

REPORT OF THE COMMITTEE ON SAFETY OF MEDICINES WORKING GROUP ON NICOTINE REPLACEMENT THERAPY

Medicines and Healthcare products Regulatory Agency

Committee on Safety of Medicines

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Foreword from Chairman

Half of all who continue to smoke die as a result and half of these deaths occur before the age of sixty. Cigarette smoking causes or worsens the majority of chronic, long-term conditions and in this way presents a major burden to public health, health service resources and greatly increases individual suffering. Considerable steps have been taken in recent years to reduce the impact of tobacco on health in the UK. Government policy involves a wide-ranging, multi-agency approach designed to create disincentives to smoke (taxation and smoking in the workplace legislation), influencing younger people not to start smoking and helping existing smokers to quit.

For many, stopping smoking is difficult, yet behavioural support and effective pharmacotherapy improves success rates. A considerable body of data exists to support the use of Nicotine Replacement Therapy (NRT) in smoking cessation; in well-conducted clinical trials it has been shown to double the chances of success.

Wider availability of NRT has been government policy for a number of years and this was achieved initially by switching NRT products from Prescription Only Medicine (POM) status to Pharmacy (P) only and, more recently, to the General Sales List (GSL).

NRT formulations are licensed medicines and therefore must conform to the safety, quality and efficacy standards expected of any medicinal product. However, NRT presents a unique challenge to the MHRA in that being the safest form of nicotine available it is also the most highly regulated, certainly when compared to cigarettes, the most deadly source of nicotine.

Current regulation of NRT products may present a barrier to wider usage of the products and, as a result, reduce NRT's effectiveness in smoking cessation. The Working Group on NRT was set up by the CSM to look at the current evidence and to make recommendations on regulatory changes that, in the light of more recent research, would justify relaxation in controls on the use of these products.

I am grateful to all the members of the Working Group for giving up their time and providing their considerable expertise in undertaking this task. The recommendations of the Working Group are given in this report and it is my sincere hope that these recommendations will, even in a small way, contribute to reducing the impact of smoking on public health.

Dr Terence Maguire, FPSNI, FPSI, MRPharmS (Hon)
Chairman, Committee on Safety of Medicines Working Group on Nicotine Replacement Therapy.

November 2005

EXECUTIVE SUMMARY

1. Smoking increases mortality and morbidity and half of all smokers die prematurely of a smoking-related ailment.
2. Stopping smoking has major health benefits. Smokers who quit before the age of about 35 years have a life expectancy only slightly less than a non-smoker and giving up at any age provides both immediate and long-term health benefits.
3. Inhaled nicotine is strongly addictive and stopping smoking results in cravings and withdrawal symptoms, but nicotine itself is not a major primary cause of smoking-related disease.
4. Nicotine replacement therapy (NRT) provides nicotine to reduce cravings and withdrawal symptoms. It is effective and can significantly increase the quit rate. In addition, NRT can be expected to deliver less nicotine and none of the potentially disease-causing agents that are in tobacco smoke.
5. When NRT was introduced in the late 1970s, there were concerns that, because nicotine can constrict blood vessels, certain groups (such as those with cardiovascular disease and pregnant women) may be at particular risk. In addition, there was a lack of information on use in adolescents. Therefore, in these groups, NRT was contra-indicated/not recommended. However, these are groups for which it is especially important smoking is stopped as soon as possible.
6. The White Paper *Smoking Kills* (December 1998) made clear the Government's commitment to helping smokers to quit and, subsequently, one of the underpinning principles of the White Paper *Choosing Health* (November 2004) was the reduction in the number of people who smoke, with an emphasis on children and adolescents, pregnant women and other disadvantaged smokers.
7. Early in 2005, the Committee on Safety of Medicines set up a Working Group on NRT (CSM WG on NRT) to consider the current evidence on the safety and efficacy of NRT, with particular reference to cardiovascular disease, use in pregnancy and during breast-feeding, and use in those under 18 years of age, and to advise changes that maximise the benefits and ensure that any risks there may be with NRT are balanced against the dangers of continued smoking.
8. As a result of the CSM WG on NRT recommendations:
 - NRT is to be licensed for adolescents, pregnant and breast-feeding women and smokers with cardiovascular and other underlying diseases;
 - some NRT products are licensed to cut down smoking as a “stepping stone” to stopping completely, for smokers who are currently unable to stop abruptly;
 - the product information for NRT will be revised to provide more clear-cut, easily assimilated information for users, maximising the benefits and ensuring that any risks there may be are seen in the context of the dangers of continued smoking.

1. BACKGROUND

1.1 The dangers of smoking

Death

The dangers of smoking have been known since the 1960s; however, the long-term risk was quantified in a 40-year cohort study of British doctors¹. Comparing the overall survival of smokers with non-smokers between 1951 and 1991, the study found that in those aged 39 to 69 years of age (“middle-age”), 41% of smokers died compared to 20% of non-smokers. In those who smoked 25 or more cigarettes daily, 50% died in middle-age. It has been estimated² that in 2000 there were 114,000 UK deaths attributable to smoking (22% of all male and 16% of all female deaths).

Cancer

Smoking is an important cause of cancers of the lung, larynx, pharynx, oesophagus, bladder, kidney and pancreas. Overall, around one-third of cancer deaths in men (36%) and one-fifth in women (21%) are attributable to smoking².

Cardiovascular disease

Smoking is an important cause of cardiovascular disease. The British doctors’ cohort study¹ found that mortality from coronary heart disease was 50% higher in smokers (over 75% in heavy smokers) than in non-smokers. Overall, over one-eighth of cardiovascular deaths (14% in men, 12% in women) are attributable to smoking.

Lung and other disorders

Smoking is the main cause of chronic obstructive lung disease, a cause of pneumonia, and also causes or aggravates a wide variety of non-fatal illnesses including asthma, osteoporosis, peptic ulcer, erectile dysfunction, chronic rhinitis and multiple sclerosis³.

