ABC of smoking cessation
Nicotine replacement therapy

Andrew Molyneux

This article outlines the mechanism of action of nicotine replacement therapy (NRT), the evidence for its effectiveness, and how and when NRT products can be used

Although products for nicotine replacement therapy (NRT) have been available for over 20 years, they have been excluded until recently from state or insurance based health service provision in the United Kingdom and many other countries. They have therefore not been widely prescribed by doctors who help smokers wanting to quit. Recent changes in funding policy in the United Kingdom and new guidance from the National Institute for Clinical Excellence (which covers England and Wales) mean that NRT products can and should now be made available to all smokers who want to stop smoking.

Like other pharmacological interventions for helping smokers to quit (see the next article in this series), NRT is most effective when used in conjunction with behavioural and other types of non-pharmacological cessation interventions.

Mechanism of action

The main mode of action of NRT is thought to be the stimulation of nicotinic receptors in the ventral tegmental area of the brain and the consequent release of dopamine in the nucleus accumbens. This and other peripheral actions of nicotine lead to a reduction in nicotine withdrawal symptoms in regular smokers who abstain from smoking.

NRT may also provide a coping mechanism, making cigarettes less rewarding to smoke. It does not completely eliminate the symptoms of withdrawal, however, possibly because none of the available nicotine delivery systems reproduce the rapid and high levels of arterial nicotine achieved when cigarette smoke is inhaled.

All the available medicinal nicotine products rely on systemic venous absorption and do not therefore achieve such rapid systemic arterial delivery. It takes a few seconds for high doses of nicotine from a cigarette to reach the brain; medicinal products achieve lower levels over a period of minutes (for nasal spray or oral products such as gum, inhalator, sublingual tablet, or lozenge) and hours (for transdermal patches).

Evidence for effectiveness

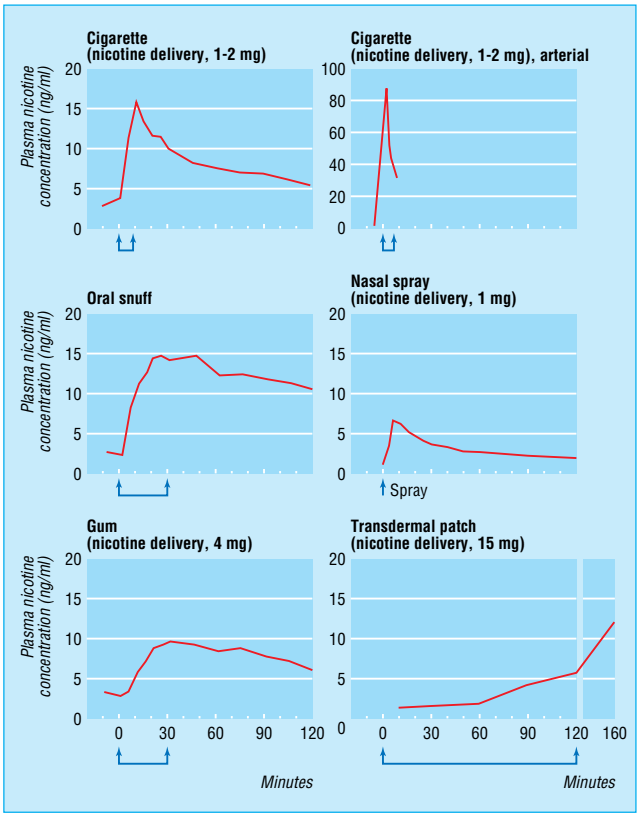
The most recent Cochrane reviews suggest that NRT leads to a near doubling of cessation rates achieved by non-pharmacological intervention, irrespective of the level of that intervention.

NRT will therefore increase the chance of success with any quit attempt but is most effective when combined with intensive behavioural support.

No evidence exists that NRT is any more or less effective in any specific subgroups of smokers, such as those in hospital or presenting with a smoking related disease. The effectiveness of NRT in adolescents and children who smoke has not been established, though studies are in progress.

Who should receive NRT?

