



EUROPE

# **REGULATION OF NICOTINE REPLACEMENT THERAPIES: AN EXPERT CONSENSUS**



**AN INITIATIVE  
OF THE WHO  
EUROPEAN  
PARTNERSHIP  
PROJECT  
TO REDUCE  
TOBACCO  
DEPENDENCE**

# Regulation of nicotine replacement therapies: an expert consensus

*This document was prepared by  
Dr Ann McNeill and Ms Anne Hendrie  
in consultation with the expert group,  
for the World Health Organization  
Regional Office for Europe*

This publication is a product of  
the WHO European Partnership Project  
to Reduce Tobacco Dependence.



World Health Organization  
Regional Office for Europe

Copenhagen 2001

### **WHO Regional Office for Europe**

The World Health Organization is a specialised agency of the United Nations with primary responsibility for international health matters and public health. The WHO Regional Office for Europe, in Copenhagen, is one of six regional offices worldwide. Each Regional Office has its own programme geared to the particular health problems of the countries it serves. The WHO European Region embraces 870 million people, from Greenland in the north-west and the Mediterranean in the south to the Pacific coast of the Russian Federation in the east. Since 1990, the number of member states has been 51.

### **WHO European Partnership Project to Reduce Tobacco Dependence**

The WHO European Partnership Project to Reduce Tobacco Dependence was set up in 1999, for an initial three-year period, with the objective of reducing tobacco-related death and disease. The Partnership Project comprises private, non-commercial and public sector partners, including the pharmaceutical sector at the European level and in four target countries, France, Germany, Poland and the United Kingdom. In 2001, the Czech Republic joined the project.

### **WORLD HEALTH ORGANIZATION**

All rights in this document are reserved by the WHO Regional Office for Europe. The document may nevertheless be freely reviewed, abstracted, reproduced or translated into any other language (but not for sale or for use in conjunction with commercial purposes) provided that full acknowledgement is given to the source. For the use of the WHO emblem, permission must be sought from the WHO Regional office for Europe. Any translation should include the words: The translator of this document is responsible for the accuracy of the translation. The Regional Office would appreciate receiving three copies of any translation. Any views expressed by named authors are solely the responsibility of those authors.

# Contents

Summary of Recommendations	1
1 WHO European Conferences on the Regulation of Tobacco Dependence Treatment Products	5
2 Regulation of NRT – overview and context	7
3 Age restrictions	9
4 Advice On Use By Pregnant Women	11
5 Smokers with cardiovascular disease	13
6 Use of NRT to support temporary abstinence	15
7 Use of NRT for reducing smoking	17
8 Use for long-term maintenance	19
9 Combinations	21
10 Wider availability of NRT products	23
11 Products that provide more acceptable alternatives to cigarettes	25
References	27
Annex 1 – Summary of the main conclusions of the first WHO European Conference on the Regulation of Tobacco Dependence Treatment Products	32
Annex 2 – Comparisons in availability and recommendations on NRT use in four European focus countries	
<i>Table 1. Variation across four European focus countries in the products available and the recommendations on: age restrictions, use by pregnant women, use by people with cardiovascular disease, and use in reducing smoking</i>	34
<i>Table 2. Variation across four European focus countries in the recommendations for use during temporary abstinence, concomitant NRT use and smoking, duration of use, combinations of different NRT products and availability</i>	36
Annex 3 – Characteristics of NRT	38
Annex 4 – Glossary	41

# Acknowledgements

*The World Health Organization would like to thank*

- Dr Ann McNeill, Chair of the WHO European Partnership Project, Dr Jonathan Foulds, University of Medicine and Dentistry, New Jersey, and Mr Clive Bates, Director, Action on Smoking and Health UK, authors of Regulation of nicotine replacement therapies (NRT): a critique of current practice published in *Addiction*, 2001; 96:1757-1768 on which the initial version of the WHO expert consensus paper was based.
- The expert group for discussing and agreeing the consensus .
- Patsy Harrington, Project Manager, the WHO European Partnership Project to Reduce Tobacco Dependence.
- Professor Gerard Dubois, for chairing the expert consensus meeting.
- Participants at the meetings in Helsinki (1999) and Barcelona (2000).
- Mr Sven Lund for design and layout of the publication.

# Summary of recommendations

These recommendations are based on the premise that virtually all potential users of NRT are already consuming substantial quantities of the drug nicotine through its most addictive and toxic delivery system – tobacco smoke. Use of NRT by a smoker can improve the chances that they will quit smoking tobacco, but will not introduce new risks not already faced by smokers and will greatly reduce or eliminate many smoking-related risks.

## **Recommendations for WHO**

1. WHO should continue to work with European and national regulatory authorities to harmonize regulation of nicotine replacement therapies (NRT) across Europe to maximise public health.

## **Recommendations for regulatory authorities**

2. Regulators should harmonise the summary of product characteristics (SPC) for NRTs. Hence for example all nicotine patches should have the same SPC unless there is some good scientific reason for not doing so.
3. Regulators should ensure that labelling should not preclude the use of NRT by adolescent smokers under supervision of a health professional, given the low risk of harm.
4. Regulators should develop a rationale for setting any minimum age for NRT use and this should be harmonised for that NRT product across Europe perhaps through the European Medicines Evaluation Agency.
5. Regulators should license NRT products available for use under medical supervision by pregnant women who have been unable to quit using non-pharmaceutical interventions, and this assessment should be made in the early stages of pregnancy or, if possible, before.

6. Regulators should allow NRT to be recommended to smokers with stable cardiovascular disease (CVD) who have tried and failed to quit without such help, and the patient's doctor should be notified. For those patients who have experienced a serious cardiovascular event, or hospitalisation for a cardiovascular complaint in the previous 4 weeks (eg stroke, MI, unstable angina, cardiac arrhythmia, coronary artery bypass graft and angioplasty) or where they suffer with uncontrolled hypertension then the patient's consulting physician should be involved in the decision to recommend NRT.
7. Regulators should remove warnings against NRT use by people with stable CVD.
8. Regulators should consider allowing NRT use by smokers during periods of temporary abstinence from smoking when the smoker has no choice but to remain in the smoke-free environment (such as in hospital or aeroplanes). In such circumstances, NRT would be used as a treatment for the withdrawal syndrome resulting from compliance with smoke-free policies.
9. Regulators should withdraw *strong* warnings against NRT use and concomitant smoking.
10. Regulators should enable package labelling to be changed to allow smokers to continue to use NRT after the recommended treatment period if they feel it would help them stay off tobacco. The potential health risks of longer-term use are far less than those associated with resuming smoking.
11. Regulators should enable package labelling to be changed to allow combinations of NRT to be used under medical supervision.
12. Regulators should make the NRT products with well-established safety records available without prescription.

### **Recommendations for physicians**

13. Doctors should assess pregnant smokers early in pregnancy or before to assess whether they will be able to quit using non-pharmaceutical interventions and prescribe or supply NRT as appropriate. Doctors should record and monitor the use of NRT in pregnancy.

14. Doctors should be involved in the decision to recommend or supply NRT to smokers who have experienced a serious cardiovascular event, or hospitalisation for a cardiovascular complaint in the previous 4 weeks or where they suffer with uncontrolled hypertension.
15. The use of combinations of NRT should be medically supervised.

### **Recommendations for all health professionals**

16. As there is little science-based evidence or guidance, use of NRT by adolescents should be supervised by a health professional. Health professionals should assess adolescents' dependence as well as motivation and readiness to quit before recommending an appropriate form of NRT, just as they would with adults. The implementation of this should be monitored: records should be kept, the use of the product monitored and outcomes noted.
17. Health professionals should advise smokers to try to discontinue using NRT after the first 12 weeks of stopping smoking, but smokers should also be informed that longer-term use is an option if they feel it would help them to stay off tobacco.

