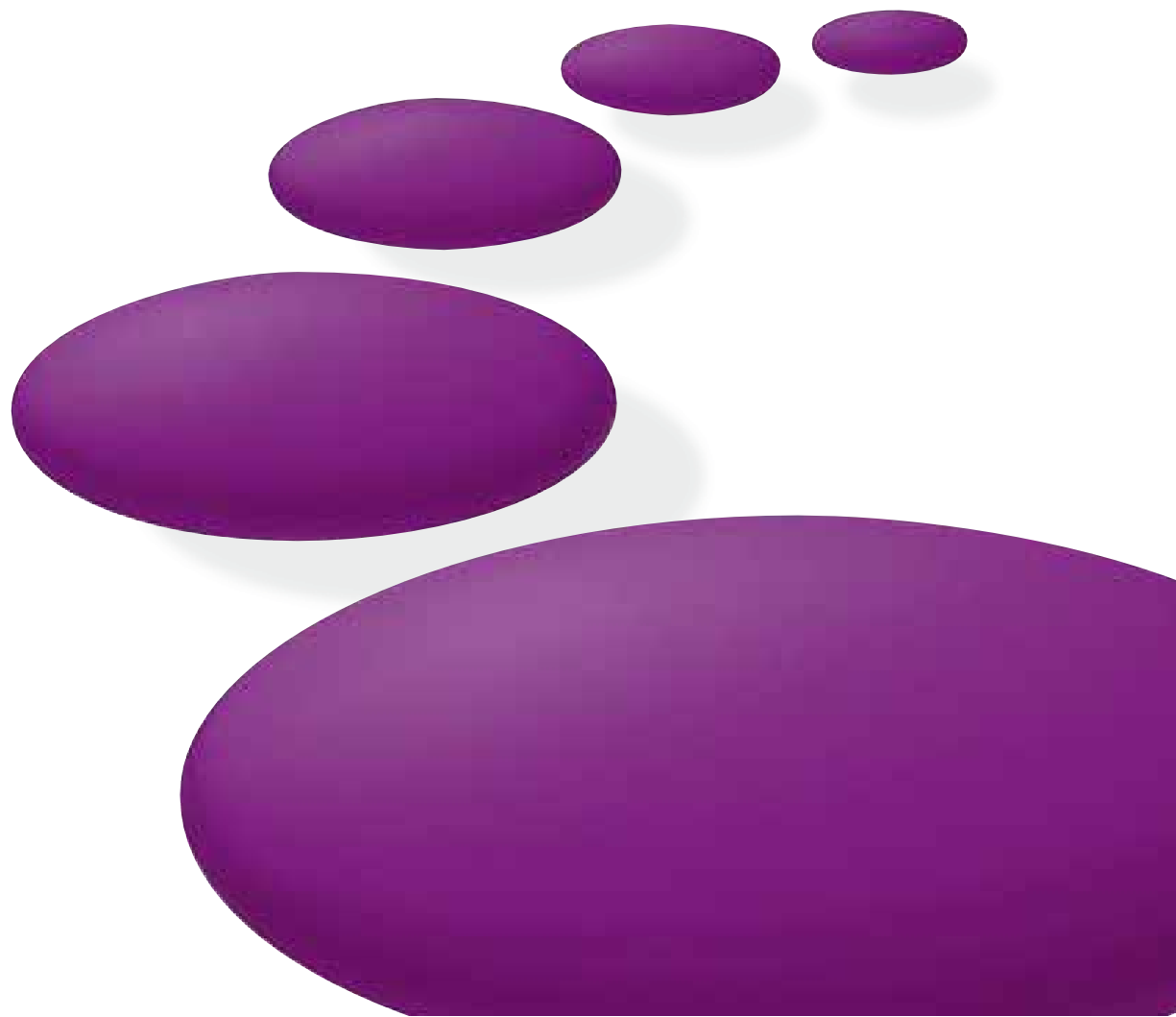


# nicorette<sup>®</sup> inhaler

product monograph

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# Nicorette® Inhaler: summary

## Characteristics

The Nicorette® Inhaler is a unique form of nicotine replacement which provides nicotine via oral inhalation. Each cartridge contains a plug containing 10 mg of nicotine, of which 4 mg is released during repeated use. As air is drawn through the nicotine-impregnated plug it is saturated with vapourised nicotine.

The amount of nicotine released from the plug depends on the volume of air passing through the plug and the temperature. At room temperature, one puff of the inhaler delivers approximately 13 µg of nicotine; 10 puffs are approximately equivalent to one puff on a cigarette.

Nicorette® Inhaler is the only dosage form of nicotine replacement therapy (NRT) which directly addresses both the hand-to-mouth behavioural activity and the pharmacological dependence associated with tobacco use.

## Dosage and administration

The treatment dosage and duration depends on the individual smoker, but it is recommended that 6–12 cartridges per day should be used for at least 3 months. The daily dose should then be gradually reduced, and treatment discontinued when the dose is reduced to 1–2 cartridges per day.

The nicotine vapour can be inhaled *ad libitum*, either by deep inhalation or by shallow puffing. Intensive use of the inhaler (continuous inhalations or puffs) for 20 minutes will release approximately 4 mg nicotine. Each cartridge should be used within 12 hours of opening.

## Pharmacokinetics

### Bioavailability

The inhalation technique (deep inhalation or shallow puffing) does not appear to affect release of nicotine from the plug. However, nicotine levels are affected by the volume of air passing through the cartridge and the ambient temperature. At temperatures up to 40°C, plasma nicotine levels following inhalation do not exceed the normal range for smokers.