The contents of cigarette smoke

Nicotine is only one element of tobacco smoke. The “tar” produced by smoking contains at least 4,000 different chemicals, including 50 agents known to produce cancer (carcinogens) and metabolic poisons. Other disease-causing elements include carbon monoxide, oxides of nitrogen and hydrogen cyanide⁴.

Passive smoking

The adverse effects of the inhalation of second-hand smoke (passive smoking) is also a significant issue, and evidence of this harm has been increasing over the past 20 years^{5 6}. It is generally accepted that, although the relative health risks from passive smoking are small in comparison with those from active smoking, because the diseases induced and/or aggravated are common, the overall impact is large⁷. Almost half of all children in the UK are exposed to tobacco smoke at home⁸ and are at increased risk of bronchitis and pneumonia and other lower respiratory tract infections. Table 1 shows “known” and “probable” risks of passive smoking.

Table 1 The potential health effects of passive smoking⁹

Conclusive evidence that passive smoking causes the following	Substantial evidence that passive smoking causes the following
Adults <ul style="list-style-type: none"> • Lung cancer • Coronary heart disease • Stroke • Nasal cancer 	<ul style="list-style-type: none"> • Aggravation of asthma • Cervical cancer • Reduced lung function
Children <ul style="list-style-type: none"> • Middle ear infection • Asthma • Bronchitis • Pneumonia 	<ul style="list-style-type: none"> • Cancers and leukaemia • Meningococcal infections • Impaired learning and behaviour
Pregnancy, childbirth & infancy <ul style="list-style-type: none"> • Cot death (SIDS) • Low birth weight 	<ul style="list-style-type: none"> • Miscarriage

In contrast to the above, a study in 2003¹⁰ comparing non-smokers with a smoking spouse over a 39-year period concluded that their results did not support a causal relationship between environmental tobacco smoke and tobacco-related mortality, although a small effect could not be ruled out. The study also pointed out that the association between second-hand smoke and coronary heart diseases and lung cancer “may be considerably weaker than generally believed”. The Committee on Carcinogenicity (COC), however, reviewed this study and concluded that there was no reason to change their previous advice¹¹, namely “taking all the supporting data into consideration we conclude that passive smoking in non-smokers exposed over a substantial part of their life is associated with a 10-20% increase in the risk of lung cancer” and the Royal College of Physicians report of 2005⁷ was “confident that passive smoking is a major public health problem in the UK”.

1.2 The introduction of NRT and initial concerns about toxicity

Nicotine replacement therapy (NRT) was first introduced in the 1970s, and at the time, there were considerable concerns about the pharmacological effects of nicotine, particularly its constrictive action on blood vessels. It was considered that this could have an adverse effect in smokers with underlying conditions such as cardiovascular disease, and also in pregnant women where the placental blood supply could be reduced and the growth of the fetus impaired. As a result of this, the product information for NRT carried a number of restrictions relating to these and other groups (including children and adolescents) where there were concerns about safety and/or lack of data on efficacy, and where a positive benefit to risk had not been established.

1.3 Currently marketed forms of NRT

There are several different NRT delivery systems available in the UK to help smokers stop – patches, chewing-gum, tablets, lozenges, inhalator, and nasal spray - with nicotine absorption taking place through either the skin or mucous membranes. Treatment aims to replace the nicotine from tobacco, thus reducing withdrawal symptoms when stopping smoking. The Cochrane Review¹² of over 90 studies found that nicotine replacement does help people to stop smoking. Overall, it increases the chances of quitting about one and a half or two times, regardless of any additional support and encouragement¹³.

1.4 Delivery of nicotine from NRT (compared with cigarette smoking)

Inhaling tobacco smoke is a highly efficient method of absorbing nicotine into the blood stream. The amount absorbed from each cigarette is typically 1-2mg which produces a rapid “hit” with arterial peak nicotine levels of 40-100ng/ml in about 15-30 seconds and a venous peak in about five minutes. These sharp peaks and troughs tend to rise over the first six to eight hours of the day with regular smoking and nicotine blood levels are also detected first thing in the morning (before the first smoke of the day) in regular smokers. Nicotine from NRT products is delivered to the blood stream more slowly than from a cigarette, over a period of minutes for oral and nasal products, and hours from a patch. It also produces lower blood nicotine concentrations than does smoking¹⁴.

1.5 Legal status and current availability of NRT

The initial NRT products were gums which when first launched were only available with a prescription (Prescription Only Medicine (POM)). In the early 1990s, the gums were reclassified as P medicines and could be bought from pharmacies; in the late 1990s, it was considered that they could safely be sold without the supervision of a pharmacist and be made available through non-pharmacy retail outlets (General Sales List (GSL) products). Currently, gums, patches and lozenges have GSL status whilst all other forms are sold/supplied where there can be input from a healthcare professional.

1.6 NHS Policy and targets for smoking reduction in the UK

1.6.1 Government White Papers

The White Paper *Smoking Kills*¹⁵ (January 1998) made clear the Government's commitment to helping smokers to quit in view of the mortality and morbidity associated with smoking. Since then there has been sustained investment in smoking cessation services; one of the underpinning principles of the recent White Paper *Choosing Health; making healthier choices easier*¹⁶ (November 2004) was a reduction in the number of smokers, with a boosted campaign for NHS Stop Smoking Services and for nicotine replacement therapy.

1.6.2 UK targets for reductions in smoking

Summaries of the smoking targets for the different parts of the UK are shown in Table 2.