### **Recommendations for Ministries of Health and others**

18. Ministries of health, regulators, policy-makers and pharmaceutical companies should make NRT available, accessible and affordable for all smokers.
19. Ministries of health and policy-makers should consider reimbursing NRT within health care systems, at least for low-income smokers, pregnant women and smokers with tobacco-related disease.
20. Ministries of Health should encourage the development of a framework to assess and monitor NRT use and smoking status in pregnant women given that NRT is sold over the counter in many countries.

### **Recommendations for the pharmaceutical industry**

21. Pharmaceutical companies should apply to have the warnings against NRT use by people with stable CVD removed.

22. Given the positive results in many existing studies, pharmaceutical companies should submit the data supporting combination therapy to the regulatory bodies.

**Research recommendations for pharmaceutical companies, Ministries of Health and research bodies**

23. A research programme should be developed to examine whether existing NRT products or other new ones are effective in helping young people to stop smoking.
24. Further research on pregnant women and NRT is needed.
25. Research should be encouraged, to increase the science-based evidence for the safety of NRT for people with unstable, severe or acute CVD.
26. Research should be commissioned into the use of NRT to treat withdrawal symptoms during short-term temporary abstinence and whether the use of NRT during temporary abstinence promotes attempts to quit. Research should also be commissioned to investigate whether using NRT for temporary abstinence reduces heavier smoking before and after the enforced abstinence.
27. Research should be commissioned into the concomitant use of NRT and smoking among all smokers and especially those in high-risk groups such as people with smoking-related disease.

# 1 WHO European Conferences on the Regulation of Tobacco Dependence Treatment Products

In October 1999, the first WHO European Conference on the Regulation of Tobacco Dependence Treatment Products was held in Helsinki, Finland (1). Annex 1 provides a summary of the main conclusions of the Conference.

Following the Conference and other discussions, a paper prepared to take forward some of the issues regarding the regulation of nicotine replacement therapy (NRT) was presented (2) and discussed at the Second WHO European Conference on the Regulation of Tobacco Dependence Treatment Products in Barcelona in October 2000 (3). A version of the paper, focusing largely on the situation in the United Kingdom, was subsequently accepted for publication in the journal *Addiction* (2).

On behalf of the WHO Regional Office for Europe, the paper was also broadened to include information relevant to the wider European context and to take account of the discussion at the Barcelona meeting. This revised paper was then discussed by a small group of experts in Copenhagen in April 2001: Dr Anil Batra (Department of Psychiatry and Psychotherapy, University of Tübingen, Germany), Professor Gerard J. Dubois (Chief, Medical Evaluation Service, Amiens' University Hospital, France), Ms Patsy Harrington (Manager, WHO European Partnership Project to Reduce Tobacco Dependence), Professor Jack Henningfield (Pinney Associates, United States), Professor Albert Hirsch (Chef, Service de Pneumologie, Hôpital Saint-Louis, France), Dr Ann McNeill (Chair, WHO European Partnership Project to Reduce Tobacco Dependence), Professor Aleksander P. Mazurek (Director, State Institute of Drug Control, Poland), Dr François Meyer (Deputy Director, Medicinal and Biological Evaluation, Agence Française de Sécurité Sanitaire des Produits de Santé, France), Dr Dawn Milner (Department of Health, United Kingdom), Dr Christina Poethko-Muller (Federal Institute for Drugs and Medical Devices, Germany) and Professor Pekka Puska (Director, Health Promotion, WHO headquarters).

This report summarizes the consensus reached at the meeting in Copenhagen in April 2001 and makes recommendations for further progress. Although this report is drawn largely from the evidence base presented in the article published in *Addiction* (2) and, where evidence is lacking, on a risk-benefit analysis (2), the recommendations differ given that this report is a consensus of the above experts and applies to the wider European situation.

The examples given in the text are largely from four focus countries of the WHO European Partnership Project to Reduce Tobacco Dependence (France, Germany, Poland and the United Kingdom). Annex 2 presents a more detailed account of the current situation in these four countries. Annex 3 summarizes issues related to the safety, potential for dependence and potential for abuse of NRT products. Annex 4 gives a glossary of some of the terms used throughout the paper.

## **2 Regulation of NRT – overview and context**

### ***2.1 Complicating factor of cigarette use***

Tobacco products are the most dangerous commonly used drug in the WHO European Region. One half of regular smokers will die from cigarettes, and half of these deaths occur prematurely in middle age (ages 35–69 years). Stopping smoking greatly reduces this risk, and using NRT increases smoking cessation rates. However, the framework in which NRT is regulated does not appear to consider the risks and benefits of NRT use in situations in which its use is qualified, restricted or contraindicated. The regulatory framework considers the risks of the medication but not the risks of failure to stop smoking.

One explanation for this derives from the specific remit and role of the agencies regulating medicines and drugs as pharmaceutical regulators. Regulators are responsible for licensing pharmaceuticals on the basis of the evidence for their safety and efficacy in individuals and not for the public health implications of requiring restrictive licensing terms which create barriers to treatment. They have no responsibility to carry out a risk benefit analysis of NRT use compared with continuing smoking.

### ***2.2 Recommended re-evaluation of NRT regulation and further development of the evidence base***

The evidence base for the efficacy of NRT is large but not complete. Research into the effects of NRT on specific smoking populations – including teenagers, pregnant women and people with cardiovascular disease – should continue. However, an incomplete evidence base cannot justify withholding treatment from dependent smokers. Pharmaceutical treatment can be reasonably expected to assist in smoking cessation and have relatively minor risks. Withholding treatment can be expected to lead to continued smoking with its severe health risks.

Regulatory agencies can only evaluate and respond to the scientific data submitted by pharmaceutical companies. Nevertheless, applications from the pharmaceutical industry are influenced by the anticipated response of the regulatory bodies; if companies anticipate a negative response, they may be less likely to devote time and expense to preparing an application. The regulatory frame-

work should recognize that the drug nicotine is unique and NRT products are used in an environment dominated by use of an extremely harmful, highly addictive and widely available nicotine delivery system – the cigarette.

This report makes recommendations for ministries of health, regulators, policy-makers, health professionals, researchers and the pharmaceutical industry.

### ***2.3 Inconsistencies in NRT regulation across Europe***

There is currently a lack of harmony between different countries in Europe because NRT was approved through the different national licensing procedures. In addition, some products were first approved almost 20 years ago, when little or no post-marketing safety data existed.

### ***2.4 Recommendation***

WHO should continue to work with European and national regulatory authorities to harmonize the regulation of NRT across Europe to maximise public health.

## 3 Age restrictions

### 3.1 *Current position*

The advice on the use of various NRT products by young people is inconsistent (see Annex 2). Some of this stems from the different pharmacokinetic properties, and potentially greater risk of abuse, of certain NRT products.

For example, products available in the United Kingdom have the following wordings in the summaries of product characteristics: not recommended for children; not recommended for children under 16 years; not recommended for children under 18 years; not recommended for children under 18 years unless under medical supervision. In Germany, the 4-mg gum, nasal spray and inhalator are contraindicated in individuals under 18 years and the 2-mg gum and patch are contraindicated in “children”. In Poland, NRT use is restricted to adults. The cut-off age is not consistent across countries – in France, the regulatory authorities consider adulthood to start at 15 years of age, so 15-year-olds can use the patch, gum and inhaler with medical supervision. In addition, the summaries of product characteristics and the patient information leaflets for the same products sometimes differ within a country.

### 3.2 *Public health position*

In their search for new customers, the tobacco industry actively targets adolescents (4). Most people who become regular smokers begin smoking during adolescence, and many teenagers who smoke daily are dependent (5). However, to date there are very few data on the use of NRT by those under 18 years old (6,7). NRT products appear to be safe for adolescent smokers but have not yet been shown to be effective as a cessation aid for them. A seminar held with experts from the United Kingdom and the United States under the auspices of the then Health Education Authority in September 1999 (8) concluded that NRT is less harmful than cigarettes and therefore should not be discouraged as a replacement for them and as a cessation aid for this age group. The Ontario Medical Association also recently concluded that NRT should be considered for all smokers who require pharmacotherapy to quit, including those under 18 years (9).

