RCTs from 2006 Cochrane review of NRT without known financial support from pharmaceutical companies	Not reported	≥ 6-month cessation rates	Effectiveness of NRT in smoking cessation in non-industry funded trials	Chewing-gum (n = 34), patch (n = 7)	NRT: OR, 1.61 (1.43–1.80) Chewing-gum: OR, 1.62 (1.43–1.83) Patch: OR, 1.51 (1.10–2.09)		With the elimination of publication bias, the overall net effect of NRT is about 5% attributable 1-year success.
Etter, Stapleton (2006) 1988–2003	12 RCTs	4792 participants in 12 placebo-controlled trials in various clinical settings	> 1-year cessation rates	Effectiveness of NRT for long-term cessation	Chewing-gum, patch, spray		OR, 1.99 (1.5–2.64)	Relative efficacy of NRT remains constant for many years. Results for only 6–12 months overestimate the lifetime benefit by 30%.
Hughes et al. (2003) 1997–2002	Eight trials in seven articles on OTC NTR compared with OTC	11 597 men and women	2.5–12-month cessation rates	Efficacy of OTC NRT	Chewing-gum, patch	OTC vs prescribed NRT (n = 4): OR, 1.4 (0.6–3.3)	Patch (n = 4): OR, 2.5 (1.8–3.6)	Cessation rates with OTC NRT similar to rates with prescribed NRT. OTC

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Mojica et al. (2004) 1974–1999	placebo or prescribed NTR 35 RCTs, 8 CCTs	5506 adolescents and adults	≥ 5-month cessation rates	Effectiveness of NRT by provider	Chewing-gum (one study with inhalers did not report provider)	Nurses: RR, 2.93 (1.08–7.94) Physicians: RR, 1.45 (0.89–2.36) Psychologists: RR, 3.22 (1.11–9.29)	NRT doubles the OR for quitting. Health providers can help people to stop smoking. NRT increases the effectiveness of nurses and psychologists.
Munafo et al. (2004) 1989–2000	11 RCTs from 2002 Cochrane review	5659 men and women in various treatment settings	< 6-month, 6-month and 12-month follow-up rates	Effectiveness of NRT by sex	Patch	12 months: Men: OR, 1.86 (1.39–2.50) Women: OR, 1.63 (1.22–2.18)	Nicotine patches have similar therapeutic efficacy for men and women.
Stead et al. (2008) 1987–2007	111 RCTs and quasi-randomized trials (Cochrane review)	43 040 men and women in smoking cessation interventions, all settings	≥ 6-month cessation rates	Effectiveness of NRT vs control in smoking cessation	Chewing-gum, patch, tablet or lozenge, spray, inhaler	RR, 1.58 (1.50–1.66)	All commercially available forms of NRT can increase the chances of stopping smoking.
Wang et al. (2008) 1992–2006	Seven RCTs of ‘cut down to quit’ cessation rates with NRT	3156 men and women enrolled in smoking reduction interventions	6-month sustained smoking cessation	Effectiveness of using NRT for ‘cut down to quit’ smoking	Chewing-gum, inhaler	RR, 2.06 (1.34–3.15)	NRT plus considerable contact between patients and investigators is effective for sustained smoking abstinence for smokers who are unwilling or unable to stop abruptly.
Woolacott et al. (2002) 1979–2001	89 RCTs in two systematic reviews and seven individual studies	35 942 men and women in smoking cessation interventions, all settings	Cessation measured at ≥ 6 months’ follow-up	Effectiveness of NRT vs control in smoking cessation	Chewing-gum, patch, tablet or lozenge, spray, inhaler	Any NRT: OR, 1.72 (1.61–1.84)	NRT is an effective intervention for smoking cessation.
Wu et al. (2006) 1993–2006	70 RCTs	28 343 men and women in interventions for smoking cessation	Chemically confirmed 1-year cessation rate	Effectiveness of NRT vs control in smoking cessation	Chewing-gum, patch, others	<i>n</i> = 70 OR, 1.71 (1.55–1.88) <i>n</i> = 49 OR, 1.78 (1.60–1.99)	NRT is therapeutic in smoking cessation.

OR, odds ratio; RR, rate ratio; CI, confidence interval; RCT, randomized controlled trial; CCT, controlled clinical trial; OTC, over the counter (non-prescription sales)

¹ All controls, including non-NRT, placebo, usual care

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They noted that population surveys do not show higher abstinence rates among smokers who use NRT than those who do not but considered that the degree of nicotine dependence in the two populations differs and that the results from experimental studies are more valid than those of correlation studies.

Other authors consider that the superiority of over-the-counter NRT with respect to unaided smoking cessation has not been demonstrated, noting that the systematic review of Hughes et al. (2003) was based on studies with relatively low participation rates (average, 67%, but < 50% in five studies), disparate eligibility requirements, poor subject blinding integrity, variable follow-up periods and low compliance rates (Walsh, 2008).

Noting that cross-sectional population studies do not show evidence of the benefits of NRT, West and Zhou (2007) concluded that the only real test is direct measurement of differences in the success rates of people who use NRT and those who do not in spontaneous quitting outside the clinical trial setting. A study of 'real-world' spontaneous use of NRT, without formal support, is the multinational ATTEMPT cohort study of smokers of five cigarettes or more per day who at baseline were intending to quit within 3 months. The cohort comprised people in Canada, France, Spain, the United Kingdom and the United States whose smoking behaviour was assessed every 3 months. Among the 1398 people who had tried to quit at the first assessment, the rate of continuous abstinence for 6 months was 7.8% with NRT and 4.0% without (OR, 2.2; 95% CI, 1.3–3.9), calculated by logistic regression analysis after adjustment for country. The authors considered that these findings provided additional confirmation of the finding from clinical research that NRT use is associated with better rates of abstinence.