Table 2 Smoking targets for the UK

England¹⁵	
Adults	Reduction of smoking from 28% in 1996 to 24% or less by 2010
Pregnant women	Reduction of smoking from 23% in 1995 to 15% by 2010
Children	Reduction of smoking from 13% in 1996 to 9% or less by 2010
Wales¹⁷	
Pregnant women	To increase the proportion of women who give up smoking at the start of pregnancy to at least 33%
Children	To reduce the proportion of 15-year olds who smoke to no more than 16% for boys and 20% for girls
Scotland¹⁸	
Adults	Reduction in the rate of smoking from an average of 35% in 1995 to 31% in 2010
Pregnant women	Reduction in the proportion from 29% in 1995 to 20% by 2010
Children (12-15 years)	Reduction from 14% in 1995 to 11% by 2010
Northern Ireland¹⁹	
Adults	To increase the proportion who do not smoke from 73% in 2000/01 to 75% by 2006/07
Pregnant women	To increase the proportion who do not smoke from 78% in 2000 to 82% by 2005
Children (11-16 years)	To increase the proportion who do not smoke from 86.5% in 2000 to 89% by 2006

1.6.3 Current effectiveness of smoking treatment services

One in seven (14.6%) of users of the English Smoking Treatment Service²⁰ successfully stopped smoking and were still not smoking after 52 weeks. The study noted that older users, those who smoked for pleasure (rather than to cope) and those who were extremely determined were more likely to quit, whereas those from low socio-economic groups who smoked their first cigarette of the day within five minutes of waking or had another smoker in the house, were less likely to succeed.

1.7 Current guidance from the National Institute for health and Clinical Excellence on the use of NRT

The current NICE *Guidance on the Use of NRT for smoking cessation*⁴ was produced in 2002 and is due for review. Since the merger with the Health Development Agency, NICE has a public health remit and therefore a decision was made to review the appraisal within the context of the forthcoming public health guidance on smoking cessation to allow incorporation of the wider public health issues. Smoking cessation intervention guidance is expected in March 2006 whereas smoking cessation programme guidance should be available in late 2007.

REFERENCES

- 1 Doll et al (1994). Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*;309:901-11
- 2 Peto et al. Mortality from Smoking in Developed Countries 1950-2000 (2nd edition). *Oxford University Press, Oxford*. Also www.ctsu.oxac.uk/-tobacco
- 3 For more details see Action on Smoking and Health website: www.ash.org.uk
- 4 NICE Technological Appraisal Guidance – no 39. March 2002. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation
- 5 In the 1980's a number of comprehensive reviews were published including reports by the US national Research Council, the 1986 report of the US Surgeon General and the UK Independent Scientific Committee on Smoking and Health. A major review of the evidence by the US Environmental Protection Agency was published in 1992. More recent reviews

- include reports of the UK Government appointed Scientific Committee on Tobacco and Health, the Californian Environmental Protection Agency and the WHO International Agency for Research on Cancer (IARC)
- 6 Action on Smoking and Health Fact Sheet – Passive Smoking: a summary of the evidence
7 A report on passive smoking by the Tobacco Advisory Group of the Royal College of Physicians. July 2005
- 8 General Household Survey, Office for National Statistics, 1999
- 9 Report of the Californian Environmental Protection Agency (1999) Health effects of exposure to environmental tobacco smoke. Smoking and Tobacco Control Monograph 10. *National Cancer Institute:USA*
- 10 Enstrom & Kabat (2003). Environmental tobacco smoke and tobacco related mortality in a prospective study in California, 1960-1989. *BMJ*;326:1057-61
- 11 Department of Health (1997). Annual report of the Committee on Toxicity, Mutagenicity and Carcinogenicity
- 12 Silagy et al (2000). Nicotine replacement therapy for smoking cessation. In : Cochrane Collaboration. *Cochrane Library*. Issue 3. Oxford: Update Software
- 13 Lancaster et al (2000). Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ*;321:355-8
- 14 Molyneux (2004). Clinical Review: ABC of Smoking Cessation Nicotine Replacement therapy. *BMJ*; 328:454-456
- 15 Department of Health (1998) Smoking Kills: A White Paper on Tobacco. *HSMO: London*
- 16 Department of Health (2004) Choosing Health: A White Paper. *HSMO: London*
- 17 The Welsh Office Health Department (1997) New Strategic Plans. DGM/(97)74. Revision of targets. *Welsh Office Circular* 11 June 1997
- 18 The Scottish Office (1999) Towards a Healthier Scotland. *HMSO: Edinburgh*
- 19 Investing for Health. A five-year tobacco plan consultation document.
www.dhsspsni.gov.uk
- 20 Ferguson et al (2005). The English smoking treatment service: one-year outcomes. *Addiction*;100:59-63

2. THE COMMITTEE ON SAFETY OF MEDICINES WORKING GROUP ON NRT – EVALUATION OF CURRENTLY AVAILABLE DATA

2.1 Background

There were several “drivers” that led to the CSM recommending the setting up of a nicotine replacement therapy Working Group which included:

- increased information available on the safe use of NRT;
- initiatives throughout the UK to drive down the rates of smoking overall and in particular groups, such as adolescents and pregnant women;
- proposals for inventive methods of providing NRT that are better tailored to the user’s requirements;
- the need to provide product information for NRT that
 - emphasises the benefit of achieving smoking cessation using NRT whilst balancing its established positive safety profile against the known increased mortality and morbidity of continuing to smoke;
 - is consistent between different forms of NRT and products produced by different companies;
 - harmonises product information within the European Union (EU).

2.2 Terms of Reference

The following terms of reference for the Working Group were agreed by the Committee on Safety of Medicines:

- to consider the available evidence of the safety and efficacy of NRT products with particular reference to cardiovascular risk, pregnancy and use in under-18s;
- to advise on the evidence in support of new indications for NRT;
- to advise on changes to product information in order to maximise the benefit and minimise the risk of NRT in relation to active and passive smoking;
- to advise on communication to health care professionals and the general public and to advise CSM.

Meetings were held on 29 June 2005 and 28 September 2005.