### Absorption

Most of the nicotine delivered with the inhaler is absorbed in the upper respiratory tract, via the buccal mucosa. Pulmonary absorption is negligible, hence the rapid, high arterial nicotine peaks that occur during cigarette smoking do not occur with Nicorette® Inhaler.

### Nicotine substitution

During *ad libitum* use, plasma nicotine levels with Nicorette® Inhaler are approximately 30% of those during smoking.

## Clinical efficacy

### Abstinence rates

To date, six randomised, placebo-controlled, double-blind studies, involving a total of 1,440 subjects, have been performed with the Nicorette® Inhaler. A meta-analysis of these studies, in which the main outcome measure was complete abstinence from week 2, showed that active treatment was significantly superior to placebo at all time points up to 1 year.

### Craving and withdrawal symptoms

Nicorette® Inhaler significantly reduced craving and withdrawal symptoms compared to placebo.

## Safety

In clinical trials, no serious systemic adverse events have been reported following use of Nicorette® Inhaler. The most common systemic adverse events are headache, gastrointestinal discomfort and nausea. Local irritation in the mouth and throat and cough are common when treatment commences, but are generally mild and decline during repeated use.

## Other Nicorette® products

The adverse health consequences of smoking are increasingly being publicised.<sup>[1,2]</sup> In addition, legislation aimed at restricting smoking in public places is also increasing.<sup>[3,4]</sup> However, although various pharmacological and psychological measures are available to help smokers quit, the highly addictive nature of tobacco use means that relapse is very common.

One of the most effective treatments available to help tobacco-dependent smokers attempt to quit, nicotine replacement therapy (NRT), has been used for more than 20 years. The rationale for NRT is based on three factors:<sup>[5,6]</sup>

- the severity of craving and tobacco withdrawal symptoms is cited as the most common reason for relapse to smoking
- tobacco withdrawal symptoms are primarily caused by nicotine depletion
- nicotine replacement alleviates craving and withdrawal symptoms, and some products also enable the smoker to cope with the non-pharmacological elements of their addiction (such as conditioned situational cues and hand-to-mouth activity).

Nicorette® was the first NRT introduced to treat tobacco dependence, and its efficacy in assisting smokers to overcome craving and withdrawal symptoms and become abstinent is well established.<sup>[7]</sup> In addition to the inhaler, four other Nicorette® products are also available.

**Nicorette® Gum** is a chewing gum formulation that provides user-controlled nicotine release for oral absorption. Available in a choice of flavours, Nicorette® Gum can be chewed whenever there is an urge to smoke, providing useful behavioural involvement. Nicorette® Gum is available in two strengths, 2 mg and 4 mg, the former for low-dependent smokers and the latter for highly dependent smokers or those who fail to quit while using the 2 mg gum.

**Nicorette® Patch** is a rectangular, beige-coloured skin patch that is worn throughout the waking hours to provide controlled, continuous nicotine replacement. Although the absorption of nicotine from the patch is slower than that from Nicorette® Gum, it is more predictable and fluctuations in plasma nicotine concentrations are smaller. The patch is discreet and easy to apply. Treatment commences by using a Nicorette® Patch that delivers 15 mg of nicotine over a 16-hour period (providing nicotine during waking hours mimics the smoker's usual nicotine profile). The dose is then tapered by using patches that deliver 10 mg and 5 mg over 16 hours.

**Nicorette® Nasal Spray** provides a fast-acting, flexible form of NRT. One 50 µL spray administered to each nostril delivers a total of 1 mg of nicotine. Intranasal absorption of nicotine is faster than that achieved with other NRT products, so the nasal spray rapidly relieves craving and withdrawal symptoms. Because of the fast onset, Nicorette® Nasal Spray is particularly suitable for highly dependent smokers.

**Nicorette® sublingual tablet** is a discreet dosage form designed to be kept under the tongue so that nicotine is released upon disintegration of the tablet. In common with Nicorette® Gum, the Nicorette® sublingual tablet provides flexible, user-controlled doses of nicotine and can be used to alleviate craving and tobacco withdrawal symptoms as required.

The needs of smokers may vary according to their individual preference or changes in their level of tobacco dependence, social situation or lifestyle. Nicorette® offers the widest range of NRT products, giving smokers the opportunity to choose an optimal nicotine replacement therapy tailored to their individual needs.

*NRT is the most extensively studied of all pharmacological agents used to treat tobacco dependence*

*Nicorette® offers the widest range of NRT products, enabling individual smokers to choose a nicotine replacement therapy tailored to their own needs*

# Smoking and its consequences

## Tobacco use

Tobacco was introduced into Europe during the 16th century and its use soon extended around the world in a variety of forms. Tobacco was first burnt in pipes, which gave way to snuff, followed by cigars and then cigarettes.<sup>[8]</sup> By the middle of the 20th century, cigarette use exceeded that of other forms of tobacco.

## Health consequences

The health risks of tobacco use have been recognised for several decades. During the 1950s, smoking was found to be linked to some important chronic diseases.<sup>[8]</sup> Collaborative research by the World Health Organization (WHO), the American Cancer Society and the Imperial Cancer Research Fund has enabled indirect estimation of annual mortality rates caused by tobacco use.<sup>[2]</sup> The results show that the tobacco epidemic is widespread and devastating.