### ***3.3 Recommendations***

- A research programme should be developed to examine whether existing NRT products or other new ones are effective in helping young people to stop smoking.
- Regulators should ensure that labelling should not preclude the use of NRT by adolescent smokers, given the low risk of harm.
- Regulators should develop an evidence-based rationale for setting any minimum age, and this should be harmonised for that NRT product across Europe perhaps through the European Medicines Evaluation Agency.
- As there is little science-based evidence or guidance, use of NRT by adolescents should be supervised by a health professional. Health professionals should assess adolescents' dependence as well as motivation and readiness to quit before recommending an appropriate form of NRT, just as they would with adults. The implementation of this should be monitored: records should be kept, the use of the product monitored and outcomes noted.
- Regulators should harmonise the summary of product characteristics (SPC) for NRTs. Hence for example all nicotine patches should have the same SPC unless there is some good scientific reason for not doing so.

## 4 Advice on use by pregnant women

### 4.1 *Current position*

Again, the advice given for different products for pregnant women (see Annex 2) is inconsistent. For example, in the United Kingdom, some forms of NRT are contraindicated in pregnant women, although the summaries of product characteristics for the sublingual tablet and all the products on general sale (gum, patch, lozenge) state that these products can be used on medical advice if the pregnant woman cannot give up smoking without it. Previous failures to quit smoking using non-pharmaceutical interventions and medical advice and supervision are prerequisites for NRT use among pregnant smokers in France and Germany. The current status in Poland is simply that NRT should not be used during pregnancy.

### 4.2 *Public health position*

The adverse effects of smoking during pregnancy include miscarriage, neonatal death and low birth weight (10–12).

For women who continue to smoke in pregnancy, expert opinion is that NRT is considerably safer than smoking in pregnancy (13). Although there is a potential danger that nicotine may be a fetal teratogen and may contribute to obstetric complications in pregnant women and to sudden infant death syndrome (see for example [www.treatobacco.net](http://www.treatobacco.net), under the safety section), NRT is likely to be less hazardous than continued smoking, which also exposes the fetus and mother to many other toxins as well as doses of nicotine (5,13–18). NRT also generally provides lower doses of nicotine than does smoking (13). The only published placebo-controlled trial of transdermal nicotine in pregnancy did not find any significant improvement in abstinence rates either 4 weeks before the expected delivery date or at 3 months postpartum. Despite this, the babies of the group receiving nicotine patches weighed significantly more at birth than did the babies of the women who received placebo patches (18).

The decision about appropriate use of NRT by pregnant women is a trade-off between the benefits to women who use NRT and stop smoking as a result compared with the risks to women who use NRT but would have been able to stop

without NRT. The following considerations are relevant in making this assessment (9).

- The rates of smoking cessation before and during pregnancy are low.
- The efficacy of NRT in raising smoking cessation rates in adults has been demonstrated.
- Continued smoking is associated with much greater exposure to toxic substances than is NRT use.

This type of advice is given on other medicinal products used to treat substance dependence, such as disulfiram for alcohol abuse. For example, the summary of product characteristics for disulfiram recommends that the risk–benefit ratio of the adverse effects of alcoholism during pregnancy should be taken into account when considering treatment of pregnant women.

The recent report on nicotine of the Royal College of Physicians (5) recommended that NRT products should be able to be used by pregnant women for whom non-pharmaceutical interventions have failed.

Overall, the balance of argument appears to favour wider use of NRT by pregnant women.

### ***4.3 Recommendations***

- Regulators should license NRT products available for use under medical supervision by pregnant women who have been unable to quit with non-pharmaceutical interventions, and this assessment should be made in the early stages of pregnancy or, if possible, before.
- Doctors should assess pregnant smokers early in pregnancy or before to assess whether they will be able to quit using non-pharmaceutical interventions and prescribe or supply NRT as appropriate. Doctors should record and monitor the use of NRT in pregnancy.
- Ministries of Health should encourage the development of a framework to assess and monitor NRT use and smoking status in pregnant women given that NRT is sold over the counter in many countries
- Further research on pregnant women and NRT is needed.

## 5 Smokers with cardiovascular disease

### 5.1 *Current position*

All NRT products contain some sort of cautionary statement about their use by people with cardiovascular disease (CVD), and people are usually advised to seek medical advice (see Annex 2). These warnings originated 20 years ago, when NRT was first approved and marketed; at that time, no data were available on the safety of nicotine replacement for people with CVD. Current warnings range from careful use for people with stable CVD to absolute contraindications in acute or unstable CVD. In addition, the cautions and contraindications given for different NRT products and brands differ within some countries.

### 5.2 *Public health position*

Smoking cessation is probably the most important risk factor modification for the primary and secondary prevention of cardiovascular disease. Stopping smoking reduces morbidity and mortality rates even among people who do not quit until after CVD is diagnosed (19) and produces considerable cost savings (20). However, recent European data indicate that more than one-fifth of the people hospitalized for coronary heart disease (coronary artery bypass graft, coronary angioplasty or acute myocardial infarction) continue to smoke (21). The safety of NRT use by people with stable CVD has been widely documented (22–25), and current research indicates that withholding NRT from smokers with CVD is not warranted. This population has much to gain by stopping smoking because of the high risk of continued smoking (9) and rapid reduction in risk that accompanies smoking cessation. Recent guidelines issued by the Ontario Medical Association (9) conclude that:

It is more dangerous for patients with heart disease to continue to smoke than to use NRT. Given the seriousness of their medical condition, cardiac patients who cannot quit should be among those first considered for NRT.

Reducing the prevalence of smoking would also considerably reduce the costs associated with treating smoking-attributed coronary heart disease (26).

McRobbie and Hajek (27) have recently published guidelines on NRT in patients with cardiovascular disease. They recommend that NRT can be used in

patients with CVD who tried and failed to quit without such help and that the patient's consulting physician only needs to be involved in patients who have experienced a serious cardiovascular event within the past four weeks.

### ***5.3 Recommendations***

- Regulators should allow NRT to be recommended to smokers with stable CVD who have tried and failed to quit without such help, and the patient's doctor should be notified. For those patients who have experienced a serious cardiovascular event, or hospitalisation for a cardiovascular complaint in the previous 4 weeks (eg stroke, MI, unstable angina, cardiac arrhythmia, coronary artery bypass graft and angioplasty) or where they suffer with uncontrolled hypertension then the patient's consulting physician should be involved in the decision to recommend NRT.
- Doctors should be involved in the decision to recommend or supply NRT to smokers who have experienced a serious cardiovascular event, or hospitalisation for a cardiovascular complaint in the previous 4 weeks or where they suffer with uncontrolled hypertension.
- Regulators should remove warnings against NRT use by people with stable CVD.
- Pharmaceutical companies should apply to have the warnings against NRT use by people with stable CVD removed.
- Research should be encouraged, to increase the science-based evidence for the safety of NRT for people with unstable, severe or acute CVD.

## 6 Use of NRT to support temporary abstinence

### 6.1 *Current position*

NRT product indications in most countries do not specify use during temporary abstinence from smoking but instead, for relieving withdrawal symptoms as an aid to smoking cessation (see Annex 2).

Most smokers who are prohibited from smoking in certain situations (such as in the workplace, on public transport or in hospital) do not use nicotine replacement but take regular cigarette breaks (28) and smoke heavily before entering and immediately after leaving the smoking-restricted situation (29). However, there is a growing recognition of the need to prevent or relieve withdrawal symptoms during enforced abstinence from smoking. An example is the recent decision to supply NRT free of charge to hospitalized smokers in France. The use of NRT during temporary abstinence from smoking has been approved recently in certain European countries, including Austria, France and Norway.