2.3 Membership of the Working Group

Dr Terence Maguire, FPSNI, FPSI, MRPharmS (Hon) - Chairman
Pharmacy Contractor, Northern Ireland

Dr Jon Battershill
Toxicologist, Department of Health, Health Protection (Toxicology and radiation)
Branch

Dr Timothy Chambers JP MB BS FRCP FRCPE FRCPI FRCPCH (First meeting)
Consultant Paediatrician, Southmead Hospital, Bristol and Senior Clinical Lecturer in
Child Health, Bristol University

Professor Keith Channon MB BCh BSc (Hon) MRCP MD FRCP (First meeting)
Professor of Cardiovascular Medicine, Honorary Consultant Cardiologist, John
Radcliffe Hospital, Oxford. British Heart Foundation.

Dr Robin Fielder

Principal Toxicologist, Centre for Radiation, Chemical and Environmental Hazards,
Health Protection Agency, Chilton, Oxfordshire.

Dr Sarah Garner

The National Institute for Health and Clinical Excellence

Dr Charmaine Griffiths (First meeting)

British Heart Foundation

Dr Anne Grosskurth

Department of Health – Tobacco Regulation

Dr Richard Hubbard MB BS BSc MRCP DM

Reader in Clinical Epidemiology, Department of Respiratory Medicine, Nottingham

Professor Martin Kendall MB ChB MD FRCP

Professor of Clinical Pharmacology, Birmingham University Medical School

Dr Ann McNeill BSc PGCE PhD

Honorary Senior Research Fellow, Department of Epidemiology & Public Health,
University College, London. Consultant to Action on Smoking & Health, England
(Charity).

Professor Klim McPherson BA MA PhD FFPH FMedSci

Visiting Professor of Public Health Epidemiology, Nuffield Dept of Obstetrics &
Gynaecology, Churchill Hospital, Oxford

Professor John Moxham MB BS MD MRCP FRCP (First meeting)

Department of Respiratory Medicine, Kings College Hospital London

Dr Douglas Seaton MD, FRCP, FRCPE (First meeting)

Consultant Physician (Respiratory Medicine), The Ipswich Hospital, Ipswich.

Dr Ross Taylor MB ChB MD FRCP (Edin) FRCGP DCH

Senior Lecturer in General Practice, University of Aberdeen & General Medical
Practitioner Principal, Grampian Health Board

Professor Jim Thornton MD FRCOG

Professor of Obstetrics and Gynaecology, University of Nottingham
Nottingham

2.4 Use of NRT compared with the dangers of continued smoking

When NRT was introduced there were concerns about its safe use. However, over time and with wide-spread use, NRT has been seen to be well-tolerated. This is mainly because smokers have a strong tendency to titrate their nicotine levels (regardless of source – smoking tobacco/using NRT) to reach their own “comfort zone” level. With NRT they are likely to maintain the same blood nicotine levels as when smoking but without the other, more dangerous, elements of tobacco smoke^{1 2} making nicotine from NRT considerably safer than that from cigarettes^{3 4}.

Conclusion of CSM WG on NRT versus continued smoking

The Working Group considered that, overall, the benefits of quitting smoking clearly outweighed any risk there may be with NRT and that the product information for both users and healthcare professionals should clearly state this.

2.5 Use of NRT in adolescents

2.5.1 Background

Until recently there were very limited data on the use of NRT in adolescents and children, with the product information for most NRT products contra-indicating or not recommending their use in this age group. Cigarettes can, however, legally be bought by 16-year olds. It is estimated⁵ that there are approximately 375,000 young regular smokers in the UK, with the proportion of regular smokers increasing with age; 1% of 11-year olds in England smoke regularly compared to 23% of 15-year olds⁶. Stopping teenagers smoking would prevent decades of continued tobacco use and subsequent ill-health.

2.5.2 Data reviewed by the Working Group

A study⁷ in a small number of teenagers concluded that nicotine patch therapy seemed safe in adolescents. In 2005 another study⁸ was carried out (with NRT patches or gum), supported by cognitive-behavioural therapy in adolescents (13-17 years) who had started smoking at 11.2 ± 1.98 years of age and had smoked for 2.66 ± 1.56 years. From 120 participants, the carbon-monoxide (CO)-confirmed prolonged abstinence rates at six months were 18% for the active patch group and 6.5% for the active gum group (compared with 2.5% for placebo). The authors stated that both the patch and gum were well-tolerated and adverse events were similar to those reported in adult trials.

Conclusion of the CSM WG on NRT on use in adolescents

The Working Group noted the considerable number of young people who smoked and that 80% of smokers start in their teens. They considered that although data in children and adolescents were limited, there was evidence of efficacy and no indication that NRT used in this population would raise specific safety issues, particularly as their underlying health was likely to be much better than that in older smokers. In addition, when considering possible abuse of NRT by adolescents, the Working Group was of the opinion that there was no evidence for this. Consequently, they recommended that the lower age limit for NRT should be changed to include 12- to 18-year olds but that the product information should indicate that the data in this group were limited and that if treatment was required for longer than 12 weeks this should be discussed with a healthcare professional (eg a doctor, pharmacist or nurse).

2.6 Use in smokers with cardiovascular disease

2.6.1 Smoking and cardiovascular disease

Smoking is a major risk factor in cardiovascular disease⁹ causing acute cardiac events by at least four mechanisms:

- hypercoagulable states leading to the promotion of thrombosis;
- the effects on inflammation and progression of atherosclerosis;

- carbon monoxide inhalation which limits myocardial oxygen delivery;
- the haemodynamic effects of nicotine including increased heart rate and blood pressure which increases myocardial work and oxygen demand, as well as constriction of the coronary arteries with consequent impairment of blood flow and oxygen supply to the heart.

However, the action of nicotine *per se* is considered to be the least important of these mechanisms.