A systematic review by Mojica et al. (2004) synthesized evidence on the effectiveness of smoking cessation interventions by type of provider. The odds ratios for interventions with and without NRT showed that interventions by nurses, psychologists and physicians resulted in significantly more cessation and that addition of NRT increased the effectiveness of psychologists and nurses but not physicians. Many studies of the control condition were available, but there were fewer of the addition of NRT by provider. The authors noted wide heterogeneity among the studies of physicians. The one study that showed no significant effectiveness of NRT involved people with smoking-related diseases in a hospital and a chest clinic; the other three studies were of healthy patients in general or family medical practices. The authors reported that other health professionals in the categories 'counsellors', 'unknown' and 'other' and self-help were not significantly effective in encouraging cessation. The mean final follow-up time was 53.6 months, but was as short as 5 months. There was no evidence of bias in relation to providers, but the authors noted possible publication bias due to the omission of small positive studies and lack of information on contact time with patients. None of the studies included psychiatrists.

Munafo et al. (2004) analysed sex differences in the efficacy of nicotine patches in a review of placebo-controlled trials. They found no evidence of heterogeneity in any of the outcomes of the meta-analysis. They compared abstinence rates for men and women with NRT patches in the short term and at 6- and 12-month follow-ups. The pooled difference by sex in the probability of quitting was not significant at any time. Although sustained, long-term abstinence was the preferred outcome, a few studies provided only self-reported point prevalences. The pooled odds ratio from the 11 studies (1.93; 95% CI, 1.58–2.36) was compared with that from 22 other studies of transdermal patches from the 2002 Cochrane review (Silagy et al., 2001), which were not included in this meta-analysis (OR, 1.69; 95% CI, 1.50–1.93). The two odds ratios did not differ significantly ($p = 0.28$), nor did the mean ratios of men to women differ between studies that were and were not included. The quit rate

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with placebo in these studies was about 10% at 6 months and 8% at 12 months. By converting the odds ratios for men (1.9) and women (1.6), the authors found that NRT would result in 4.2% more women and 6% more men quitting smoking, with no significant difference. The authors concluded that there is no difference by sex in the efficacy of transdermal nicotine patches. They did not assess sex differences in the effectiveness of other types of NRT.

The full text of a study by Myung et al. (2007) was not available, and only data in the abstract are presented here. (This study is not included in Table 3 or 5.) In this review of 16 studies of abstinence 1 year after use of a nicotine patch or placebo by 9457 people, the pooled odds ratio for sustained abstinence with patch versus placebo (12 studies) was 1.75 (95% CI, 1.49–2.05).

The main systematic review of the effectiveness of NRT for smoking cessation is the Cochrane review, which is updated regularly. The latest version is that of 2008 (Stead et al., 2008), which covers 111 randomized and quasi-randomized controlled studies of the effectiveness of NRT among 43 040 men and women, irrespective of setting, in comparison with placebo or non-nicotine controls at ≥ 6 months of follow-up. The pooled fixed risk ratios for smoking cessation in various analyses in this review are shown in Table 4. On the basis of various comparisons, the authors concluded that:

- All forms of NRT are effective as part of a strategy to promote smoking cessation. There is little evidence for the effectiveness of NRT in people who smoke fewer than 10–15 cigarettes a day.
- The choice of device should reflect the person's needs, its tolerability, previous experience and its cost. Patches are easier to use but cannot be used for acute relief and thus may be supplemented with use of gum, spray, or lozenges *ad libitum* (Fiore et al., 2000, 2008).
- An 8-week course of patch therapy is as effective as longer ones. Tapering off is not better than abrupt cessation. A 16-h patch is as effective as a 24-h patch.
- Nicotine chewing-gum can be used at either a fixed or an *ad libitum* dose; 4-mg chewing-gum can be offered to people who fail to quit with 2-mg chewing-gum.
- There is evidence that combining a nicotine patch with an *ad libitum* dose type of NRT or combining NRT with clinical counselling is beneficial.
- NRT does not increase the risk for adverse cardiovascular events in smokers with a history of cardiovascular disease.

The authors of the review state that, although the chances of long-term abstinence after each attempt remain low even with NRT, its use should be encouraged for smokers interested in quitting (Stead et al., 2008).

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Table 4. Pooled odds ratios for smoking cessation from comparisons made in the Cochrane review of nicotine replacement therapy (NRT), 2008

Outcome	No. of studies	No. of participants	RR (95% CI)
Any NRT vs control	111	43 040	1.58 (1.50–1.66)
Nicotine chewing-gum sustained (\geq 12-month) abstinence vs control	53	19 090	1.43 (1.33–1.53)
Nicotine patch sustained (\geq 12-month) abstinence vs control	41	18 237	1.66 (1.53–1.81)
Nicotine chewing-gum plus various levels of behavioural support vs control ^a	52	18 268	1.43 (1.34–1.54)
Nicotine patch plus various levels of behavioural support vs control ^b	42	18 236	1.67 (1.53–1.81)
Long vs short support vs control	3	800	1.14 (0.88–1.47)
Nicotine chewing-gum according to recruitment or treatment setting vs control ^c	53	19 090	1.43 (1.33–1.53)
Nicotine patch according to recruitment or treatment setting vs control	41	18 237	1.66 (1.53–1.81)
Nicotine inhaler according to recruitment or treatment setting vs control	4	976	1.90 (1.36–2.67)
Nicotine tablet or lozenge according to recruitment or treatment setting vs control	6	3 109	2.00 (1.63–2.45)
Nicotine intranasal spray according to recruitment or treatment setting vs control	4	887	2.02 (1.49–2.73)
Combination of NRT according to recruitment or treatment setting vs control	1	245	1.07 (0.57–1.99)
Choice of NRT according to recruitment or treatment setting vs control	1	182	2.50 (0.81–7.68)
Nicotine chewing-gum 4 mg vs 2 mg	7	856	1.43 (1.12–1.83) ^d
Nicotine chewing-gum fixed vs ad lib dosage	2	689	1.22 (0.92–1.61)
Nicotine patch high vs standard dose	7	4 634	1.15 (1.01–1.30)
Nicotine patch weaning vs tapering dose at end of treatment	41	16 342	1.59 (1.47–1.73)
Combinations of NRT vs one type NRT or no NRT control on long-term smoking cessation	7	3 202	1.35 (1.11–1.63)
Direct comparison of NRT types	3	1 494	0.86 (0.62–1.18)
Physician-prescribed NRT vs NRT without support (all NRT purchased)	2	820	4.58 (1.18–17.88)
Pre-cessation treatment with nicotine patch vs NRT without pre-cessation treatment	4	424	1.79 (1.17–2.72)