Tobacco-related diseases are the single most important cause of preventable deaths in the world. Cigarette smoking is a causative and/or aggravating factor in more than 40 fatal and disabling diseases, including:<sup>[8-11]</sup>

- lung cancer, and cancers of the oral cavity, larynx, oesophagus, pancreas, kidney and bladder
- cardiovascular disease (coronary heart disease, angina pectoris, peripheral vascular disease and aortic aneurysm)
- cerebrovascular disease, including stroke
- respiratory disease, primarily chronic bronchitis and emphysema
- infections of the upper respiratory tract
- gastric and duodenal ulcers
- complications of pregnancy and birth (spontaneous abortion, prematurity, low birth-weight infants, perinatal mortality).

*Tobacco causes 4 million deaths each year, and half of all long-term smokers will be killed by tobacco*

Several extensive reviews of the links between smoking and disease conducted by the US Surgeon General have concluded that cigarette smoking is responsible for:<sup>[9,10,12]</sup>

- 80–90% of all chronic lung disease
- approximately 30% of all deaths from coronary heart disease
- approximately 30% of all cancer deaths.

In addition, exposure to environmental tobacco smoke (also known as enforced, second-hand or passive smoking) increases the risk of lung cancer, coronary heart disease, respiratory illness and, among infants, sudden infant death syndrome.<sup>[13,14]</sup>

## Trends in tobacco-related death and disease

Tobacco use already causes 4 million deaths per year worldwide, and this figure is expected to rise to around 10 million by 2025.<sup>[15]</sup> Based on current smoking trends, tobacco is predicted to be the leading cause of disease burden by the 2020s, causing more than 1 in every 8 deaths – more than any other single cause. In Europe, more than 30% of adults are regular daily smokers.<sup>[16]</sup> In north-western Europe, smoking prevalence rates are similar for men and women, whereas in southern and eastern countries considerably fewer women than men smoke. In two thirds of European countries cigarette use is increasing among young people. Cigarettes caused 1.2 million deaths in Europe in 1995, and it is estimated that this will double to 2 million by 2020, partly because of a dramatic increase in tobacco-related death among women.<sup>[16]</sup>

## Hazards for individual smokers

Prolonged tobacco use represents a huge risk to individual users – half of all regular smokers will die prematurely as a result of smoking (about one-quarter in middle age plus one-quarter in old age).<sup>[17]</sup> Those killed by tobacco in middle age (35–69 years) lose an average of 20–25 years life expectancy compared to non-smokers. The risk is particularly high for those who start smoking regularly when teenagers.

## Health benefits of stopping smoking

Stopping smoking improves health, and it is never too late to stop.<sup>[18]</sup> Even in middle age, stopping smoking avoids most of the excess risk of death from tobacco, and the benefits of stopping smoking at an earlier age are even greater (Figure 1).<sup>[19]</sup> The dose response of smoking (in terms of cigarette consumption and number of years) across disease process is marked and consistent. The relative risk of death for both male and female smokers versus that for never-smokers ranges between 1.5 and 2.5, but 15 years after stopping smoking the risk of death among ex-smokers is equivalent to that in never-smokers.<sup>[18]</sup>

Stopping smoking clearly decreases the risk of lung cancer, and the incidence of lung cancer is reduced by 80–90% in ex-smokers who have been abstinent for 15 years or more.<sup>[18]</sup> There is also a complete or partial reversal of the risk of stroke within 5–10 years of stopping smoking.<sup>[20]</sup> The incidence of cardiac disease and death from coronary heart disease are also greatly reduced in those who stop smoking, and reversal of the short-term cardiovascular effects of smoking are rapid. Many of the effects of smoking on the cardiovascular system are mediated by short-term mechanisms, such as activation of the adrenergic nervous system, coronary vasoconstriction, endothelial damage and leucocyte activation.<sup>[20]</sup> Most of these risk factors improve within days of stopping smoking.<sup>[20]</sup>

*Stopping smoking, even in middle age, substantially reduces the risk of death from tobacco*

*Many of the cardiovascular risk factors improve within days of stopping smoking*

Finally, stopping smoking also reduces the harm caused to spouses, partners or children who live with smokers.