2.6.2 NRT in cardiovascular disease – published data

When initially introduced, there were concerns that nicotine could precipitate cardiovascular events in susceptible individuals because of its ability to cause constriction of blood vessels, and there have been a few anecdotal reports of smokers on NRT developing angina and atrial fibrillation^{10 11 12}. However, there has been a considerable amount of work on the use of NRT in this population of smokers and the data generated indicates that for smokers who have stable cardiovascular disease (ie are not acutely ill), the benefits of using NRT to quit smoking outweigh any risks there may be with NRT^{13 14 15 16 17 18 19 20 21}. For those with severe and/or unstable cardiovascular disease who are in hospital there are only limited data. In one study²², 40 smokers were given NRT (patch or gum) in the days immediately following admission to hospital, mainly for MI or angina (Group A). These were compared with 40 historic controls admitted during the time when NRT was not used (Group B). One year after hospitalisation, 45% of Group A versus 15% of Group B had completely stopped smoking. The author states that NRT was well-tolerated and did not contribute to any increase in ischaemic attacks during the patients' stay in the coronary care unit. In addition, there were no significant differences in the number of deaths, ischaemic attacks or re-admissions to hospital during the one-year follow up.

2.6.3 NRT in cardiovascular disease – computerised general practice database study

In addition to the published data, there has been a recent observational study using a large computerised UK general practice database of in excess of 30,000 NRT users²³. The occurrence of MIs and strokes were analysed both before and after the prescription for NRT and there was no evidence of an increase in these events or in deaths related to NRT use. During the first 56 days after NRT therapy, there were 33 deaths which were fewer than expected – the incident rate ratio (IRR) was 0.86, 95% confidence intervals of 0.60 to 1.23.

Conclusion of the CSM WG on NRT on use in cardiovascular disease

The Working Group considered these findings of the recent study reassuring and that they reinforced the current view of a positive benefit to risk of NRT in most people with cardiovascular disease. They therefore supported revisions of the product information to include the following:

- *in stable cardiovascular disease, NRT presents a lesser hazard than continuing to smoke;*
- *dependent smokers hospitalised with a recent myocardial infarct, severe dysrhythmia or recent cerebrovascular accident and/or who are considered to be haemodynamically unstable should be encouraged to stop smoking with non-pharmacological interventions. If this fails, NRT may be considered but as data on safety in this group are limited, initiation should be under medical supervision.*

2.7 Use in pregnancy and by breast-feeding women

2.7.1 Smoking in pregnancy

It is well-established that smoking during pregnancy can result in miscarriage, premature birth, still-birth and low-weight babies^{24 25}. There is also a risk of increased neonatal mortality and sudden infant death syndrome (SIDS), and there may even be longer-term effects in the children of mothers who smoked during pregnancy such as respiratory disorders and increased cognitive/behavioural problems.

2.7.2 NRT in pregnancy

There are some data on the use of NRT in pregnancy but the results, to date, have not clearly shown that NRT helped pregnant patients to stop smoking^{26 27 28}. However, the studies were small and not always of a design that would allow the results to determine whether NRT was effective or not. In addition, nicotine is more rapidly metabolised in pregnancy²⁹, so NRT theoretically could be less effective.

NRT (gums and patches) has been shown to cause dose-related increase in maternal blood pressure and heart rate with lesser effects on the fetal heart rate, but these changes are less pronounced than those caused by smoking³⁰. Overall, although the data currently available are limited, the use of NRT in pregnancy does not give undue concern and any harm caused by nicotine replacement must be compared with that caused by continued smoking – which is extremely harmful to both the woman and her child³¹.

2.7.3 Nicotine in breast milk

Nicotine is both water- and lipid-soluble and has a wide volume of distribution in the body, freely passing in and out of breast milk with concentrations rising and falling in line with maternal plasma levels. In smokers, concentrations in breast milk are highly dependent on the number of cigarettes smoked, the frequency of breast-feeding and the time between smoking and breast-feeding. It has been estimated that the breast milk of heavy smokers may contain 0.5mg of nicotine/litre. It is not clear how much nicotine is transferred into breast milk from NRT.

Conclusion of the CSM WG on NRT on use in pregnancy and lactation

The Working Group noted there was limited clinical data available on the use of NRT in pregnancy and breast-feeding women, but also that concerns about the potential adverse effects of nicotine on the fetus and the new-born were often theoretical, whereas the dangers of continuing to smoke were well-established and considerably more damaging to mother and baby.

The Working Group advised that pregnancy and lactation should not be a contra-indication to the use of NRT and that the warnings in the product information should be revised and put into the context of the dangers of continuing to smoke. Ideally, a pregnant woman should stop smoking without NRT, but if this is not possible, NRT may be recommended to assist a quit attempt as the risk of using NRT on the fetus is lower than that expected with smoking. There is also no exposure to the other dangerous elements. However, as nicotine does pass to the fetus, the decision to use NRT should be made as early on in pregnancy as possible with the aim of discontinuing after two to three months' use.

The product information should advise that slow-release 24-hour patches should not be used in pregnancy and lactation to avoid the administration of nicotine overnight when the fetus would not normally be exposed to smoking-derived nicotine. However, if the woman suffers from nausea and/or vomiting, a 16-hour patch, removed at night, is preferable. For breast-feeding mothers, intermittent NRT products will allow the time between NRT use and feeding to be as long as possible.

2.8 Use in smokers who are not currently able to quit abruptly

2.8.1 Background

Until recently in the UK NRT was only authorised for stopping smoking abruptly, although smoking reduction indications for various NRT products had been authorised elsewhere in Europe. The CSM WG on NRT considered an application submitted by Pfizer Consumer Healthcare for Nicorette gums (2mg & 4mg) and an inhalator (10mg) to be used to help smokers cut down smoking prior to stopping completely.