From Stead et al. (2008); RR, rate ratio; CI, confidence interval

^a The quit rates with behavioural support alone in nicotine chewing-gum trials: low intensity, 5.9%; high intensity, 9.8%; group-based support, 11.7%

^b The quit rates with behavioural support alone in nicotine patch trials: low intensity, 6.3%; high intensity, 6.7%; group-based support, 14.8%

^c Quit rates of smokers in control groups in nicotine chewing-gum trials: primary care settings, 5%; community volunteers, 11%; specialist smoking clinics, 16%

^d Effect found only for highly dependent smokers; no evidence of an effect for low dependence or unselected smokers

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The paper by Woolacott et al. (2002) was a systematic review and an economic evaluation of NRT and bupropion for smoking cessation produced for the National Health Service R&D Health Technology Assessment programme of the United Kingdom. The authors analysed 157 studies, comprising two systematic reviews and seven individual studies of the effectiveness of NRT, four systematic reviews and 112 individual studies of adverse events and safety and 17 economic studies. The conclusions of the review were that “the evidence indicates unequivocally that NRT as an aid to smoking cessation is more effective than placebo”, that the incidence of adverse events with NRT is very low, that smoking cessation interventions are cost-effective, and that adding NRT to current practice is also cost-effective. The authors noted that information is needed on how to maximize the effectiveness and suggested that motivational support might be useful. Their meta-analysis of the effect of any NRT product, based on 96 published studies with 35 942 men and women, showed that the rate of cessation at ≥ 6 months was 16.8% with NRT and 10.3% with placebo or no treatment (OR, 1.72; 95% CI, 1.61–1.84). The results at 12 months are shown in Table 2.

Wang et al. (2008) conducted a systematic review for the National Health Service R&D Health Technology Assessment programme of the United Kingdom to assess the effectiveness and cost-effectiveness for cessation of programmes to reduce smoking. In a meta-analysis of five randomized controlled trials, 5.3% of people who reduced their consumption with NRT and 2.6% of those given placebo stopped smoking completely for 12 months. The studies involved considerable patient–investigator contact, which the authors recommended for further programmes of this type. In comparison with not quitting, programmes for ‘cutting down to quit’ with a gradual reduction in tobacco consumption were cost-effective for cessation.

Wu et al. (2006) analysed 70 randomized controlled trials with chemically confirmed 1-year cessation rates after interventions with NRT in comparison with placebo or with any control condition (including placebo). They found little difference in the effect ratios for NRT versus placebo and NRT versus control, and similar results for 11 studies of bupropion and four of varenicline. This review was funded by a pharmaceutical educational grant. The authors noted methodological variations in the quality of the studies: of the 70 studies in the review, 22 had involved sequence generation to ensure randomization, 11 had concealed allocation to the intervention or control arm, 45 had appropriate blinding, 67 had based the analysis on intention to treat, and 44 gave appropriate descriptions of loss to follow-up. This information was not used in the synthesis of results.

9.3 *Quality of available data*

In the procedure outlined in the health technology assessment (National Health Service, 2001, cited by Woolacott et al., 2002), the criteria for assessing the quality of systematic reviews are the inclusion and exclusion criteria, the extent of the search strategy, whether the validity of the studies was assessed, the amount of detail presented, the heterogeneity of the studies, use of the validity assessments in synthesizing the studies and use of more than one reviewer. The systematic reviews showed good adherence to the procedure, as shown in Table 5.

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Table 5. Assessment of the quality of systematic reviews of the effectiveness of nicotine replacement therapy (NRT) published since 2002

Reference	Search	Validity assessment	Validity judges (n)	Validity used in final synthesis	Details of studies	Heterogeneity of meta-analysis χ^2 (df; p); Q (df; p); I ²	Number of independent data extractors	Number of judges on inclusion and exclusion
Bala, Lesniak, Strzaskzynski (2008)	25 electronic databases; 2004 Cochrane review	Yes, of exclusion criteria	Not reported	Yes	Yes	NRT + simple advice: Q, 23.3 (15; 0.08) NRT + counselling: Q, 52.6 (18; 0.03) NRT + group: Q, 7.3 (14; 0.9)	Not reported	Not reported
Cepeda-Bonito, Reynoso, Erath (2004)	4 databases, 2003 Cochrane review	Yes	2	Yes	Yes	Q, 3.34 (8; 0.6988)	2	2
Eisenberg et al. (2008)	4 databases	No, but included only placebo-controlled, double-blind RCTs	2	No	Yes	Not reported	2	Not reported
Etter et al. (2007)	All studies in the 2006 Cochrane review	Yes, of funding of original research	2	Yes	Yes	Industry-funded trials: χ^2 84; I ² = 43% Non-industry-funded: χ^2 30; I ² = 0%	2	Not applicable
Etter, Stapleton (2006)	5 databases including 2005 Cochrane review	Yes, of exclusion criteria	2	Yes	Yes	Q, 18.7 (11; 0.08)	2	2
Hughes et al. (2003)	2 databases	Yes	Not reported	No	Yes	Heterogeneity found for trials of over-the-counter NRT vs prescribed NRT (figures not given)	Not reported	Not reported
Mojica et al. (2004)	Medline, 2002; Cochrane review; United States Public Health Service review	Methods of the Southern California Evidence-based Practice Center (no details given)	Not reported	Yes	Yes	For some results, not given	Not reported	Not reported
Munafo et al. (2004)	Trials from 2002 Cochrane review of patch vs control with results for men and for women	Not reported	Not reported	No	Yes	12 months: χ^2 5.9 (10 studies; p = 0.75)	2	Not reported
Stead et al. (2008)	Building on previous Cochrane reviews, new studies up to July 2007 in the Cochran Tobacco Addiction Group trials	Yes	Not reported	Yes	Yes	NRT vs placebo or non-NRT control Chewing-gum: χ^2 64 (52; 0.12); I ² = 18.8% Patch: χ^2 50.05 (40; 0.13); I ² = 20.1% Inhaler: χ^2 1.93 (3; 0.59); I ² = 0.0% Tablets or lozenges: χ^2 7.32 (5; 0.20);	2	Not reported