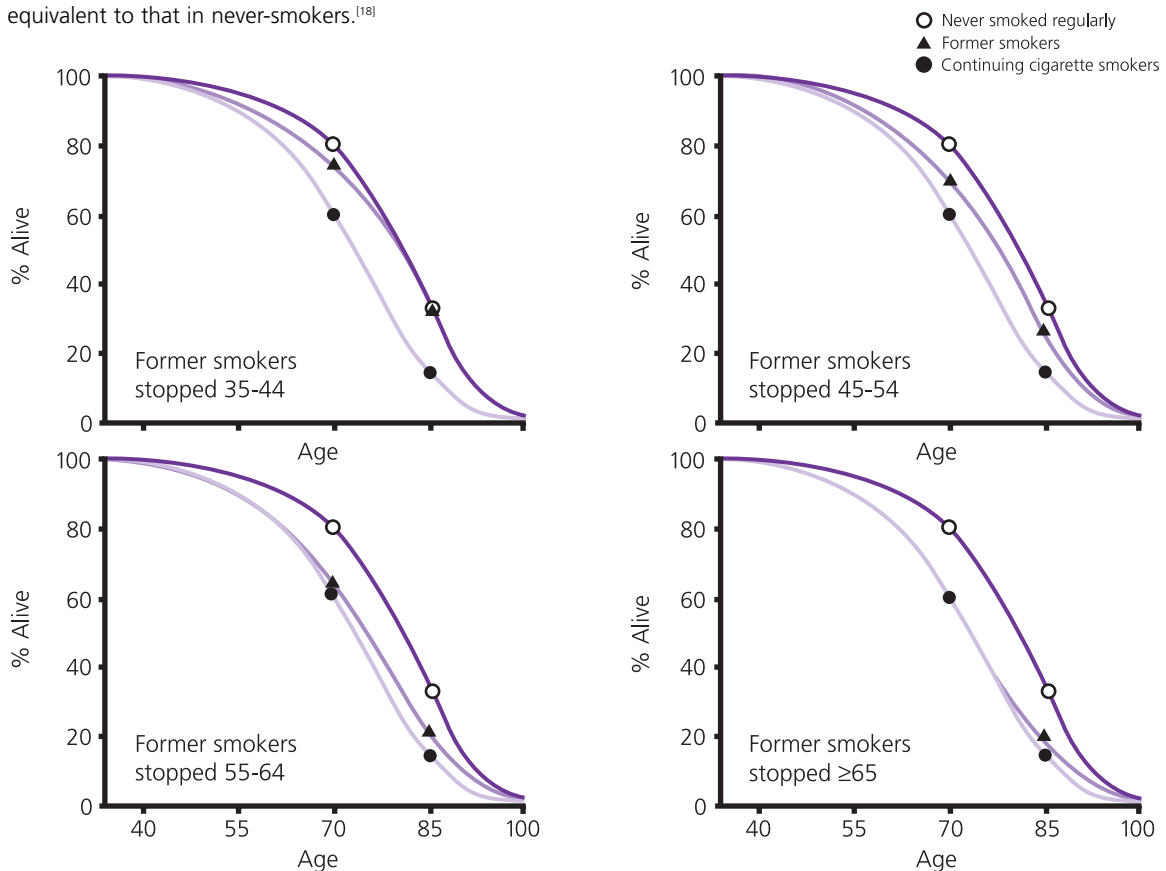


Figure 1. Effects on survival after ages 45, 55, 65 or 75 of stopping smoking during the previous 10 years.<sup>[19]</sup> Br Med J 1994; 309:901-911, with permission from the BMJ Publishing Group.

# Tobacco dependence

## Constituents of tobacco smoke

Tobacco smoke is a complex mixture that contains approximately 4,000 compounds. More than 40 are carcinogenic, and 9 of these (including benzene, cadmium and nitrosamines) have been classified as group I carcinogens.<sup>[21]</sup> The majority of tobacco smoke components can be subdivided into nicotine, carbon monoxide, tar and other irritants. The tar, irritants and carbon monoxide are the causative factors in tobacco-related disease.<sup>[22,23]</sup> Polycyclic aromatic hydrocarbons and nitrosamines are the probable causative agents for lung cancer and other cancers, while irritant gases are responsible for pulmonary disease and carbon monoxide is implicated in cardiovascular disease.<sup>[23]</sup> Nicotine has not been shown to cause cancer.<sup>[24,25]</sup>

Tobacco smoke contains 4,000 compounds, more than 40 of which are carcinogenic

## Pharmacology of nicotine

Nicotine is a tertiary amine derived from the tobacco plant, *Nicotiana tabacum* L. (Figure 2).

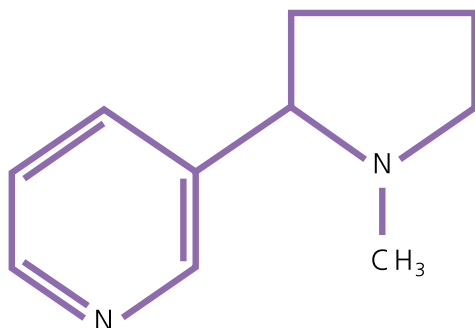


Figure 2. Structural formula of nicotine.

Tobacco contains the most potent enantiomer, s-nicotine, which is also used in nicotine replacement products. In its base form, nicotine is alkaline, colourless and freely soluble in both water and lipids. Nicotine acts through nicotinic cholinergic receptors in the brain, autonomic ganglia and the neuromuscular junction.<sup>[26]</sup> Nicotinic receptor activation causes the release of neurotransmitters, including acetylcholine, noradrenaline, dopamine, serotonin, beta endorphin, and glutamate.<sup>[27]</sup> Addiction to nicotine has been most strongly linked to dopamine release, although other neurotransmitters probably also play a role.

Two issues are important in understanding the pharmacodynamics of nicotine: the dose-response relationship is complex, and tolerance develops after a relatively brief period of exposure. Tolerance means that repeated doses of the drug produce less effect than the first dose. The diverse pharmacological effects of nicotine depend on the number and frequency of cigarettes smoked and the extent of the individual's tolerance to the drug.<sup>[28-30]</sup>

## Central nervous system

Nicotine readily crosses the blood-brain barrier, and is rapidly distributed throughout the brain, with highest concentrations in the hypothalamus, hippocampus, thalamus, midbrain, brain stem and in areas of the cerebral cortex. Nicotine binds to nicotinic cholinergic receptors that are located both on cell bodies and at nerve terminals.<sup>[31]</sup> Na<sup>+</sup>, K<sup>+</sup> and Ca<sup>++</sup> ions can permeate nicotinic receptors. The fact that Ca<sup>++</sup> can permeate nicotinic receptors reinforces the role that nicotine may play in modulating the release of neurotransmitters such as acetylcholine, noradrenaline, dopamine, serotonin,  $\gamma$ -aminobutyric acid (GABA) and glutamate through presynaptic nicotinic receptors.<sup>[31]</sup> Most of the effects of nicotine on the central nervous system are believed to result from direct action on the brain. However, activation of central neural pathways through stimulation of afferent nerves or chemoreceptors in the carotid bodies or the lung may also contribute.<sup>[32]</sup>

## Cardiovascular system

The acute cardiovascular effects of tobacco smoking include:<sup>[26]</sup>

- increased heart rate, cardiac stroke volume, cardiac output and coronary blood flow
- increased blood pressure
- peripheral vasoconstriction
- increased circulating levels of adrenaline and noradrenaline
- increased levels of circulating free fatty acids and alterations in the lipid profile.