2.8.2 Data reviewed

Seven well-designed (double-blind, randomised and placebo-controlled) studies were submitted to demonstrate efficacy and safety – five with nicotine gum and two with a nicotine containing inhalator. The primary objective of all the studies was a sustained reduction in the number of cigarettes smoked daily by at least 50%, with secondary objectives including complete abstinence and the intention and attitudes to stopping smoking. All studies recruited subjects who smoked at least 15 cigarettes a day and who were interested in reducing their smoking but were unable, unwilling and/or not planning to quit at the time.

2.8.3 Results - efficacy

Over 2,500 smokers were recruited and, overall, the studies showed a significant reduction in smoking compared with placebo, with 16% of subjects on NRT becoming “sustained reducers” (ie reduced their cigarette consumption by 50%). Table 3 shows the number and percentage of those who had quit by month 12.

Table 3 All seven studies: Effect of NRT on point prevalence abstinence

	Successful reducers*	Successful quitters
NRT	193/1,215 (15.9%)	58/193 (30.1%)
Placebo	81/1,209 (6.7%)	15/81 (18.5%)
* reduced cigarette smoking by at least 50% from week six to month four		
	Unsuccessful reducers	Successful quitters
NRT	1,022/1,215 (84.1%)	47/1,022 (4.6%)
Placebo	1,128/1,209 (93.3%)	39/1,128 (3.5%)

From all seven studies and regardless of whether they were successful reducers, NRT (gums plus inhalator) led to one-year abstinence by 105 subjects (47+58)/1215 (8.6%) compared with 54 (15+39)/1209 (4.5%) of those on placebo, giving an odds ratio for success of 2.10.

2.8.4 Results – attitudes to stopping smoking

Subjects were asked if participation in the studies changed their attitude to quitting and between 50% and 87% of participants said it had increased their interest in stopping smoking.

2.8.5 Results - safety

Adverse events in the smoking reduction studies did not substantially differ from those seen in other smoking cessation studies, with the most commonly reported events overall being headache, 'flu-like symptoms, dyspepsia and nausea/vomiting. Throat irritation or pharyngitis and cough were mainly related to inhalator use – 56/415 (13.5%) compared with 26/414 (6.3%) for placebo. Gastro-intestinal symptoms, such as nausea and/or vomiting, hiccups and dyspepsia, were mainly related to gum use and occurred more frequently with NRT gum than with placebo.

Conclusion of CSM WG on NRT on the use of Nicorette (gum and inhalator) to cut down prior to stopping

The Working Group noted that a “smoking reduction” indication had been authorised in ten other European countries, the first in 1997, and that post-marketing surveillance did not indicate a different profile of adverse events that could be related to the smoking reduction indication. When considering those who had not significantly reduced the number of cigarettes smoked whilst using Nicorette gum or inhalator, the Working Group were satisfied that the majority of smokers titrated nicotine to their individual preferred level regardless of the source of nicotine (ie smoking alone, smoking combined with NRT) and that even if higher than usual plasma nicotine levels were attained, this was not likely to be associated with an increased risk of adverse effects in most smokers. The Working Group considered that, as the studies were carried out in smokers not motivated to stop, the 8.6% quit rate indicated a satisfactory outcome, and the specific data of adverse events recorded in the studies did not indicate any areas for concern. The Working Group therefore advised that for this indication there was no need to specifically contra-indicate use in any particular patient group.

2.9 Concurrent use of more than one NRT product

Currently, the product information for many NRT products contra-indicates or warns against the concurrent use of more than one NRT product. Because of the differing profiles of nicotine delivery, there would seem to be considerable advantages of allowing flexibility to use more than one form of NRT that could match the need of the quitting smoker - for example, the background level produced by a patch supplemented by a “burst” of nicotine from one of the oral forms when cravings become a problem. It is also established that smokers appear to be adept at titrating their nicotine levels to their own “comfort level” regardless of source (NRT or tobacco). There is evidence that combining products (such as patch and nasal spray, or patch and inhalator) is more effective than using single agents alone^{3 32 33 34 35 36 37} without any specific safety concerns. Although increased efficacy has not always been found³⁸, a pooled analysis from 7 studies³⁹ suggest a clinically modest but statistically significant benefit (OR 1.42, 95%CI : 1.14-1.76) of combinations of NRT products.

Conclusions of CSM WG on NRT on the concurrent use of more than one form of NRT in smokers quitting abruptly

The Working Group recommended that the current warnings on NRT products not to use more than one product at a time should be removed. This would permit users to identify and use the combination that was most appropriate for them.

2.10 Other product information revisions

In order for NRT to be used as effectively as possible, the information for healthcare professionals and smokers trying to quit needs to be clear and consistent between different formulations. In addition, it needs to ensure that the benefits of NRT are maximised and that any risks that there may be with NRT are seen in the context of the well-established dangers of continued smoking. In particular, they considered relevant data in those with diabetes mellitus^{40 41}, renal and/or hepatic impairment and those on other medication^{42 43}, in addition to the duration of therapy^{44 45}.

Conclusions of CSM WG on NRT on product information

The WG concluded that NRT product information, in respect of stopping smoking abruptly, should include the following:

- *smokers with diabetes mellitus should be advised to monitor their blood sugar levels more closely than usually when NRT is initiated because catecholamine release can affect carbohydrate metabolism and vasoconstriction may delay/reduce insulin absorption;*
- *NRT should be used with caution in patients with moderate to severe hepatic impairment and/or severe renal impairment as they may be at risk of increased adverse effects;*
- *for the duration of use of NRT, users should still be encouraged to stop usage as soon as possible, but if it is necessary to use NRT beyond nine months, they could do so if advised to do so by a healthcare professional;*
- *there should be a statement that no definite clinically relevant interactions between NRT and other drugs have been identified but the product information should refer to the possible haemodynamic interaction with adenosine;*
- *stopping smoking may result in slower metabolism and consequent rises in blood levels of drugs catalysed by CYP 1A2 (and possibly CYP 1A1) because the inhalation of induction agents such as polycyclic aromatic hydrocarbons has stopped.*