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	registry					I ² = 31.7%		
Wang et al. (2008)	7 bibliographic databases; research registries	Yes	1, reviewed by 1 other	Yes	Yes	Intranasal spray: χ^2 1.63 (0.65); I ² = 0.0% Chewing-gum: 5.65 (3; 0.13) Inhaler + chewing-gum: 8.61 (4; 0.07)	1, checked by 1 other	2
Woolacott et al. (2002)	Comprehensive: 25 electronic databases	Yes	1, checked by 1 other	Yes	Yes	96 studies; χ^2 115.06 (95; 0.08)	1, checked by 1 other	2
Wu et al. (2006)	10 databases	Yes	2	No, but discussed	Yes	NRT vs control 12 months: I ² = 26.5	2	2

RCT, randomized control trial; χ^2 , chi-square statistic; df, degrees of freedom; p, probability statistic; Q test approximates χ^2 for number of effect sizes; I² = [(Q-df)/Q] x 100%. A value greater than 50% indicates moderate to substantial heterogeneity.

9.4 *Place of nicotine replacement therapy in management of tobacco dependence*

Smoking cessation is difficult, and most people who stop for a certain time relapse. Often, the perceived difficulty of quitting and staying a nonsmoker inhibits smokers from attempting to stop. Over time, it has become apparent that the more options available to smokers, the more likely they are to attempt cessation (Aveyard, West, 2008). For adult daily smokers who want to stop, NRT is a useful tool which has been shown to increase the rate of success.

A recent systematic review of 23 systematic reviews provided evidence for the effectiveness of the following smoking cessation interventions for adults: group behavioural therapy (OR, 2.04; 95% CI, 1.37–3.45), bupropion (OR, 2.06; 95% CI, 1.77–2.40), intensive advice from physicians (OR, 2.04; 95% CI, 1.71–2.43), NRT (OR 1.77; 95% CI, 1.66–1.88), individual counselling (OR, 1.56; 95% CI, 1.32–1.84), telephone counselling (OR, 1.56; 95% CI, 1.38–1.77), nursing interventions (OR,1.4; 95% CI, 1.29–1.67) and tailored self-help interventions (OR, 1.42; 95% CI, 1.26–1.61). The authors calculated that a 10% increase in price increased cessation rates by 3–5%, and a clean indoor air policy increased quit rates by 12–38% (Valery et al., 2008). All these strategies should be put in place throughout the world, giving all smokers more options to help them stop smoking. NRT should be one of the options available to adult daily smokers who want to stop smoking.

9.5 *Conclusions*

A vast body of evidence shows that NRT increases the likelihood of smoking cessation. Systematic reviews, which generally include the most methodologically sound randomized and quasi-randomized controlled studies, show that smoking cessation rates are modestly but significantly increased by the use of NRT. Access to NRT could increase the chances of many smokers to quit and to definitively stop smoking. The accumulated data demonstrate that NRT is a major public health tool in the management and treatment of tobacco dependence.

10. Evidence for safety

10.1 *Estimated total exposure to date*

It is difficult to know how many people have been exposed to NRT to date, but available sales data and estimates of use indicate that the number is in the tens of millions, mainly among people in high-income countries.

10.2 *Adverse effects and reactions*

The toxicological effects of nicotine derived from tobacco use are generally considered to be more modest compared to those of the many carcinogens and other toxins present in tobacco products and those produced when tobacco products are burnt. The nicotine delivered by nicotine replacement is substantially less than that of tobacco smoking, and no approved nicotine replacement medicine delivers the very high spiking arterial doses of nicotine that are produced by lung delivery of cigarette smoke (Henningfield et al., 1993; Royal College of Physicians, 2000). NRT is not, however, without risk and the instructions for use on the label should be followed. It can have a variety of adverse effects, depending on the dose and pattern of administration (United States Department of Health and Human Services, 1988).

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Symptoms of withdrawal from tobacco smoking include aggressiveness, anxiety, confusion, impatience, inability to concentrate, irritability, craving, restlessness, constipation, dizziness, headache, sweating, sleep difficulties and increased appetite (American Psychiatric Association, 1994). Some of the adverse effects attributed to NRT may be difficult to differentiate from smoking withdrawal symptoms; however, some may not occur until withdrawal of NRT, which alleviates some nicotine withdrawal symptoms (Woolacott et al., 2002).