### 6.2 *Public health position*

There is good evidence that clinically significant signs and symptoms of nicotine withdrawal (that is, worsening of mood and cognitive performance and slowing of frequency on electroencephalography) begin within a few hours of abstinence (30,31). NRT can be used during periods of temporary abstinence as a means of treating the nicotine withdrawal syndrome and thus of helping the dependent smoker to successfully abstain for a period of time when this is perceived as necessary or desirable. For example, a smoker who took an adequate dose of NRT during a smoke-free work shift, aeroplane flight or hospital stay could substantially reduce the severity of nicotine withdrawal-related bad mood, poor concentration and tobacco craving (32,33). In one study of highly dependent smokers abstinent for 8 hours (34), nicotine gum prevented an increase in aggressive responding (here defined as pulling a lever that resulted in the ostensible subtraction of one point from another person paired with the subject during each session), although there was no significant difference between NRT and placebo gum.

Use of NRT during temporary abstinence supports other tobacco control strategies, by facilitating compliance with smoke-free policies. Fewer cigarettes

smoked before and after temporary abstinence will also mean less environmental tobacco smoke, which is an added public health benefit.

### ***6.3 Recommendations***

- Research should be commissioned into the use of NRT to treat withdrawal symptoms during short-term temporary abstinence and whether the use of NRT during temporary abstinence promotes attempts to quit. Research should also be commissioned to investigate whether using NRT for temporary abstinence reduces heavier smoking before and after the enforced abstinence.
- Regulators should consider allowing NRT use by smokers during periods of temporary abstinence from smoking when the smoker has no choice but to remain in the smoke-free environment (such as in hospital or aeroplanes). In such circumstances, NRT would be used as a treatment for the withdrawal syndrome resulting from compliance with smoke-free policies.

# 7 Use of NRT for reducing smoking

## 7.1 *Current position*

In many countries, smokers are frequently advised to cut down despite the dearth of evidence supporting this as a useful strategy in protecting smokers' health (35). The use of NRT alongside cutting down has not been recommended, although there is evidence supporting this (see below). In most countries, the current indications for NRT products are that smokers should stop smoking cigarettes before using the product as part of a cessation attempt. However, Denmark recently accepted that NRT can be used as an aid to reducing smoking as a prelude to cessation (36), and this indication was subsequently approved in other countries (Austria and Belgium).

## 7.2 *Public health position*

There is good evidence that smoking-related morbidity and mortality are highly related to the dose or amount of smoking (37). However, there is also some evidence (such as from studies of the effects of passive smoking) of a non-linear relationship between dose and health effects (38). Given that studies on reducing smoking would take many years and require very large study populations and given the evidence from short-term and cross-sectional studies (39), it seems reasonable to assume that the reduction in health risk will be related to the reduction in toxin intake, although the exact nature of this relationship is not well defined (37).

When smokers smoke fewer cigarettes, they compensate for this by inhaling more smoke from each cigarette, although compensation is not complete (39). The use of NRT to facilitate smoking reduction has been proposed (39), as this would top up nicotine levels and make compensation less likely. A few studies have demonstrated that the use of NRT can help in reducing the number of cigarettes smoked and in reducing the amount of compensatory smoking (40,41). Another study showed that short-term reduction in smoking had a mixed effect on various biomarkers of harm (42).

Nevertheless, concomitant NRT use and smoking does not appear to be harmful (43), and there is growing evidence that it facilitates smoking reduction among dependent smokers who are unable to quit.

It remains to be seen whether the use of NRT alongside a reduction in cigarette smoking could be sustained in the long term in a non-research context in which smokers have to pay for the medication.

### ***7.3 Recommendations***

- Regulators and pharmaceutical companies should withdraw *strong* warnings against NRT use and concomitant smoking.
- Research should be commissioned into the concomitant use of NRT and smoking among all smokers and especially those in high-risk groups such as people with smoking-related disease.

## 8 Use for long-term maintenance

### 8.1 *Current position*

Current product licences indicate that NRT is supposed to be used for a relatively short time, usually coinciding with the first 3 months of the cessation attempt, although there are some inconsistencies between the recommended treatment duration for the different NRT products (see Annex 2). NRT is not intended for indefinite use, during which the user continues to obtain nicotine from the product. However, there is some flexibility: for example, in Germany, the duration of treatment is only a recommendation, and the current summary of product characteristics allows longer treatment in certain cases. In addition, some summaries of product characteristics specify that repeated treatment is possible.

### 8.2 *Public health position*

Tobacco dependence is a chronic relapsing disorder, and the ongoing use of NRT may represent a defence against relapse (9). The duration of use currently specified in summaries of product characteristics reflects clinical trial data, but in real life a longer duration of use may be required. Long-term use (dependence potential) appears to be more likely for products with more rapid delivery (such as nasal spray), but for conditions for which the users are required to pay for the NRT, only about 10% were still using the spray 4 months after attempting to quit smoking (44). When intensive support and NRT are provided free of charge under an optimum clinical use setting, up to 25% of those who remain free of tobacco for 1 year may continue to use the gum (45) and 43% the spray (46). The available evidence on the long-term use of NRT supports the idea that extremely heavy smokers are more prone to becoming long-term NRT users (47).

As more smoking cessation medications become available over the counter from pharmacies or on general sale, individual smokers will increasingly be able to decide how long to continue using NRT. The available evidence suggests that consumers generally make rational choices about this (that is, heavier smokers use medication for longer periods) and, if anything, the problems with dosage are more commonly related to insufficient dosage and using NRT for too brief a period (such as less than 3 weeks) rather than many people becoming long-

term users. Even a 5-year study of concomitant use of nicotine gum and smoking concluded that such use was safe (43).

### ***8.3 Recommendations***

- Health professionals should advise smokers to try to discontinue using NRT after the first 12 weeks of stopping smoking, but they should also be informed that longer-term use is an option if they feel it would help them to stay off tobacco.
- Regulators should enable package labelling to be changed to reflect that smokers can continue to use NRT after the recommended treatment period if they feel it would help them stay off tobacco. The potential health risks of longer-term use are far less severe than those associated with resuming smoking.

# 9 Combinations

## 9.1 *Current position*

In almost all countries, all NRT products caution that the user should stop smoking when using the product, and most also state that the user should also stop using other sources of nicotine. This advice effectively cautions the smoker against using more than one type of NRT at a time. However, the summary of product characteristics for NRT in France does not counsel against the use of more than one form of NRT.

## 9.2 *Public health position*

A growing body of evidence supports improved abstinence rates with combination NRT therapy, in which a fixed-dose formulation (patch) is combined with a flexible, self-administered dosage form (such as gum, inhaler or nasal spray) (48). Most research has suggested that combining the patch with other flexible-dosage forms of NRT is both safe and effective (49–52), although increased efficacy has not always been found (53). Combination NRT therapy may be especially appropriate for highly dependent smokers (48), who have the greatest risks of developing tobacco-related illness.

There is a movement towards acknowledging the potential benefits of combination therapy. For example, the updated smoking cessation guidelines for England (54) stated: “There is no scientific basis for disallowing different forms of NRT to be combined and there may be some benefit for certain combinations.” The United States smoking cessation guideline (48) indicated that combining the patch with an acute form of NRT was more efficacious than monotherapy and should be encouraged if the smoker is unable to quit using monotherapy.

## 9.3 *Recommendations*

- The use of combinations of NRT should be medically supervised.
- Regulators should enable package labelling to be changed to reflect that combinations of NRT may be used under medical supervision.

- Given the positive results in many existing studies, pharmaceutical companies should submit the data supporting combination therapy to regulatory bodies.