REFERENCES

1. Benowitz et al (1983). Smokers of low-yield cigarettes do not consume less nicotine. *N Eng J Med*;309:139-142
2. Kozlowski et al (1998). Smokers' misperceptions of light and ultra-light cigarettes may keep them smoking. *Am J Prev Med*;15:9-16
3. Molyneux (2004). Clinical Review: ABC of Smoking Cessation Nicotine Replacement Therapy. *BMJ*; 328:454-456
4. McNeill et al (2001). Regulation of nicotine replacement therapies (NRT): a critique of current practice. *Addiction*;96: 1757-68
5. Petersen and Peto (2004). British Heart Foundation Statistics – Smoking Statistics. *Published by BHF Education Department*
6. Office of National Statistics (2003) Smoking, drinking and drug use in England in 2002. *The Stationery Office: London*
7. Smith et al (1996). Nicotine patch therapy in adolescent smokers. *Pediatrics*;98:659-667
8. Moolchan et al (2005). Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics*;115:407-414
9. Doll et al (1994). Mortality in relation to smoking: 40 years' observations on male British doctors. *BMJ*;309:901-11
10. Coragudi et al (2003). Nicotine gum induced atrial fibrillation. *Heart Dis*;5:100 -101

11. Stewart & Catterall (1985). Chronic nicotine ingestion and atrial fibrillation. *Brit H J* ;54:222-223
12. DaCosta et al (1993). Myocardial Infarction and nicotine patch: A contributing or causative factor? *European Heart J*;14:1709-11
13. NICE Technological Appraisal Guidance – no 39. March 2002. Guidance on the use of nicotine replacement therapy (NRT) and bupropion for smoking cessation.
14. Society for Research on Nicotine and Tobacco (SRNT) and the World Health Organisation (WHO)
15. West et al (2000). Smoking cessation guidelines for health care professionals; an update. *Thorax*;55:987-999
16. McNeill and the expert Working Group of the WHO Regional Office for Europe (2001). Regulation of nicotine replacement therapies; an expert consensus. *Copenhagen, WHO*
17. McRobbie and Hajek (2001). Nicotine replacement therapy in patients with cardiovascular disease: guidelines for health professionals. *Addiction*;96:1547-1551
18. Joseph et al (1996). The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Eng J Med*;335:1792-8
19. Tivoni et al (1998). Cardiovascular safety of transdermal nicotine patches in patients with coronary artery disease who try to quit smoking. *Cardiovasc Drug Ther*;12:239-244
20. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease (1994). Nicotine replacement therapy for patients with coronary artery disease. *Arch Intern Med*;154:989-995
21. Joseph and Fu (2003). Safety issues in pharmacotherapy for smoking in patients with cardiovascular disease. *Progress in Cardiovascular Disease*;45:429-441
22. Adler et al (2003) Effectiveness and Tolerance of Early Use Nicotine Replacement Therapy in a Coronary Care Unit - Abstract *Nicotine & Tobacco Research*;5:273-4.
23. Hubbard et al (In Press). Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke and death. *Tobacco Control (in press)*
24. Royal College of Physicians (1992). Smoking and the young. *London:RCP*
25. Charlton (1996). Children and smoking: the family circle. *Br Med Bull*;52:90-107
26. Wisborg et al (2000). Nicotine patches for pregnant smokers: a randomised controlled study. *Obstet Gynecol*;96:967-71
27. Kapur et al (2001). Randomised, double-blind, placebo-controlled trial of nicotine replacement therapy. *Curr Ther Research Clin Exp*;62:274-278
28. Hegaard et al (2003). Multimodal intervention raises smoking cessation rate in pregnancy. *Acta Obstet Gynecol Scand*;82:813-819
29. Dempsey et al (2002). Accelerated metabolism of nicotine and cotinine in pregnant smokers. *J Pharmacol Exp Ther*;301:594-598
30. Dempsey and Benowitz (2001). Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety*;24(4):277-322
31. Coleman et al (2004). Nicotine replacement therapy in pregnancy. *BMJ*;328:965-6
32. Kornitzer et al (1995). Combination use of nicotine patch and gum in smoking cessation: a placebo controlled clinical trial. *Preventative Medicine*;25:41-47
33. Puska et al (1995). Combined use of nicotine patch and gum compared with gum alone in smoking cessation: a clinical trial in north Karelia. *Tobacco Control*;4:231-5
34. Blondal et al (1997). Efficacy of nicotine nasal spray added to transdermal nicotine patches in smoking cessation [Abstract]. Proceedings of the 10th World Conference on Tobacco or Health; August 24-28; Beijing:48
35. Fagerstrom (1994). Combined use of nicotine replacement products. *Health Values*;18:15-20
36. Bohadana et al (2000). Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation. *Arch Intern Med*;160:3128-3134
37. Fagerstrom et al (1993). Effectiveness of nicotine patch and nicotine gum as individual versus combined treatments for tobacco withdrawal symptoms. *Psychopharmacology*;111:271-77
38. Tonnesen et al (2000). Smoking cessation with four nicotine replacement regimens in a lung clinic. *The European Respiratory Journal*;15,717-22
39. Silagy et al (2000). Nicotine replacement therapy for smoking cessation. In : Cochrane Collaboration. *Cochrane Library*. Issue 3. Oxford: Update Software
40. Klemp et al (1982). Smoking reduction reduces insulin absorption from subcutaneous tissue. *BMJ*;284;237
41. Madsbad et al (1980). Influence of smoking on insulin requirements and metabolic status in diabetes mellitus. *Diabetes Care*;3:41-3
42. Smits et al (1989). Nicotine enhances the circulatory effects of adenosine in human beings. *Clin Pharmacol Ther*;46;272-278
43. Sylven et al (1990). Nicotine enhances angina-pectoris-like chest pain and atrio-ventricular blockade provoked by intravenous bolus of adenosine in healthy volunteers. *J Cardiovasc Med*;16:9962-5
44. West et al (2000). A comparison of abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology (Berl)*;149(3):198-202