The adverse effects and safety of NRT were analysed by Woolacott et al. (2002) in a systematic review of two systematic reviews and 63 individual studies, including 18 RCTs, three non-RCTs, one case-control study, 19 uncontrolled studies, five surveillance studies and 17 case reports or case series (Fiore et al., 2000; Silagy et al., 2001; da Costa e Silva, David, 2003; Foulds et al., 2006). Adverse events were measured by incidence, as part of the safety profile, in pregnancy, in surveillance and in individual cases. The findings are presented in Table 6 and are listed below:

- Nicotine chewing-gum: hiccups, gastrointestinal disturbances, jaw pain, orodental problems
- Nicotine patch: skin sensitivity, skin irritation (50%), sleep disturbances
- Nicotine inhaler: throat irritation (40%), coughing, oral burning
- Nicotine nasal spray: nasal irritation, runny nose, dependence (10–20%)
- Nicotine sublingual tablets: hiccups, nausea, burning mouth, sore throat, coughing, dry lips, mouth ulcers.

Table 6. Adverse effects and safety of nicotine replacement therapy (NRT)

Safety issue	Effects seen
Cardiovascular	No significant adverse effects in healthy adults No short-term adverse events in patients with coronary artery disease
Blood lipid profile	NRT may inhibit the normalization of the lipid profile that usually occurs upon smoking cessation
Endothelial dysfunction	Effects of NRT reflect those of nicotine acquired from smoking
Use in pregnancy	Limited information indicates no harmful effect on the fetus, but caution is advised for use of patches, which might deliver more nicotine than smoking.

Adapted from Woolacott et al. (2002)

The Cochrane review found that the commonest adverse events were skin irritation with use of patches and nasal irritation with use of sprays (Silagy et al., 2001).

In the United States, over-the-counter NRT devices are used by nonsmokers, particularly among young people. A cross-sectional survey in the United States in 1998 showed that 5% of 7932 nonsmoking young people reported using NRT (Klesges et al., 2003). Two surveys of adolescents conducted in 1996–1997 ($n = 562$) and 1998–1999 ($n = 501$) gave NRT abuse rates of 2.7% and 4.6%, which are well below those of other over-the-counter abusable substances, such as diet pills and inhalants (Hyland, Bradford, Gitchell, 2005). Biochemically validated data from the National Health and Nutrition Examination Surveys in 1999–2006

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showed that 0.08% (95% CI, 0.02–0.28%) of 8415 adults who had never smoked regularly and 0.12% (95% CI, 0.04–0.36%) of 5510 adolescents who had never smoked reported using NRT (Gerlach et al., 2008).

Smokers also use NRT for reasons other than cessation. The International Tobacco Control Four Country Survey, a cohort survey conducted every 12 months with adult smokers in Australia, Canada, the United Kingdom and the United States, showed that about 17% of the 6532 adult daily smokers surveyed had used NRT, and about one third of them had used it for a reason other than quitting, possibly to avoid smoking in some places or to reduce the number of cigarettes they smoked (Hammond et al., 2008).

The number of quitting smokers who persistently use NRT has been estimated to be relatively low ($\leq 1\%$ at 12 months) for chewing-gum or patches (Shiffman et al., 2003) but substantial (up to 20%) for nasal spray (Foulds et al., 2006). It should nevertheless be noted that more than half of quitting smokers who use NRT do so at lower doses and for a shorter time than those recommended (Burns, Levinson, 2008).

10.3 Differences in safety by health system and patient

This section addresses the effectiveness, adverse events and safety of NRT for smoking cessation in specific population groups: pregnant women, patients with cardiovascular disease, adolescents, people living in low-income countries and other adult groups.

Pregnant women

The products in tobacco smoke, especially carbon monoxide, are toxic to the fetus. Smoking causes growth restriction, premature birth, miscarriage and stillbirth (United States Department of Health and Social Security, 2004). Nicotine from cigarettes or from NRT metabolizes more quickly in pregnancy (Coleman, Britton, Thornton, 2004), which could result in higher intake to maintain nicotine concentrations in the blood. As pregnant women are usually excluded from drug trials (Rayburn, Bogenschutz, 2004), little information is available about effectiveness or safety in that group. The little evidence available is mixed. A study in Denmark showed that, although nicotine patches did not significantly increase cessation, the infants of women who used them were heavier at birth than those of women who did not (Wisborg et al., 2000). A more recent study of pregnant women in the United States showed better cessation rates, but the trial was suspended when a higher rate of negative birth outcomes were found in an NRT arm (Pollak et al., 2007). Another study showed that women who were prescribed NRT had higher risks for low birthweight, pre-term births than those not using it (Gaither et al., 2008).

NRT cannot be considered a reasonable strategy for smokers who are pregnant, unless there is clear evidence that it will lead to smoking cessation. Such evidence has not yet been obtained, but regulatory bodies have allowed use of NRT during pregnancy on the basis of the concept that NRT is likely to be safer than continued smoking (Coleman, 2008). Pregnant smokers should use nicotine replacement medications only if counselling fails.

Patients with cardiac disease

The four principal mechanisms by which cigarette smoking causes cardiovascular damage are hypercoagulation, reduced oxygen delivery, coronary vasoconstriction and nicotine-induced haemodynamic effects (Ludvig, Miner, Eisenberg, 2005). Complete, permanent smoking cessation is the most clinically effective means of managing atherosclerosis (Hobbs, Bradbury, 2003). Systematic reviews have shown that NRT increases the likelihood of

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permanent cessation among patients with peripheral artery disease (Hobbs, Bradbury, 2003) and coronary artery disease (Ludvig, Miner, Eisenberg, 2005), but a systematic review by Wiggers et al. (2003) found no evidence that NRT is effective in patients with cardiovascular disease. The safety of pharmacotherapy in patients with acute coronary syndromes (Joseph, Fu, 2003) has not been established, but there was no evidence of adverse effects in trials of short-term use of NRT in patients with cardiovascular diseases (Balfour et al., 2000; Woolacott et al., 2002). For patients with acute cardiovascular disease (e.g., acute myocardial infarction), use of NRT should be accompanied by medical monitoring.