# 10 Wider availability of NRT products

## *10.1 Current position*

Some moves have taken place recently to increase treatment availability in many European countries, and all the licensed NRT products in France, Poland and the United Kingdom are now available over the counter (see Annex 2). The 2-mg gum is already available from herbal drugstores in Poland, and nicotine gum (2-mg and 4-mg), patches and the 1mg lozenge are on general sale in the United Kingdom. In addition, in the United Kingdom all NRT products are now available on National Health Service prescription, that is, reimbursed by the national health care system. Specially trained nurses, known as nurse prescribers, can now prescribe NRT in the United Kingdom: the Nurse Prescribers' Formulary has included all NRT products since May 2001. However, in other countries the availability of NRT remains strictly limited. For example, in Portugal all tobacco dependence treatment products require a physician's prescription, as is normally the case for any product with a pharmaceutical action (but not tobacco). In Germany, some NRT products (gum, patch and sublingual tablet) are available over the counter, whereas others (inhaler and nasal spray) require a prescription.

## *10.2 Public health position*

Evidence from the United States has demonstrated public health benefits from the increased availability of NRT, with no significant potential for abuse or dependence (55). The estimated number of attempts to quit increased from about 3 million during 1993–1995 to 6 million in 1996, which coincided with the availability of nicotine gum and the nicotine patch as over-the-counter products (equivalent to the United Kingdom general sale category) (56). The potential public health benefit from NRT is determined by how many people use it which, in turn, is determined by how many restrictions are placed on its sale and marketing by its licensing status. Studies of the nicotine patch sold over the counter have shown a treatment effect, although some of the absolute success rates were low (57–60). Detractors against wider availability often use the argument of lower efficacy in a less controlled environment, but a meta-analysis of the few well designed, placebo-controlled over-the-counter trials to date showed that NRT more than doubled abstinence rates (odds ratio 2.4) compared with placebo in over-the-counter conditions (61).

Moreover, there is some evidence that the 2-mg gum is not effective for heavy or highly dependent smokers (62). Putting only this product on general sale (as in Poland) thus makes those most in need unlikely to be effectively treated, and heavier smokers may get the impression that NRT is ineffective.

Recent research in the United States suggests that promoting sales of over-the-counter NRT plays a significant role in reducing cigarette consumption (63). There is also an ethical argument that NRT should not be less widely available than cigarettes (9).

Changing the products to general sale status does not diminish the added value that health professionals can offer. Health professionals still need to be involved in advising smokers to stop and offering pharmaceutical treatment, as overall cessation rates increase as more support is given.

### ***10.3 Recommendations***

- Ministries of health, regulators, policy-makers and pharmaceutical companies should make NRT available, accessible and affordable for all smokers.
- Regulators should make the NRT products with well established safety records available without prescription.
- Ministries of health and policy-makers should consider reimbursing NRT within health care systems, at least for low-income smokers, pregnant women and smokers with tobacco-related disease.

# 11 Products that provide more acceptable alternatives to cigarettes

The most “satisfying” form of nicotine delivery is the most dangerous one – the cigarette. A significant barrier to treating tobacco dependence is that existing NRT products are not readily acceptable alternatives to tobacco products to many cigarette smokers who have become accustomed to the rapid relief of withdrawal provided by inhaling cigarette smoke. Cigarettes are also engineered to maximize their palatability and to enable consumers to readily extract doses of nicotine on demand. In contrast, existing nicotine replacement medications were designed to provide sufficient nicotine to treat withdrawal symptoms and aid cessation in highly motivated smokers who can accept the lower nicotine dose. Broadening the range of nicotine delivery systems has proven useful in increasing the number of cigarette smokers who can choose an acceptable formulation to help them quit. There appears to be potential to treat an even wider range of smokers by developing and making widely available delivery systems that provide more aggressive and acceptable nicotine delivery. Encouraging the creative development of new forms of NRT that will be acceptable to and effective among a broader range of smokers is therefore important.

Meanwhile, tobacco products, which are particularly addictive and possess much greater respiratory, cardiovascular and carcinogenic toxicity, continue to be freely sold. The current regulatory framework surrounding NRT products unwittingly gives tobacco products a huge advantage in the marketplace over other nicotine delivery systems. The production and widespread availability of more satisfying alternative forms of nicotine delivery might lead to more people being addicted to nicotine but to less morbidity and mortality in populations.



# References

1. *Conference on the Regulation of Tobacco Dependence Treatment Products: conclusions* (<http://www.who.dk/tobacco/treatment.htm>). Copenhagen, WHO Regional Office for Europe, 1999 (accessed 3 October 2001).
2. McNeill, A. Foulds, J Bates C Regulation of nicotine replacement therapies. A critique of current practice. *Addiction* (in press).
3. *Second Conference on the Regulation of Tobacco Dependence Treatment Products: Conclusions* (<http://www.who.dk/Document/Tob/WhoSecondConference.pdf>). Copenhagen, WHO Regional Office for Europe, 2000 (accessed 3 October 2001).
4. Koh, H.K. Kids, cancer and the Joe Camel connection. *Journal of Clinical Oncology*, **15**: 2181–2182 (1997).
5. *Nicotine Addiction in Britain. A Report of the Tobacco Advisory Group of the Royal College of Physicians*. London, Royal College of Physicians, 2000, p. 155.
6. Hurt, R.D. et al. Nicotine patch therapy in 101 adolescent smokers: efficacy, withdrawal symptom relief, and carbon monoxide and plasma cotinine levels. *Archives of Pediatric and Adolescent Medicine*, **154**: 31–37 (2000).
7. Smith, T.A. et al. Nicotine patch therapy in adolescent smokers. *Pediatrics*, **98**: 659–667 (1996).
8. Foulds, J. *Smoking Cessation in Young People. Should We Do More to Help Young Smokers to Quit?* London, Health Development Agency, 2000.
9. *Rethinking Stop-smoking Medications: Myths and Facts* (<http://www.oma.org/phealth/stopsmoke.htm>). Toronto, Ontario Medical Association, 1999.
10. *International Consultation on Environmental Tobacco Smoke (ETS) and Child Health. Consultation Report* (<http://tobacco.who.int/en/health/papers/ets-report.pdf>). Geneva, World Health Organization, 1999.
11. Cook, D.G. & Strachan, D.P. Summary of effects of parental smoking on the respiratory health of children and implications for research. *Thorax*, **54**: 357–366 (1999).
12. Bartecchi, C.E. et al. The human costs of tobacco use. *New England Journal of Medicine*, **330**: 907–912 (1994).

13. Benowitz, N. Nicotine replacement therapy during pregnancy. *JAMA*, **22**: 3174–3177 (1991).
14. Ogburn, P.L. et al. Nicotine patch use in pregnant smokers: nicotine and cotinine levels and fetal effects. *American Journal of Obstetrics and Gynecology*, **181**: 736–743 (1999).
15. Oncken, C.A. et al. Effects of short-term use of nicotine gum in pregnant smokers. *Clinics in Pharmacological Therapy*, **59**: 654–661 (1996).
16. Oncken, C.A. et al. Effects of transdermal nicotine or smoking on nicotine concentrations and maternal-fetal hemodynamic effects. *Obstetrics and Gynecology*, **90**: 569–574 (1997).
17. Wright, L.N. et al. Transdermal nicotine replacement in pregnancy: maternal pharmacokinetics and fetal effects. *American Journal of Obstetrics and Gynecology*, **176**: 1090–1094 (1997).
18. Wisborg, K. et al. Nicotine patches for pregnant smokers: a randomised controlled study. *Obstetrics and Gynecology*, **96**: 967–971 (2000).
19. Rigotti, N.A. & Pasternak, R.C. Cigarette smoking and coronary heart disease: risks and management. *Cardiology Clinics*, **14**: 51–68 (1996).
20. Lightwood, J.M. & Glantz, S.A. Short-term economic and health benefits of smoking cessation: myocardial infarction and stroke. *Circulation*, **96**: 1089–1096 (1997).
21. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: principal results from EUROASPIRE II Euro Heart Survey Programme. *European Heart Journal*, **7**: 554–572 (2001).
22. Joseph, A.M. et al. The safety of transdermal nicotine as an aid to smoking in patients with cardiac disease. *New England Journal of Medicine*, **335**: 1792–1798 (1996).
23. Tzivoni, D. et al. Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovascular Drugs Therapy*, **12**: 239–244 (1998).
24. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. Nicotine replacement therapy for patients with coronary artery disease. *Archives of Internal Medicine*, **154**: 989–995 (1994).
25. Benowitz, N.L. & Gourlay, S.G. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *Journal of the American College of Cardiology*, **29**: 1422–1431 (1997).