Nicotine replacement therapy, preferably in conjunction with behavioural support (see the previous article in this series), should generally be offered to any regular cigarette smoker



Rise in blood nicotine concentrations after smoking a cigarette and after using different NRT products (after overnight abstinence from cigarettes). Values are for venous blood, except where shown. Adapted from Henningfield JE. *N Engl J Med* 1995;333:1196-203

Proportion of smokers abstaining from smoking long term, by cessation intervention. Adapted from West et al, 2000*

Intervention	Long term abstinence (%)
No intervention (willpower alone)	3
Brief, opportunistic advice from doctor to stop	5
Plus NRT	10
Intensive support from specialist	10
Plus NRT	18

*See Further Reading box

prepared to make a quit attempt. NRT is relatively unlikely to help smokers who are not motivated to quit or do not experience or expect to experience nicotine withdrawal symptoms. Any healthcare professionals can assess these characteristics in the following ways:

- Motivation to quit: smokers should be asked whether they would like to stop smoking. Those willing to stop within the next 30 days should set a quit date and their dependence should be assessed.
- Dependence: smokers should be asked whether they have tried to quit smoking before, whether they experienced symptoms of nicotine withdrawal, and whether they anticipate these symptoms in a future quit attempt.

Formulations and use of NRT

Six NRT formulations are currently available. In the United Kingdom, all of these are now available on prescription through the NHS and most can also be bought over the counter at pharmacies. In addition, patch, gum, and lozenge formulations are on general sale in supermarkets and other outlets. As little evidence exists that any one of these formulations is more effective than any other or that any is more effective in particular subgroups of smokers, the choice of product should generally be guided by the smoker's preference and clinical considerations relating to duration of action.

Evidence exists, however, that higher dose gum is more effective than lower dose gum in those smoking 20 or more cigarettes a day, that higher dose patches are more effective than low dose patches in those smoking more than 10 cigarettes a day, and that combining products (such as patch and nasal spray, or patch and inhalator) is more effective than using single agents alone. NRT, and nicotine gum in particular, has also been shown to help to control the weight gain commonly experienced after cessation.

NRT should be prescribed in blocks, usually of two weeks, be continued in those maintaining abstinence from cigarettes for a total of six to eight weeks, and then discontinued. If possible, NRT prescriptions should be linked to the delivery of follow up behavioural support. The prescriptions can be issued through delegated prescribing by nurses or other health professionals.

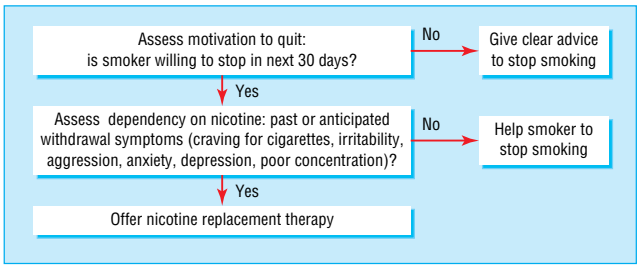
No evidence shows that gradual withdrawal of NRT is better than abrupt withdrawal. The risk of dependence on NRT is small, and only a small minority of patients (about 5%) who quit successfully continue to use medicinal nicotine regularly in the longer term.

Studies investigating the use of NRT to help smokers to abstain from smoking for certain periods (for example, at work or in a public place) or to reduce the number of cigarettes they smoke each day are in progress.

Safety of NRT

Obtaining nicotine from NRT is considerably safer than doing so from cigarettes, as the patient is not exposed to any of the many harmful products of tobacco combustion.

Long term use of NRT is not thought to be associated with any serious harmful effects. Concerns over the safety of NRT in circumstances in which nicotine might be harmful—such as in pregnancy, cardiovascular disease, or in adolescents—therefore need to be considered in relation to the safety of the likely alternative, which is continued intake of nicotine from cigarettes.



Decision pathway for giving nicotine replacement therapy

NRT formulations and their availability

Transdermal patch—On general sale,* at pharmacies, and on prescription
Gum—On general sale,* at pharmacies, and on prescription
Nasal spray—On prescription
Inhaler—At pharmacies and on prescription
Sublingual tablet—At pharmacies and on prescription
Lozenge—On general sale,* at pharmacies, and on prescription

*In supermarkets and other outlets

Nicotine gum products

Smokers should be advised not to smoke while using NRT products

Prescribing details for NRT formulations

Formulation (dose)	Use
Patch (16 h patch: 15, 10, or 5 mg; 24 patch: 21, 14, or 7 mg)	One daily on clean, unbroken skin; remove before bed (16 h patch) or next morning (24 h); new patch, fresh site
Gum (2 or 4 mg per piece)	Chew gum until taste is strong, then rest gum between gum and cheek; chew again when taste has faded
Inhalator (10 mg per cartridge)	Inhale as required
Sublingual tablet (2 or 4 mg per piece)	Rest under tongue until dissolved
Lozenge (1, 2, or 4 mg per piece)	Place between gum and cheek and allow to dissolve
Nasal spray (10 mg/ml, 0.5 mg per spray)	One spray each nostril as required

Side effects for all formulations: sore throat, hiccups, indigestion, nausea, headache, palpitations (but without hiccups for the inhalator and plus itching, erythma, and rash for patches).