Adolescents

Two systematic reviews of smoking interventions in adolescents found limited evidence of their efficacy and no evidence of long-term effectiveness (Garrison et al., 2003; Grimshaw, Stanton, 2006). Only two studies included NRT, but neither study achieved statistically significant results (Grimshaw, Stanton, 2006). The evidence reinforces the recommendation that NRT should be used by adult daily smokers.

Low-income countries

Almost all the available data on NRT comes from high-income countries, implying that it is a strategy only for those regions. Limited data suggest that poor acceptance of NRT, poor adherence to duration and under-dosing are problems in particular ethnic groups in high-income countries and the populations of low-income countries (Lam et al., 2005; Levinson et al., 2006; Fu et al., 2008). Many smokers in high-income countries do not wish to use NRT or other medicines for cessation but prefer non-pharmaceutical strategies. This should of course also be the case for low-income countries. In a country where there is little tobacco control and where people's motivation and readiness to stop smoking are weak and not aided by the social context, the effectiveness of any intervention is likely to be extremely low.

Smoking cessation interventions in health systems should include a wide variety of interventions, and clinicians and patients should not expect instant success with the arrival of NRT. Nevertheless, a few trials in low-income countries showed significantly better cessation rates among people using NRT. A trial of 341 patients in Brazil showed a 25.4% 12-month cessation rate among people receiving counselling and NRT and 14.5% among those receiving counselling alone. An even better result was found with counselling plus NRT plus bupropion (38.5%) (Chatkin et al., 2004). In another study in Brazil, with 1999 adults, a better cessation rate at 12 months was found for people receiving behavioural treatment and NRT (30–34%) than among those receiving behavioural treatment alone (17–23%) (Otero et al., 2006). A double-blind, randomized placebo-controlled trial of 322 smokers in Venezuela analysed the effectiveness of several combinations of NRT with behavioural treatment. The cessation rates at the 2-year follow-up were 34% with 4-mg chewing-gum and 16% with 2-mg chewing-gum for highly dependent smokers, and 39% with 2-mg chewing-gum and 17% with placebo chewing-gum for smokers with medium or low dependence. All the differences were statistically significant (Herrera et al., 1995). The results in a smoking cessation clinic in Hong Kong (China) among 1203 smokers given a 1-week free supply of NRT on an intent-to-treat basis showed a 12-month follow-up cessation rate of 27%; there were no controls (Abdullah et al., 2004).

Other special populations

Hospitalized patients: The systematic review and meta-analysis of Rigotti, Munafo and Stead (2007) of interventions for smoking cessation among patients in hospital is part of the Cochrane Library. This review showed that intensive therapy significantly increased cessation

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rates (17 studies; OR, 1.65; 95% CI, 1.44–1.90) over those obtained with less intensive therapy. Adding NRT did not statistically significantly increase the rates over those achieved with intensive counselling alone (OR, 1.47; 95% CI, 0.92–2.35). The studies were assessed for random sequence generation and allocation concealment, and sensitivity analyses were conducted on the effect of excluding those with a potential recruitment bias. The sensitivity analyses also led to exclusion of studies in which NRT was optional in high-intensity interventions. The authors concluded that, although NRT did not add significantly to the effect of intensive interventions in hospital patients, the trend was in the expected direction, and the quit rates were compatible with those of studies in other settings which have shown it to be effective.

Patients with chronic obstructive pulmonary disease: Wagena et al. (2004) conducted a systematic review of five trials of the efficacy of smoking cessation strategies for 6491 patients with chronic obstructive pulmonary disease. The results were heavily weighted by the Lung Health Study population of 5587 people, who received an intensive intervention including nicotine chewing-gum or usual care. The behavioural interventions did not make a significant difference from control conditions. In the Lung Health Study, the risk ratio for long-term cessation in the group receiving intensive counselling, nicotine chewing-gum and a placebo medication or usual care was 3.81 (95% CI, 3.27–4.44). The authors concluded that the combination of nicotine chewing-gum and intensive counselling for a sustained period significantly increases abstinence from smoking by patients with mild airway obstruction.

Pre-surgical patients: A new systematic review from the Cochrane Library addressed the effectiveness of smoking cessation interventions before surgery. Seven trials of cessation among patients awaiting elective surgery were included, but in only two was cessation measured after 6 months. No significant differences were found between people who had received an intervention and those who had not (Cropley et al., 2008).

Smokers with alcohol problems: Although alcohol use is often associated with smoking, a literature search for a systematic review of the effectiveness of pharmacotherapy for smoking cessation among smokers with a history of alcohol problems revealed only 11 studies. The results were mixed, but, overall, the authors concluded that people with a history of alcohol problems could benefit from pharmacotherapy (Leeman, Huffman, O'Malley, 2007).

Other special adult groups: A systematic review of cessation interventions among mainly psychiatric and substance abuse patients comprised 43 primary studies, only five of which were considered of good quality. The strategies that included NRT showed a significant added effect on cessation, and the authors concluded that psychiatric patients should receive the smoking cessation treatment recommended for the general population. The results were mixed for patients abusing non-nicotine substances (Ranney et al., 2006).

10.4 Summary

The risks for morbidity and mortality associated with continued smoking are far greater than the small risk for serious adverse events associated with use of NRT or its closest comparison, sustained-release bupropion.

Use of NRT by patients with atherosclerotic cardiovascular disease is a concern because of some of the cardiotoxic effects of smoking that are attributable to nicotine. NRT, however, generally leads to lower blood nicotine levels than does cigarette smoking, even if the person continues to smoke during treatment. Use of NRT is therefore likely to result in fewer

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cardiovascular effects than cigarette smoking (Joseph et al., 1996; Benowitz, 1998). The risk for serious cardiovascular adverse events associated with concurrent use of NRT and smoking does not appear to be higher than that with NRT alone (Hubbard et al., 2005).