Although nicotine is involved in many of these effects, regular smokers develop tolerance to most of the cardiovascular effects of nicotine. Tolerance also explains the flat cardiovascular dose-response curve observed after nicotine administration.<sup>[27]</sup>

It is important to note that it is not nicotine but other components of tobacco smoke that cause cardiovascular disease by producing carboxy-haemoglobin, raising blood and plasma viscosity, increasing platelet aggregation and serum fibrinogen levels, reducing erythrocyte deformability, activation of leucocytes and activating various coagulation factors.<sup>[33-35]</sup>

### Endocrine and metabolic effects

Nicotine affects the metabolic rate, and smokers weigh up to 4.5 kg less than non-smokers, probably as a result of appetite suppression and increased energy expenditure.<sup>[26]</sup> Stopping smoking is associated with an increase in appetite and weight gain is common following quitting. Nicotine has a variety of endocrine effects, including release of adrenocorticotrophic hormone and growth hormone.<sup>[26]</sup> Smoking is also associated with an earlier menopause and increased risk of osteoporosis in women.<sup>[26]</sup>

### Therapeutic effects

Although nicotine is addictive, the mechanisms underlying its addictive properties are not fully understood. Research on the diversity of central nicotinic cholinergic receptors illustrates the complexity of the effects that nicotine has on neurotransmitters and highlights gaps in our understanding of the way these mechanisms operate.<sup>[31]</sup> Smoking is an efficient way to self-administer nicotine because smokers can control the dose of nicotine delivered to the brain on a puff-by-puff basis.<sup>[32]</sup> Through this dose regulation, smokers can control their mood and cognitive functioning, probably because they are directly modulating nicotine availability to the dopaminergic and cholinergic systems. Indeed, chronic smoking has recently been shown to inhibit monoamine oxidase B (MAO-B), suggesting that it has antidepressive effects.<sup>[36]</sup> Such observations have raised new interest in the use of nicotine as a therapeutic agent, particularly for individuals with neurological or psychiatric disease.<sup>[28,30]</sup>

### Tobacco dependence

Cigarette smoking is associated with both pharmacological and behavioural dependence. These components of dependence vary between individual smokers and may also change considerably during an individual's smoking history.

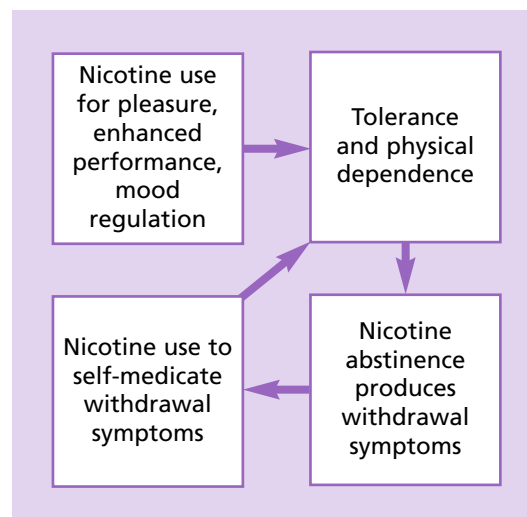


Figure 3. Classical model of addiction as applied to nicotine.<sup>[93]</sup>

The addictive nature of nicotine follows a classical cycle (Figure 3) that has been likened to that of heroin or cocaine.<sup>[37]</sup> The intensity of the addictive nature of cigarette smoking is highlighted by the following facts:<sup>[37]</sup>

- although 70% of smokers in the USA want to stop smoking, and 30% make a serious attempt each year, only 3% succeed in quitting each year
- 50% of people continue to smoke after a heart attack, despite knowing that smoking may kill them.

Continual reinforcement of smoking in social situations is also common. In addition to positive situations that encourage smoking (e.g. social drinking and following meals), negative situations (e.g. times of stress) may also trigger smoking. Following tobacco use, smokers undergo changes in mood, including increased pleasure, reduced anger and decreased tension, and relaxation, especially during stressful situations.<sup>[26]</sup> Many smokers also believe that smoking improves their concentration and problem-solving skills and enhances their reaction time.



Tobacco dependence is a recognised disease listed in the WHO International Classification of Diseases

Tobacco dependence is a recognised disease according to the WHO *International Statistical Classification of Diseases* (ICD-10, item F17.2).<sup>[38]</sup> The primary reason for tobacco dependence is nicotine addiction, the extent of which can be measured using methods such as the Fagerström Test for Nicotine Dependence (FTND)<sup>[39]</sup> which rates pharmacological dependence on a scale of 1 to 10 according to responses to 6 questions (Table 1).

Table 1. Items and scoring on the Fagerström Test for Nicotine Dependence.<sup>[39]</sup> Reproduced with permission.