26. Naidoo, B. et al. Modelling the short term consequences of smoking cessation in England on the hospitalisation rates for acute myocardial infarction and stroke. *Tobacco Control*, **9**: 397–400 (2000).
27. McRobbie, H. & Hajek, P. Nicotine replacement therapy in patients with cardiovascular disease. Guidelines for health professionals. *Addiction*, **96**: 1547–1551 (2001).
28. Orland, R. et al. Leaving work to smoke. *Addiction*, **92**: 1361–1368 (1997).
29. Chapman, S. et al. Do work-place smoking bans cause smokers to smoke “harder”? Results from a naturalistic observational study. *Addiction*, **92**: 607–610 (1997).
30. Parrott, A.C. et al. Cigarette smoking and abstinence: comparative effects upon cognitive task performance and mood state over 24 hours. *Human Psychopharmacology*, **11**: 391–400 (1996).
31. Pickworth, W.B. et al. Spontaneous EEG changes during tobacco abstinence and nicotine substitution in human volunteers. *Journal of Pharmacology and Experimental Therapeutics*, **251**: 976–982 (1989).
32. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC, American Psychiatric Association, 1994, pp. 242–247.
33. Fagerstrom, K.O. et al. Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology*, **111**: 271–277 (1993).
34. Cherek, D.R. et al. Human aggressive responding during acute tobacco abstinence: effects of nicotine and placebo gum. *Psychopharmacology*, **104**: 317–322 (1991).
35. Owen, L. & McNeill, A.D. The role of health professionals in reducing smoking in pregnancy. *Contemporary Reviews in Obstetrics & Gynaecology*, December: 235–238 (1999).
36. West, R. Addressing regulatory barriers to licensing nicotine products for smoking reduction. *Addiction*, **95**(suppl 1): S29–S34 (2000).
37. Stratton, K. et al., ed. *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction* (<http://www.nap.edu/books/0309072824/html>). Washington, DC, National Academy Press, 2001 (accessed 3 October 2001).
38. Law, M. & Hackshaw, A.K. Environmental tobacco smoke. *British Medical Bulletin*, **52**: 22–34 (1996).
39. Hughes, J.R. Reduced smoking: an introduction and review of the evidence. *Addiction*, **95**(suppl 1): S3–S7 (2000).

40. Fagerstrom, K.O. et al. Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker? *Tobacco Control*, **6**: 311–316 (1997).
41. Bolliger, C.T. et al. Smoking reduction with oral nicotine inhalers: double blind, randomised clinical trial of efficacy and safety. *BMJ*, **321**: 329–333 (2000).
42. Hurt, R.D. et al. Does smoking reduction result in reduction of biomarkers associated with harm? A pilot study using a nicotine inhaler. *Nicotine & Tobacco Research*, **2**: 327–336 (2000).
43. Murray, R.P. et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest*, **109**: 438–445 (1996).
44. West, R. et al. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology*, **149**: 198–202 (2000).
45. Hajek, P. Withdrawal oriented therapy for smokers. *British Journal of Addiction*, **84**: 591–598 (1989).
46. Sutherland, G. et al. Randomized controlled trial of nasal nicotine spray in smoking cessation. *The Lancet*, **340**: 324–329 (1992).
47. Foulds, J. Nicotine replacement therapy: availability, abuse liability and dependence potential. In: Tudor-Smith, C., ed. *Tackling Tobacco*. Cardiff, Health Promotion Wales, 1999, pp. 11–16.
48. US Department of Health and Human Services. *Treating Tobacco Use and Dependence – a Clinical Practice Guideline*. Washington, DC, US Government Printing Office, 2000.
49. Kornitzer, M. et al. Combined use of nicotine patch and gum in smoking cessation: a placebo controlled trial. *Preventive Medicine*, **24**: 41–47 (1995).
50. Puska, P. et al. Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in North Karelia. *Tobacco Control*, **4**: 231–235 (1995).
51. Blondal, T. et al. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ*, **318**: 285–288 (1999).
52. Bohadana, A. et al. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation. A randomised, double-blind, placebo-controlled trial. *Archives of Internal Medicine*, **160**: 3128–3134 (2000).
53. Tonneson, P. & Mikkelsen, K.L. Smoking cessation with four nicotine replacement regimes in a lung clinic. *European Respiratory Journal*, **160**: 3128–3134 (2000).

54. West, R. et al. Smoking cessation guidelines for health professionals: an update. *Thorax*, **55**: 987–999 (2000).
55. Shiffman, S. et al. Public health benefit of over-the-counter nicotine medications. *Tobacco Control*, **6**: 306–310 (1997).
56. Burton, S.L. et al. Use of FDA-approved pharmacologic treatments for tobacco dependence – United States, 1984–1998. *MMWR Mortality and Morbidity Weekly Report*, **49**: 665–668 (2000).
57. Davidson, M. et al. Efficacy and safety of an over-the-counter transdermal nicotine patch as an aid for smoking cessation. *Archives of Family Medicine*, **7**: 569–574 (1998).
58. Hays, J.T. et al. Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled and open label trials. *American Journal of Public Health*, **89**: 1701–1707 (1999).
59. Leischow, S. et al. OTC nicotine patch: effectiveness alone and with brief physician intervention. *American Journal of Health Behavior*, **23**: 61–69 (1999).
60. Sonderskov, J. et al. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *American Journal of Epidemiology*, **145**: 309–318 (1997).
61. Hughes, J.R. & Shiffman, S. A review of studies of the efficacy of over-the-counter nicotine replacement. Presented at the Society for Research on Nicotine and Tobacco 7th Annual Meeting, Seattle, Washington, USA, 23–25 March 2001.
62. Silagy, C. et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews*, **2**: CD000146 (2000).
63. Hu, T. et al. Cigarette consumption and sales on nicotine replacement products. *Tobacco Control*, **9**: 60–63 (2000).

# Annex 1

## ***Summary of the main conclusions of the first WHO European Conference on the Regulation of Tobacco Dependence Treatment Products***

1. Treatment of tobacco dependence is essential to reverse current trends of escalating mortality.
2. Regulations need to be transnational and coordinated with tobacco product regulation.
3. Treatment works. There is now a strong evidence base demonstrating that current methods of treating tobacco dependence are safe and effective.
4. Tobacco dependence treatment is cost effective relative to other health care interventions.
5. Opportunities to purchase cigarettes should increasingly be opportunities to obtain treatment for tobacco dependence.
6. Diversity of treatment types is needed.
7. Treatment provision should be integrated with tobacco control policies so that their effects are mutually enhancing.
8. Treatment and prevention efforts go hand in hand.
9. For people who are unable or unwilling to quit using tobacco, consideration should be given to developing treatments that reduce their risk of premature mortality.
10. Regulatory authorities need to consider the reality of ubiquitous cigarette availability as they balance the risks and benefits of treatment medication in the approval process.
11. For treatments with strong safety records, general sales approvals should be considered as a means of improving access in a way acceptable to the consumer.
12. Reimbursement of proven treatments should be considered to ensure that financial limitations of cigarette smokers do not pose a major barrier to treatment.
13. Tobacco product regulation, including labelling and advertising, should consider its impact on treatment utilization.

14. European Union directives should be implemented in a manner that encourages treatment utilization.
15. The regulatory process must be guided by the best available science and the effects tracked so as to maximize health benefits and minimize unintended consequences and to thereby foster self-correction.