45. Hughes et al (1998). Dependence on and abuse of nicotine replacement medications: an update. *In Nicotine safety & Toxicity*. Ed Benowitz; OUP: 147-157

3 FURTHER RESEARCH

3.1 Temporary cessation

A possible “indication” for NRT is to relieve nicotine craving and withdrawal symptoms during periods of temporary abstinence from smoking, for example during journeys, in restaurants and in other “smoke-free” environments. However, there has been considerable debate about the value of this approach. Those who consider it to be an advantage contend that it might, if effective, encourage the smoker to quit entirely by going for longer or more frequent periods without smoking. In addition, if it encourages smokers not to smoke where other people are exposed to their second-hand smoke, this reduction in passive smoking could have considerable benefit to the population at large. The arguments against temporary abstinence are that it might encourage the smoker to adopt this use of NRT without any intention of quitting.

Conclusions of CSM WG on NRT on temporary cessation

In principle, the Working Group supported the use of NRT for temporary cessation of smoking. They considered that the indication had an important public health benefit of reducing passive smoking for people around smokers who might use NRT for temporary abstinence, and that this potential impact, together with the Government’s action to ban smoking in public places, made the proposed indication extremely important but that any application submitted for evaluation would need to be supported by data.

3.2 Non-NRT medicines to aid smoking cessation

3.2.1 Background

NRT and bupropion (Zyban) are the only pharmacological products authorised in the UK to help smokers quit. Studies carried out with a number of other medicines (including antidepressants, anxiolytics, antihypertensives and opioid antagonists) not currently authorised for nicotine dependency/smoking cessation have shown varying degrees of efficacy in this indication. Most studies were placebo-controlled and there are only very limited data on long-term quit rates in comparison with NRT^{1 2 3 4}.

3.2.2 Data reviewed

From the Cochrane Review¹ it would appear that nortriptyline (as monotherapy) doubles the smoking quit rate when compared with placebo, and there is an indication that this effect may be independent of its anti-depressive action. However, as would be expected, typical cholinergic effects were significantly commoner than with placebo. Currently, it is unclear if nortriptyline has a positive benefit to risk, particularly in view of the good tolerability profile of NRT.

Conclusion of CSM WG on NRT on non-NRT medicine to aid smoking cessation

The Working Group advised that the possible use of nortriptyline as an aid to quitting smoking should be explored.

3.3 Medical Research Council (MRC) study – use of NRT in pregnancy

The Working Group noted the progress in setting up a randomised placebo-controlled trial designed to investigate both the efficacy and safety of NRT in pregnancy, and that recruitment is due to start in March 2006.

REFERENCES

1. Hughes et al (2004). Antidepressants for smoking cessation. *The Cochrane Database of Systematic Reviews*, Issue 4.
2. Hughes et al (2004). Anxiolytics for smoking cessation. *The Cochrane Database of Systematic Reviews*, Issue 4.
3. Gourlay et al (2004). Clonidine for smoking cessation. *The Cochrane Database of Systematic Reviews*, Issue 3.
4. David et al (2001). Opioid antagonists for smoking cessation. *The Cochrane Database of Systematic Reviews*, Issue 3.

RECOMMENDATIONS OF THE COMMITTEE ON SAFETY OF MEDICINES WORKING GROUP ON NICOTINE REPLACEMENT THERAPY

1. All forms of nicotine replacement therapy should be licensed for abrupt cessation of smoking for:
 - adolescents of 12 years and over;
 - pregnant women – although they should be encouraged to stop smoking without NRT if possible;
 - smokers with cardiovascular disease – although for those with the severest forms, NRT should be initiated under medical supervision.
2. Seven products (Nicorette original, mint and freshmint 2mg gum: Nicorette original, mint and freshmint 4mg gum: Nicorette inhalator) should be licensed to cut down smoking as a “stepping stone” to stopping completely, for smokers who are currently unable to stop abruptly.
3. The product information for all forms of NRT is being revised to:
 - ensure the benefits of NRT are maximised;
 - ensure that any risks there may be with NRT are seen in the context of the well-established dangers of continued smoking;
 - provide clear-cut and easily assimilated information for both users and healthcare professionals.
4. The product information for all forms of NRT should not contra-indicate use:
 - in pregnancy and lactation;
 - in those with cardiovascular disease;
 - in adolescents aged 12-18 years;
 - of more than one form of NRT used concurrently
5. The product information for all NRT products should advise that:
 - those with diabetes mellitus should monitor their blood sugar levels more closely than usual when NRT is initiated;
 - NRT should be used with caution in those with moderate to severe impairment of hepatic function;
 - NRT should be used with caution in those with severe renal impairment;
 - if it is necessary to continue NRT beyond nine months, a healthcare professional should be consulted.
6. More data are required before an indication for temporary cessation could be granted.
7. The use of nortriptyline as an aid to stopping smoking should be explored.

GLOSSARY OF ACRONYMS

AE	Adverse event
CI	Confidence interval
CO	Carbon monoxide
COC	Committee on Carcinogenity
CSM	Committee on Safety of Medicines
IRR	Incident rate ratio
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarct
MRC	Medical Research Council
NICE	National Institute for Clinical Excellence
NRT	Nicotine replacement therapy
OR	Odds ratio
P	Pharmacy
POM	Prescription only medicine
ppm	parts per million
SIDS	Sudden infant death syndrome
SPC	Summary of product characteristics
THIN	The Health Improvement Network
VAS	Visual analogue scale
WG	Working Group