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6–30 minutes	2
	31–60 minutes	1
	After 60 minutes	0
2. Do you find it difficult to refrain from smoking in places where it is forbidden e.g. in church, at the library, in the cinema, etc.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	all others	0
4. How many cigarettes per day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

## Tobacco withdrawal

Abstinence from smoking results in clinically significant withdrawal symptoms

Nicotine withdrawal is a disorder listed in the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Health Disorders* (DSM-IV).<sup>[40]</sup> According to the DSM-IV, nicotine withdrawal is considered to be present following daily use of nicotine for several weeks and when abrupt withdrawal precipitates at least four of the following subjective/physiological events in the subsequent 24 hours:

- dysphoric or depressed mood
- irritability, frustration or anger
- anxiety
- difficulty in concentrating
- restlessness
- insomnia
- decreased heart rate
- increased appetite.

Most subjective symptoms of nicotine withdrawal peak approximately 48 hours after stopping smoking and then gradually decline over 3–4 weeks.<sup>[40–42]</sup> However, craving for nicotine (the most characteristic feature of tobacco withdrawal), hunger and weight gain may continue for several months.<sup>[26,40,43]</sup>

Studies of craving and withdrawal as a function of time of day have shown that craving and total withdrawal scores increase throughout the day, with lowest scores in the morning and the highest scores observed in the evening.<sup>[44,45]</sup>

Most withdrawal symptoms peak around 48 hours after the last cigarette, but craving may persist for several months

# Treatment of tobacco dependence

## Need for treatment

Apart from HIV, tobacco is the only major cause of death that is increasing rapidly. Smoking is also the major preventable cause of disease worldwide. Epidemiological evidence demonstrates a long delay between cause (starting smoking) and effect (tobacco-related death or disease),<sup>[46]</sup> so an increase in smoking prevalence among young adults will result in a large increase in tobacco deaths around 50 years later. Thus, in countries where smoking has only become widespread within the last 30 years, the health consequences will only emerge in the next few decades (Figure 4).

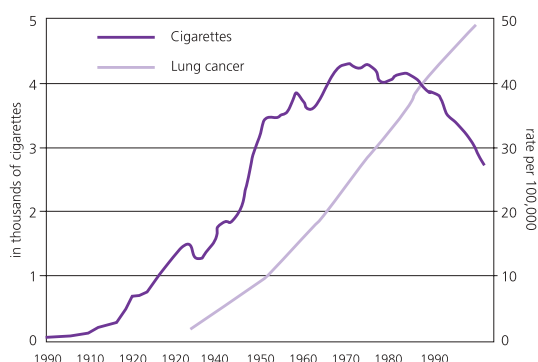


Figure 4. Change in *per capita* cigarette consumption and lung cancer death rate in the United States between 1900 and 1990, indicating the time lag between peak rates of smoking and peak incidence of lung cancer.

Source: US National Center for Health Statistics.

As preventing young people from starting to smoke will take half a century to achieve any health benefits, the only way to substantially reduce tobacco-related death and disease in the near future is for existing smokers to stop smoking. However, the addictive nature of cigarette smoking means that dependent smokers have great difficulty in stopping. More than two-thirds of smokers would like to quit, but only a tiny fraction (3%) manage to do so each year.<sup>[37]</sup> Over the past decade, consensus statements and clinical guidelines have increasingly focused on the need to improve smoking cessation efforts.<sup>[47-51]</sup>

## Smoking cessation

The difficulties experienced by smokers who are trying to give up smoking are well documented. Over the last 30 years, many methods have been employed in attempts to help smokers succeed, with varying degrees of success.<sup>[52-54]</sup> Interventions can be divided into behavioural or pharmacological treatment.

*500 million current smokers will be killed by tobacco if they do not stop smoking*

## Behavioural strategies

Behavioural intervention is founded on psychological techniques such as aversion therapy (e.g. rapid or focused smoking), self-management (e.g. self-monitoring and stimulus control) and relapse prevention (e.g. avoidance of circumstances likely to trigger relapse or specific coping strategies).<sup>[53]</sup> These methods (alone or in combination) may be provided on an individual or group basis.<sup>[53]</sup> However, results from randomised, controlled trials do not support the use of behaviour modification therapy in smoking cessation.<sup>[53]</sup> Other methods such as hypnosis and acupuncture are also either unproven or ineffective.<sup>[53,55]</sup>

*Most behavioural and non-nicotine treatments are not effective in the treatment of tobacco dependence*

## Pharmacological treatment

Numerous pharmacological therapies, with varying rationales for use, have been tested in the treatment of tobacco dependence. These include anxiolytics (buspirone), antidepressants (bupropion, fluoxetine, moclobemide, nortriptyline), anorectics, nicotine antagonists (mecamylamine), symptomatic treatment with an  $\alpha_2$ -noradrenergic agonist (clonidine), sensory stimulants (citric acid) and aversive treatment (silver acetate).<sup>[56,57]</sup> Bupropion, combined with counselling, has demonstrated efficacy in placebo-controlled trials.<sup>[58]</sup> However, results to date with other non-nicotine medications have either failed to prove any lasting efficacy, or their use is limited by adverse events or their clinical utility in smoking cessation remains unclear.<sup>[56,57]</sup> In contrast, nicotine replacement therapy has consistently demonstrated efficacy in the treatment of tobacco dependence.<sup>[5,7,53]</sup>

*NRT doubles quit rates, irrespective of adjunctive support*

## Efficacy of NRT in smoking cessation

A landmark randomised, double-blind trial with biochemical validation reported in 1982 that nicotine chewing gum doubled abstinence rates compared to placebo,<sup>[59]</sup> and the efficacy of NRT has consistently been confirmed in subsequent studies. A meta-analysis of 91 randomised, placebo-controlled trials with follow-up for at least 6 months, involving more than 33,000 smokers, showed that NRT doubles quit rates irrespective of the intensity of additional support (i.e. through minimal to maximum intervention).<sup>[7]</sup> All five existing NRT products (nicotine gum, transdermal patch, inhaler, nasal spray and sublingual tablet) have similar efficacy in smoking cessation.<sup>[7]</sup> The efficacy of the Nicorette® Inhaler in treating tobacco dependence is detailed on pages 24 to 26.