## Annex 2 – Comparisons in availability and recommendations on NRT use in four European focus countries

Country	Products available	Age restrictions	Use by pregnant women	Use by people with cardiovascular disease	Use in reducing smoking
United Kingdom	Gum (2 & 4mg)	SPCs state that inhaler, tablet and spray and 2-mg and 4-mg lozenges are contraindicated by those under 18	Spray and inhaler are contraindicated although tablet and lozenge state that they can be used on medical advice by women who are unable to give up smoking without nicotine substitution. GSL gum and patch products state on labelling 'Nicotine crosses the placenta and is excreted in breast milk; thus it may be a hazard to the foetus or infant. Patients should be advised to try to give up smoking without the use of nicotine replacement therapy. Should this fail a medical assessment of the risk/benefit ratio of nicotine gum (patch) should be used	All NRT products contain some sort of cautionary statement about their use by people with stable cardiovascular disease. This usually advises the potential user to seek medical advice  Contraindicated in unstable or severe CVD such as acute myocardial infarction, unstable or worsening angina pectoris, severe cardiac arrhythmia and acute stroke	Current indication does not include use for smoking reduction - only licensed as an aid to smoking cessation
	Inhaler				
	Lozenge (1-mg, 2-mg, and 4-mg)				
	Patch (various strengths, 16 and 24 hours)				
	Spray				
Tablet	Individuals younger than 18 years of age except under the advice of a doctor				
France	Gum	Gum, inhaler, patch: for use by people over 15 years of age only	Gum, inhaler, patch: it is advisable to recommend that pregnant women stop smoking completely, without using NRT. However if this fails, highly dependent women may use the medication with the advice of a physician  For highly dependent lactating women, recourse to bottle-feeding should be considered. The patch should not be used if the woman is breastfeeding, and other NRT products should be taken just after nursing  Tablet: use of the tablet by a highly nicotine-dependent pregnant woman should only be initiated when prescribed by a physician	All NRT products contain some sort of cautionary statement about use by people with stable CVD. This usually advises the potential user to seek medical advice. NRT products are contraindicated in people with recent myocardial infarction, unstable or worsening angina pectoris, Prinzmetal's angina or severe cardiac arrhythmia.	Current indication does not include use during smoking reduction
	Inhaler				
	Patch				
	Tablet				

Table 1. Variation across four European focus countries in the products available and the recommendations on: age restrictions, use by pregnant women, use by people with cardiovascular disease, and use in reducing smoking

Germany	<p>Gum Inhaler Patch Spray Tablet</p> <p>Recommendations vary across products Spray and inhalator are contraindicated in those under 18 years However, other products (such as tablet and recently licensed patches) are not to be used by those under 18 years unless recommended by a physician</p>	<p>A pregnant smoker should always be recommended to stop smoking without the aid of nicotine substitution. The use of the product should only ensue after consulting a physician and if the user has been unable to quit without NRT The summary of product characteristics for one patch states that it is contraindicated for pregnant women.</p>	<p>The summaries of product characteristics of all NRT products warn against and contraindicate use by people with CVD. Recent myocardial infarction, unstable or worsening angina pectoris, Prinzmetal's angina, severe cardiac arrhythmia and acute stroke are absolute contraindications, whereas in stable cardiovascular diseases, NRT treatment should be used with special precaution and medical advice.</p>	<p>Current indications do not specify use during smoking reduction</p>
Poland	<p>Gum Patch</p> <p>Gum and patch: for those 18 years or older</p>	<p>Gum and patch: should not be used during pregnancy and lactation</p>	<p>Gum: people suffering from coronary artery disease should consult their physician before starting treatment. Contraindicated in non-stable CVD (myocardial infarction, unstable angina pectoris, etc.) Patch: some patches require physician consultation. All suggest caution or careful use by people with CVD. Some suggest that they should not be used unless cessation is not possible without NRT. Contraindicated in non-stable CVD (myocardial infarction, unstable angina pectoris, etc.)</p>	<p>Current indications include smoking reduction</p>

## Annex 2 – Comparisons in availability and recommendations on NRT use in four European focus countries

Country	Temporary abstinence	Concomitant NRT use and smoking	Duration of use	Combination of different NRT products	Availability
United Kingdom	Current indication does not allow use during temporary abstinence	Not recommended. Smokers should stop smoking cigarettes before using the products	NRT products are generally recommended to be used for the first 6-12 weeks after quitting. Summaries of product characteristics for patches vary - some can be reviewed after 3 months and further treatments may be recommended if abstinence is not achieved; others state a maximum of 3 months only. Some (eg gum and tablet) recommend a reduction regime after the first 3 months of use. For the 2-mg and 4-mg lozenge, there is 12 weeks treatment, followed by 12 weeks limited 'relapse' use	Not recommended. Most NRT products caution that the user should stop using other sources of nicotine	Gum 2-mg and 4-mg: general sales list Inhaler: over the counter Lozenge 1-mg: general sales list 2-mg and 4-mg - over the counter Patch: general sales list Spray: over the counter Tablet: over the counter All products are now available on prescription and over the counter
France	Current indication does not specify for use during temporary abstinence. However, NRT is available free of charge for inpatients and is advocated by Air France as a treatment for passengers with withdrawal symptoms	Current indication is that smokers should stop smoking before using NRT	Recommended treatment is for 3 months, but can vary according to the individual response. It is recommended not to use NRT for more than 6 months	Not mentioned in the summary of product characteristics - combination NRT treatment is neither recommended nor prohibited	Gum: over the counter Inhaler: over the counter Patch: over the counter Spray: application rejected Tablet: over the counter

Table 2. Variation across four European focus countries in the recommendations for use during temporary abstinence, concomitant NRT use and smoking, duration of use, combinations of different NRT products and availability

Germany	Current indication does not specify for use during temporary abstinence. Current indications are that smokers should stop smoking as part of a cessation attempt	Current indication does not include use for smoking reduction. Current indications for NRT are that smokers should stop cigarette smoking before using the product as part of a cessation attempt	Generally not more than 6 months is recommended, but one patch has a maximum of 3 months Another patch is recommended for 10 weeks, but repeated treatment sequences are allowed The current wording of some summaries of product characteristics allows longer treatment in certain cases	Most summaries of product characteristics state that the user should also stop using other sources of nicotine	Gum: over the counter Inhaler: prescription Patch: over the counter Spray: prescription Tablet: over the counter
Poland	Current indication does not include use during temporary abstinence	Summaries of product characteristics state that users should stop smoking before using gum or patch	Recommended use 3 months for some products, plus gradual tapering with some products	No restrictions given	Gum: 2-mg general sales list, 4-mg over the counter Patch: over the counter

# Annex 3 – Characteristics of NRT

## *Safety*

Nicotine is addictive, but it is the tobacco smoke, not the nicotine, that causes most of the harm (*see for example* [www.treatobacco.net](http://www.treatobacco.net), *under the safety section*). Nicotine is not a significant risk factor for cardiovascular events and is not a substantial cause of cancer (1–6). NRT products are much safer than cigarettes, which are exceedingly “dirty” delivery systems for nicotine (1).

Although *in vitro* and *in vivo* studies with mice provide some evidence that some metabolites of nicotine can be transformed into nitrosamines (2) or that nicotine could stimulate angiogenesis and promote tumour growth and atherosclerosis in mice (3), there is no evidence that this happens in people using NRT. There is now a great deal of experience with NRT products among smokers in the United States (4) and the United Kingdom, and the evidence clearly indicates that the products are safe (5).

NRT has an extremely good safety profile; the incidence of clinically significant adverse events is very low, and there are few contraindications against use. The most common adverse events associated with NRT use are local effects at the site of application or use, including sore mouth or throat, hiccups, dyspepsia, jaw ache (gum), skin irritation (patch), mouth or throat irritation, cough, rhinitis (inhaler), nasal irritation, eye watering (nasal spray) and mouth or throat irritation (sublingual tablet) (6). These symptoms are generally rated as mild and transient.