Pregnancy and breast feeding

Smoking during and after pregnancy poses a serious risk to the health of both mother and baby. NRT may also have adverse effects on placental function and fetal development, but although the magnitude of these pure nicotine effects in humans is uncertain, the likelihood is that obtaining nicotine from cigarette smoke is far more harmful.

Complete avoidance of all nicotine should therefore be the objective in pregnancy and breast feeding, and 30% of pregnant women succeed in stopping smoking during pregnancy without pharmacological support. However, for those who do not succeed, or have previously failed in an attempt to quit, the use of NRT to support smoking cessation in pregnancy is justifiable in relation to the risk of continued smoking. Pregnant or breast feeding women who make an informed choice to try NRT should probably be advised to use shorter acting products to minimise fetal exposure to nicotine overnight.

Cardiovascular disease

Nicotine replacement therapy is safe in smokers with stable cardiovascular disease. In acute cardiovascular conditions, such as unstable angina, acute myocardial infarction, or stroke, NRT should be used with caution because nicotine is a vasoconstrictor. However, as medicinal nicotine is unlikely to be more harmful in this context than continued intake of nicotine (and the associated tar, carbon monoxide, and other products) from cigarettes, it is appropriate to offer NRT to help in smoking cessation in patients with acute cardiovascular disease who continue to smoke. In these circumstances it is probably advisable to use rapidly reversible preparations—such as gum, inhalator, nasal spray, or lozenge—as absorption of nicotine ceases when the product is withdrawn; after removal of a transdermal patch, however, the skin can continue to absorb nicotine slowly from the skin for some time.

Young smokers

Most adult smokers established their smoking habit as children. Even in adolescence, many smokers are addicted to nicotine and would like to stop smoking. Over two thirds of adolescent smokers have tried to stop, and failed. Although no randomised controlled trials of the effectiveness of NRT in young smokers have been published, several NRT products are licensed for use in smokers aged under 18, on medical advice. In addition, the recent National Institute for Clinical Excellence guidance on NRT suggests that smokers under 18 who want to quit using NRT should discuss this with a relevant healthcare professional. Until further evidence arises to the contrary, it therefore seems reasonable to use NRT in adolescent smokers who are motivated to quit and show evidence of nicotine dependence.

Competing interests: AM has received research funding and been reimbursed for attending conferences by Pharmacia, a manufacturer of NRT. He has also received speaking fees and been reimbursed for attending a conference by GlaxoSmithKline, which manufactures bupropion and NRT. See first article in this series (24 January 2004) for the series editor's competing interests.

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Key points

- Nicotine replacement therapy is an effective aid to smoking cessation
- Smokers who are motivated to quit and are dependent on nicotine should be offered NRT
- The choice of NRT product should normally be guided by the patient's preference
- NRT should be prescribed for six to eight weeks, in blocks of up to two weeks, contingent on continued abstinence
- Obtaining nicotine from NRT is considerably safer than smoking
- NRT is safe in stable cardiac disease, but caution is needed in unstable, acute cardiovascular disease, pregnancy, or breast feeding, or in those aged under 18

Further reading

- Silagy C, Mant D, Fowler G, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2000;CD000146.
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- West R, McNeill A, Raw M. Smoking cessation guidelines for health professionals: an update. *Thorax* 2000;55:987-99.
- Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Fox BJ, Goldstein MG, et al. A clinical practice guideline for treating tobacco use and dependence. *JAMA* 2000;283:3244-54.

The photo of the pregnant woman is with permission from Faye Norman/SPL.

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The ABC of smoking cessation is edited by John Britton, professor of epidemiology at the University of Nottingham in the division of epidemiology and public health at City Hospital, Nottingham. The series will be published as a book in the late spring.

Interactive case report

Treating nausea and vomiting during pregnancy

This case was described on 31 January and 7 February (*BMJ* 2004;276,337). Debate on the management of this case and the n of 1 trial continues on bmj.com (http://bmj.com/cgi/content/full/328/7434/276). On 7 March we will publish the outcome of the case together with commentaries on the issues raised by the management and online discussion from a general practitioner, an obstetrician, a statistician, and an educationalist.