Clinical guidelines in the United States and England now recommend that, except in special circumstances, all smokers should use NRT during quit attempts.<sup>[48,49]</sup>

## Combination treatment with NRT for smoking cessation

Although NRT doubles quit rates, absolute success rates remain modest (generally 10–30% at 1 year).<sup>[60]</sup> One possible explanation is underdosing; when used at standard doses, NRT tends to produce trough plasma nicotine levels that are lower than those in moderate to heavy smokers while smoking. The nicotine patch is easy to use, which encourages compliance, but as nicotine is absorbed slowly and steadily throughout the day the user has no control over dosing. In contrast, the gum, inhaler, nasal spray and sublingual tablet offer flexible dosing; the use of these products also includes some behavioural activity and provides sensory stimulation.

Four double-blind, placebo-controlled, randomised studies have evaluated the effect of combination NRT treatment on smoking cessation; two of these used the nicotine 16 hour patch plus nicotine gum,<sup>[61,62]</sup> one investigated nicotine 16 hour patch plus nasal spray<sup>[63]</sup> and one combined nicotine 16 hour patch plus nicotine inhaler.<sup>[64]</sup> In all four studies, combination treatment achieved higher 1-year abstinence rates than single NRT. The pooled results of the first three studies<sup>[61-63]</sup> give an odds ratio of 12-month abstinence for combination versus single treatment of 1.8 (95%

confidence interval 1.2–2.8).<sup>[60]</sup> In other words, the improvement in abstinence rates with combination treatment versus single NRT is approximately equal to that for any single NRT versus placebo. These results support the utility of combining a fixed-dose formulation (patch) with a formulation that allows individual control over dosing.

## Smoking reduction

Smoking cessation should be the goal for every individual smoker. However, for many heavily dependent smokers the highly addictive nature of cigarette use represents a major obstacle to becoming abstinent.<sup>[37]</sup> It is now recognised that smoking cessation is not a dichotomous process but a continuum involving several stages. Stages of change, the transtheoretical model (TTM) of behaviour, categorises smokers according to their readiness and motivation to quit into five distinct stages (Figure 5).<sup>[65,66]</sup>

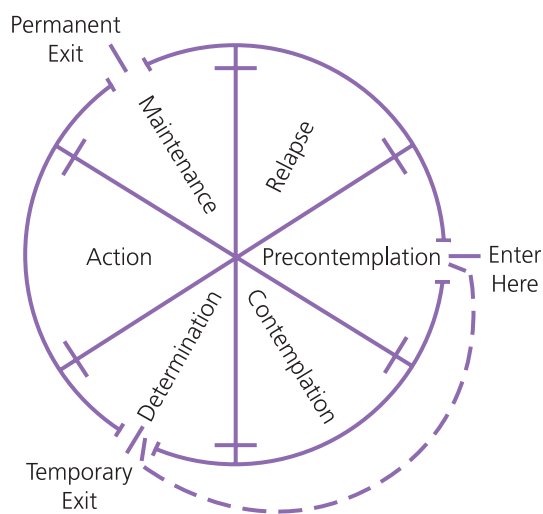


Figure 5. Stages of change model of smokers' behaviour according to readiness and motivation to stop smoking.

Given that only a small proportion of smokers are ready to quit at any one time,<sup>[67]</sup> and many smokers attempt to quit several times before succeeding, clinicians and public health professionals need to consider alternative treatment approaches for smokers who are unable or unwilling to stop smoking.

*Clinical guidelines recommend routine use of NRT during quit attempts*

*Combining fixed-dose plus flexible NRT further improves abstinence rates*

Because disease risk is related to the amount of exposure, the toll of tobacco-related death and disease could be reduced if more smokers were able to reduce smoking.<sup>[68]</sup> Smokers generally try to reduce their cigarette consumption unaided, but most are unable to do so because of withdrawal symptoms and craving. Also, smokers who reduce their smoking unaided tend to compensate by smoking the remaining cigarettes more intensively, with detrimental health consequences.<sup>[69]</sup> However, as NRT effectively controls tobacco withdrawal symptoms and craving, it can be used to reduce smoking.<sup>[70]</sup>

One preliminary study showed that short-term smoking reduction with NRT over a period of 5 weeks was possible, and that the combination of reduced smoking with NRT was well tolerated.<sup>[70]</sup> A long-term study involving 400 smokers confirmed that NRT could achieve and sustain smoking reduction over a period of 2 years.<sup>[71]</sup> As there is no consensus regarding what level of reduction defines 'success', the study by Bolliger *et al.*, selected a reduction in daily cigarette smoking of  $\geq 50\%$  compared to baseline, verified by a reduction in exhaled CO levels. Sustained smoking reduction reduces exposure to tobacco smoke, and may also motivate smokers to quit by gradually allowing them to take control of their smoking.<sup>[70]</sup> Indeed, in the study by Bolliger *et al.*, 10% of subjects in the NRT group (21/200) who stated that they were 'unwilling or unable to stop smoking' at baseline were abstinent at 2 years.