There are, however, concerns about nicotine safety in pregnancy (section 4.2).

At high doses nicotine can intoxicate, but this is very rare because of the rapid development of tolerance and the fact that most nicotine delivery products are designed to minimize acute overdosing.

## *Dependence potential*

The dependence potential of NRT products is relatively low compared with the cigarette. The dose and speed of delivery are important factors (7). The products delivering relatively low doses of nicotine slowly are much less addictive

than cigarettes. The patch releases nicotine slowly, gradually peaking after 4–9 hours, whereas nicotine levels from the gum, inhalator and lozenge or micro-tab peak after about 30 minutes, and those from the nasal nicotine spray peak within 10 minutes of use (8). This compares with a concentrated bolus of nicotine reaching the brain within 10 seconds of each puff on a cigarette.

A small proportion of NRT users do become long-term users. This ranges from as few as 3% of patch users who pay for their medication still using it after 15 weeks (7) to 43% of those remaining tobacco free for 1 year and receiving the nasal spray free of charge still using it at 1 year (9). However, the evidence indicates that those who become dependent on NRT are heavy smokers who would otherwise have remained dependent on tobacco at far greater cost to their health (10).

### ***Abuse potential***

The abuse potential of NRT products has been shown to be very low. We are unaware of any published reports of non-smokers becoming NRT users. Novice users generally perceive nicotine as moderately unpleasant (11). A comparative study of four NRT products found generally low ratings of pleasantness and satisfaction from using the NRT products for 4 weeks and concluded that the likelihood of abuse was low for all four products (7). Surveillance in the United States following the release of the gum and patch on general sale showed no evidence of significant abuse (4).

### ***References***

1. *Nicotine addiction in Britain. A Report of the Tobacco Advisory Group of the Royal College of Physicians.* London, Royal College of Physicians, 2000, p. 155.
2. Hecht, S.S. et al. 2 $\alpha$ -Hydroxylation of nicotine by cytochrome P450 2A6 and human liver microsomes: formation of a lung carcinogen precursor. *Proceedings of the National Academy of Sciences of the United States of America*, **97**: 12493–12497 (2000).
3. Heesch, C. et al. Nicotine stimulates angiogenesis and promotes tumor growth and atherosclerosis, *Nature Medicine*, 2001; **7**: 833–839.
4. Shiffman, S. et al. Public health benefit of over-the-counter nicotine medications. *Tobacco Control*, **6**: 306–310 (1997).
5. West, R. Addressing regulatory barriers to licensing nicotine products for smoking reduction. *Addiction*, **95**(suppl 1): S29–S34 (2000).

6. US Department of Health and Human Services. *Treating Tobacco Use and Dependence – a Clinical Practice Guideline*. Washington, DC, US Government Printing Office, 2000.
7. West, R. et al. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology*, **149**: 198–202 (2000).
8. Fagerstrom, K.O. Nicotine replacement therapies. In: Ferrence, R. et al., ed. *Nicotine and Public Health*. Washington, DC, American Public Health Association, 2000, pp. 199–207.
9. Sutherland, G. et al. Randomized controlled trial of nasal nicotine spray in smoking cessation. *The Lancet*, **340**: 324–329 (1992).
10. Hajek, P. et al. Long term use of nicotine chewing gum: outcome, determinants and effect on weight gain. *JAMA*, **260**: 1593–1596 (1988).
11. Foulds, J. et al. Mood and physiological effects of subcutaneous nicotine in smokers and never-smokers. *Drug and Alcohol Dependence*, **44**: 105–115 (1997).

## **Annex 4 Glossary**

### ***Health professional***

A health or health care professional is a person with an appropriate health care qualification working within the health system. Such a definition includes physicians, nurses, pharmacists, midwives and health visitors.

### ***Under medical supervision***

This means being supervised by a health professional who has undergone medical training successfully and is a member of a recognized medical body.

### ***Regulators and regulatory bodies***

In this paper, regulators are the people working within the relevant national or regional drug regulatory bodies. In England, these include the Medicines Commission, the Medicines Control Agency and the Committee on Safety of Medicines.

Tobacco products are the most dangerous commonly used drug in the WHO European Region. One half of regular smokers will die from cigarettes, and half of these deaths occur prematurely in middle age (ages 35-69 years). Stopping smoking greatly reduces this risk, and using NRT increases smoking cessation rates. However, the framework in which NRT is regulated does not appear to consider the risks and benefits of NRT use in situations in which its use is qualified, restricted or contraindicated. The regulatory framework considers the risks of the medication but not the risks of failure to stop smoking.

One explanation for this derives from the specific remit and role of the agencies regulating medicines and drugs as pharmaceutical regulators. Regulators are responsible for licensing pharmaceuticals on the basis of the evidence for their safety and efficacy in individuals and not for the public health implications of requiring restrictive licensing terms which create barriers to treatment. They have no responsibility to carry out a risk benefit analysis of NRT use compared with continuing smoking.

In October 1999, the first WHO European Conference on the Regulation of Tobacco Dependence Treatment Products took place in Helsinki, Finland. Following the Conference, a paper taking forward some of the issues regarding the regulation of nicotine replacement therapy (NRT) was prepared. The paper was discussed at the Second WHO European Conference on the Regulation of Tobacco Dependence Treatment Products in Barcelona in October 2000.

On behalf of the WHO Regional Office for Europe, the paper was broadened to include information relevant to the wider European context and to take account of the discussion at the Barcelona meeting. This revised paper was then discussed by a small group of experts in Copenhagen in April 2001. This report, "Regulation of nicotine replacement therapies: an expert consensus", summarizes the consensus reached at the meeting in Copenhagen in April 2001 and makes recommendations for further progress with regard to the regulation of nicotine replacement therapies. The examples given in the text are largely from four focus countries of the WHO European Partnership Project to Reduce Tobacco Dependence (France, Germany, Poland and the United Kingdom).

For further information about this initiative and the partnership project, please contact:

**Tobacco free Initiative**  
**WHO Regional Office for Europe**

Tel.: +45 39 17 17 17  
Fax: +45 39 17 17 18

8 Scherfigsvej  
DK-2100 Copenhagen Ø  
Denmark

<http://www.who.dk/tobacco/home.html>  
[isl@who.dk](mailto:isl@who.dk)

Nicotine replacement therapy (NRT) is a medically-approved way to take nicotine by means other than tobacco. It is used to help with quitting smoking or stopping chewing tobacco. It increases the chance of quitting smoking by about 55%. Often it is used along with other behavioral techniques. NRT has also been used to treat ulcerative colitis. Types of NRT include the adhesive patch, chewing gum, lozenges, nose spray, and inhaler. The use of multiple types of NRT at a time may increase effectiveness. Submit an Inquiry to Nicotine Replacement Therapy Experts for free. Start receiving relevant responses within a few hours.Â

1. Provide a clear description of your needs and your expectations of an expert, consultant or job candidate and Zintro will match it with the most relevant professionals in our platform.
2. Within a day or two typically 6 - 12 Experts, who have opted-in, will contact you with a brief explanation of their qualifications and how they can help.
3. You can communicate back and forth, qualify each other, connect and pay fees to Experts through Zintro.

Zintro is free, anonymous and without obligation. Nicotine replacement therapy (NRT) describes a group of products delivering nicotine that are licensed for the relief of withdrawal as an aid to smoking cessation. This paper examines areas where public health considerations suggest changes should be made to the current indications and characteristics for NRT products.Â

@article{McNeill2001RegulationON, title={Regulation of nicotine replacement therapies (NRT): a critique of current practice.}, author={Ann McNeill and Jonathan Foulds and Cristina Bates}, journal={Addiction}, year={2001}, volume={96 12}, pages={. 1757-68 } }. Ann McNeill, Jonathan Foulds, Cristina Bates. Published in Addiction 2001. Medicine.