Sustained-release bupropion is contraindicated for people with a history of seizures, a history of an eating disorder, who are using another form of bupropion or who have used a monoamine oxidase inhibitor in the past 14 days. The risks for serious adverse events associated with bupropion in 8000 patients in the United States were 0.1% for seizures and 0.12% for hypersensitivity (Ferry, Johnston, 2003). In France, serious adverse events occurred at a rate of 0.07% among 698 000 people who were prescribed sustained-release bupropion, (Beyens et al., 2008).

In a systematic review of varenicline, a nicotine receptor partial agonist, the main adverse effect was nausea, but the results suggested that it might also be associated with depressed mood, agitation or suicidal behaviour. Its use is being monitored (Cahill, Stead, Lancaster, 2007).

11. Cost and cost–effectiveness by pharmacological class or therapeutic group

11.1 Costs of proposed medicines

Ranson et al. (2002) used industrial marketing data on NRT from 1998 to estimate that each person in low- and middle-income countries who attempted to quit would spend US\$ 50 for short-term use. In high-income countries, the amount would be US\$ 100 per smoker. Only one out of 11 people would be expected to succeed.

11.2 Cost–effectiveness

The World Bank (1999) estimated that 25% coverage with NRT would cost US\$ 276–297 per disability-adjusted life year saved in low-income countries.

Ranson et al. (2000) estimated the cost–effectiveness of NRT in low- and middle-income countries on the basis of the estimated smoking prevalence for each world region, by age, sex and number of cigarettes smoked per day, assuming that one third of current smokers would later die of a smoking-related disease and that men and women would respond to the intervention equally. As few people in low- and middle-income countries currently stop smoking and the acceptability of NRT in those countries is unknown, the estimated overall effectiveness of NRT use was 0.5%. For a cohort of smokers in 1995, provision of NRTs with an effectiveness of 0.5% was predicted to result in about 4.7 million people stopping and 1.1 million smoking-attributable deaths averted. An updated analysis was conducted for a greater effectiveness for NRT using the same static model for the cohort of smokers alive in 2000. It was predicted that provision of NRT with an effectiveness of 1 percent would result in the avoidance of about 3.5 million smoking attributable deaths; NRT of 5 percent effectiveness would have about five times the effect. Low and middle income countries would account for roughly 80 percent of the averted deaths (Jha P et al, 2006). The cost–effectiveness of NRT in low- and middle-income countries was estimated to be US\$ 276 per disability-adjusted life year saved, as compared with US\$ 749 in high-income countries. Gilbert et al. (2004) estimated that the incremental cost per life year saved for a 45-year-old person in the Seychelles was US\$ 360–643.

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Woolacott et al. (2002) examined the clinical and cost effectiveness of NRT on the basis of six studies in the United Kingdom and five in other countries, as well as general reviews of the cost-effectiveness of smoking cessation. They estimated that adding NRT to a smoking cessation intervention added less than £1000 to the cost per quitter. The direct medical costs associated with smoking-related morbidity in the United Kingdom in 1999 was estimated to be about £28.3 billion after 20 years at an annual discount rate of 6%. Decision analysis modelling of the data for assessing the cost-effectiveness of NRT showed that the incremental cost per life-year saved was £1000–2399, the average cost per life-year saved was about £750 (range, £500–1500), and the incremental cost per quality-adjusted life year saved was £741–1777.

An analysis of the cost-effectiveness of NRT by the French Haute Autorité de Santé (2007) was based on the latest assessments from studies in the Netherlands, New Zealand, the United Kingdom and the United States. The estimates depended on the assumptions made about the rate of spontaneous cessation, the cessation rate with NRT, the cost of the treatment, the number of life years saved by cessation, the relapse rate, the discount rate for life years saved and quality-adjusted life years saved. In all the assessments, even the lowest assessed effect remained cost-effective. The results are presented in Table 7.

Table 7. Estimates of the cost-effectiveness estimations of nicotine replacement therapy (NRT), in euros

Reference	Added cost per abstinent smoker			Cost per life years saved of brief advice + NRT	Cost per quality-adjusted life year saved		
	Brief advice	Brief advice + NRT	Cognitive-behavioural therapy + self-help / medical follow-up + NRT		Brief advice or counselling	Brief advice/counselling + NRT	More intensive support + NRT
van den Bruel et al (2004)*	372	1367	2349	574–1378	Study 1: 1121–4063 Study 2: 1258	Study 1: 1185–2434 (patch) 1866–4651 (chewing-gum) Study 2: 4362	
United States, 2001*			913				
United States, 2002*	211 (pharmacist)	839–1104					
Woolacott et al. (2002)		2756	1150			1021	426

From Haute Autorité de Santé (2007)

* Cited in Centre Fédéral d'Expertise des Soins de Santé (2004)

11.3 Including NRT as an essential medicine is predicted to further improve cost effectiveness of smoking cessation

The World Bank report on the cost–effectiveness of NRT in smoking cessation (World Bank, 1999) did not make the assumption that NRT would be included as an essential medicine, nor did it factor in the potentially substantially lower costs of generic or ‘private label’ (i.e. ‘store brands’) of NRT. Essential medicine status would be expected to increase the attractiveness of regional markets for the introduction of NRT products. Furthermore, nicotine chewing-gum and patches are available as generic or ‘private label’ brands from several manufacturers (United States Food and Drug Administration, 2008). Generic products are generally sold at a substantially lower cost than the original products, and their introduction onto a market generally drives down the price of the original products and increases their affordability and accessibility by stimulating production, particularly in developing countries. This measure would be in line with Article 14, paragraph 2(d), of the WHO FCTC, which states that each Party shall endeavour to “collaborate with other Parties to facilitate accessibility and affordability for treatment of tobacco dependence including pharmaceutical products pursuant to Article 22. Such products and their constituents may include medicines, products used to administer medicines and diagnostics when appropriate.” To date, over 160 WHO Member States are bound by international law to implement the measures outlined in Article 14 of the WHO FCTC. In other words, increased access to tobacco dependence treatment is mandated by the force of international law.

WHO encourages the access of all cigarette smokers to the full range of evidence-based smoking cessation therapies to meet their needs. It is recognized in this application, however, that the main priority is to expand access and availability in low-income countries. In those countries, the highest priority should therefore initially be for medicines that can be obtained without a prescription and do not require monitoring by a medical professional, as these requirements would reduce the access of many cigarette smokers, particularly in under-resourced areas. Therefore, the application does not include bupropion or varenicline; instead, the request is for inclusion of NRT, the most widely used products of which are marketed without prescription in most countries. Nicotine nasal sprays and nicotine inhalers require a prescription in some countries, but in others they are available in pharmacies or for general sale. As they are available in some countries without a prescription, nicotine nasal sprays and inhalers should also be included on the Essential Medicines List. The most widely used and apparently preferred forms of NRT are nicotine chewing-gum, lozenges and patches, which are available without a prescription over the counter; furthermore, as stated above, the chewing-gum and lozenge are often available as low-cost generic brands. Therefore, all forms of NRT should be included on the Essential Medicines List, with priority for chewing-gum, lozenges and patch because of their wide use and availability.

12. Regulatory status by country

The following data are compiled from Annex 2 of the *WHO report on the global tobacco epidemic* (WHO, 2008).

Africa

NRT is available in 24 countries:

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Over-the-counter NRT: Algeria, Benin, Burkina Faso, Cameroon, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Gabon, Guinea, Kenya, Lesotho, Madagascar, Mali, Namibia, Niger, Nigeria, Senegal, South Africa and Swaziland

Prescription NRT: Botswana, Cape Verde, Mauritius, Togo, Zambia and Zimbabwe

Not available: Angola, Burundi, Central African Republic, Chad, Comoros, Equatorial Guinea, Eritrea, Ethiopia, Gambia, Ghana, Guinea-Bissau, Liberia, Malawi, Mauritania, Mozambique, Rwanda, Sao Tome and Principe, Seychelles, Sierra Leone, Uganda and United Republic of Tanzania

Americas

NRT is available in 35 countries:

Over-the-counter NRT: Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Bolivia, Brazil, Canada, Colombia, Costa Rica, Dominica, Guyana, Honduras, Jamaica, Mexico, Panama, Peru, Saint Kitts and Nevis, Suriname, Trinidad and Tobago, United States of America, Uruguay and Venezuela

Prescription NRT: Chile, Dominican Republic, El Salvador, Grenada, Guatemala, Haiti, Nicaragua and Saint Vincent and the Grenadines

Not available: Cuba and Paraguay

No information: Saint Lucia

Eastern Mediterranean

Nicotine replacement therapy is available in 16 countries:

Over-the-counter NRT: Afghanistan, Bahrain, Djibouti, Egypt, Islamic Republic of Iran, Jordan, Kuwait, Lebanon, Oman, Tunisia, United Arab Emirates, West Bank and Gaza Strip

Prescription NRT: Iraq, Morocco, Qatar and Syrian Arab Republic

Not available: Libyan Arab Jamahiriya, Pakistan, Saudi Arabia, Somalia, Sudan and Yemen

Europe

NRT is available in 43 countries:

Over-the-counter NRT: Andorra, Armenia, Austria, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Georgia, Germany, Greece, Hungary, Iceland, Ireland, Italy, Kazakhstan, Kyrgyzstan, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Republic of Moldova, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, The former Yugoslav Republic of Macedonia, Ukraine, United Kingdom of Great Britain and Northern Ireland and Uzbekistan

Prescription NRT: Lithuania

No information: Albania, Azerbaijan, Israel, Monaco, San Marino, Tajikistan and Turkmenistan

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South-East Asia

NRT is available in six countries:

Over-the-counter NRT: Bangladesh and India

Prescription NRT: Maldives, Nepal, Sri Lanka and Thailand

Not available: Bhutan, Democratic People's Republic of Korea, Indonesia, Myanmar and Timor-Leste

Western Pacific

NRT is available in 11 countries:

Over-the-counter NRT: Australia, China, Cook Islands, Japan, Malaysia, Mongolia, New Zealand, Palau, Republic of Korea and Singapore

Prescription NRT: Philippines

Not available: Cambodia, Lao People's Democratic Republic, Niue and Viet Nam

No information: Brunei Darussalam, Fiji, Kiribati, Marshall Islands, Micronesia, Nauru, Papua New Guinea, Samoa, Solomon Islands, Tonga, Tuvalu and Vanuatu

13. Pharmacopoeial standards

13.1 *British Pharmacopoeia*

Trademark names: Nicopass®, Nicopatch®, Nicorette®, Nicotivelle®, NiQuitin®

Devices: nicotine lozenge, nicotine nasal spray, nicotine medicated chewing-gum, nicotine transdermal patches, nicotine sublingual tablets, nicotine inhalation cartridge for oromucosal use

13.2 *International Pharmacopoeia*

Nicotine replacement devices are not currently included.

13.3 *United States Pharmacopoeia*

Nicotine chewing-gum. nicotine transdermal patch

14. Proposed new text for the WHO Model Formulary

In the context of population-wide tobacco control strategies to reduce the prevalence of tobacco use globally—strategies that include the delivery of brief tobacco cessation advice in health-care settings—nicotine replacement medications should be added to the evidence-based treatments for adult smokers in the management of tobacco dependence in countries at all levels of development. The data do not support recommending NRT for occasional (non-daily) smokers, and it should not be used by nonsmokers. Pregnant smokers should use nicotine replacement medications only if counselling fails. Patients with acute cardiovascular disease (e.g., acute myocardial infarction) should use NRT under medical monitoring.

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