By the beginning of 2001, the use of NRT in smoking reduction had been approved in several European countries. As the regulatory status is changing on an ongoing basis, the local data sheet should be consulted for information on individual countries. Pressure for such change is growing among official bodies. For example, the Ontario Medical Association recently recommended that smokers who are not ready to quit should reduce their smoking as an interim step towards abstinence.<sup>[72]</sup>

## Temporary abstinence

Given the role that nicotine plays in tobacco dependence, and the withdrawal symptoms associated with abstinence from tobacco use, it has been proposed that NRT could control nicotine craving and withdrawal symptoms during situations in which smokers are unable to smoke.<sup>[25]</sup> Tobacco dependence is a medical condition, according to the World Health Organization *International Classification of Diseases*,<sup>[38]</sup> and the American Psychiatric Association lists nicotine withdrawal in the *Diagnostic and Statistical Manual (DSM-IV)*.<sup>[40]</sup> As nicotine withdrawal causes clinically significant symptoms that may occur within 2 hours of smoking the last cigarette,<sup>[73]</sup> smokers who have to abstain from smoking e.g. in the workplace or public places, on long-haul flights, in hospital etc, should have access to treatment that prevents or relieves their discomfort.

The efficacy of NRT in relieving tobacco withdrawal symptoms is well documented<sup>[44,74]</sup> and NRT can be utilised in such situations. The Ontario Medical Association recently recommended that NRT may be useful for smokers who are unable to quit by helping them to abstain from cigarettes in situations where smoking is not permitted.<sup>[72]</sup> By the beginning of 2001, the use of NRT in temporary abstinence had already been approved in several European countries. As the regulatory status is changing on an ongoing basis, the local data sheet should be consulted for information on individual countries.

*The risk of tobacco-related disease is dose dependent. NRT can reduce smoking in individuals unable to quit*

*NRT can control craving and withdrawal symptoms in smokers who are forced to temporarily abstain from smoking*

## Cost-effectiveness of treatment

*In terms of cost-effectiveness, NRT for smoking cessation is the 'gold standard' of healthcare interventions*

The considerable morbidity caused by smoking represents a significant cost burden to healthcare providers. In high-income countries, smoking-related healthcare accounts for 6–15% of all annual healthcare costs.<sup>[75]</sup> There are also significant costs to the economy resulting from absence from work, both in terms of statutory sick pay and other benefits and lost productivity. Effective treatment for tobacco dependence such as NRT can reduce morbidity and mortality from smoking-related disease. For example, cost-effectiveness analyses have shown that smoking cessation is the 'gold standard' of healthcare effectiveness,<sup>[76]</sup> and that using NRT to save life years is far less costly than many other medical interventions. According to current UK estimates, brief advice plus NRT costs £696 per life year saved, compared to a median of £17,000 per life year saved for 310 other medical interventions.<sup>[77]</sup> US figures also show that in comparison with the cost-effectiveness of treating other conditions, the cost per net year of life gained by treating tobacco dependence is relatively inexpensive.<sup>[76,78]</sup>

*Effective treatment for tobacco dependence needs to be made widely and easily available*

## Accessibility of treatment

The public health benefit of treatment for tobacco dependence is a function of efficacy and reach. Although tobacco products, the most deadly form of nicotine delivery, are widely available and largely unregulated, in many countries NRT is stringently regulated.<sup>[79]</sup> In order to reduce tobacco-related death and disease among existing smokers, effective treatment needs to be made widely and easily available. For example, in countries where NRT remains prescription-only, the need to obtain a prescription represents a considerable barrier to access and use. The World Bank<sup>[75]</sup> and WHO<sup>[80]</sup> both support widening the access to effective treatments for tobacco dependence, such as NRT.

Experience from the US demonstrates that increased availability of treatment does translate into public health benefits. In 1996, the Food and Drug Administration approved NRT (nicotine patch and nicotine gum) for over-the-counter (OTC) sale. Since then, it has been estimated that NRT use has increased by 150% compared with prior prescription use, with a corresponding increase in smoking cessation of 10–25% in the entire American population of smokers.<sup>[81]</sup> Those opposed to 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 trials of OTC use to date showed that NRT more than doubled abstinence rates (odds ratio 2.4) compared to placebo under OTC conditions.<sup>[82]</sup>

# Nicotine replacement therapy

## Rationale for development

Tobacco dependence is perpetuated by regular doses of nicotine, which releases a cascade of neurotransmitters to produce stimulation, pleasure and other rewards. Regular smoking results in tolerance to these effects, and the presence of nicotine in the brain becomes necessary to maintain normal function. When tobacco use ceases, the sudden lack of nicotine results in abnormal levels of dopamine, noradrenaline and serotonin, which cause the associated tobacco withdrawal symptoms. NRT substitutes some of the nicotine obtained from smoking, thereby controlling craving and withdrawal symptoms.

## Historical background

In the late 1960s, Dr Ove Fernö, head of research at what is now Pharmacia, was studying why smokers found it so difficult to give up. One of his friends, Dr Claes Lundgren, had noticed that submariners who were not allowed to smoke could cope by switching to chewing tobacco.<sup>[83]</sup> Fernö was convinced that the key to the problem was abstinence from nicotine, and postulated that tobacco craving and withdrawal symptoms could be controlled by providing smokers with nicotine from an alternative source.<sup>[84]</sup> However, pure nicotine is not easy to deliver – nicotine is an unstable compound that rapidly oxidises, and following oral administration the drug undergoes extensive first-pass metabolism.<sup>[85]</sup> Various nicotine delivery forms were tested, and a chewing gum formulation in which nicotine was bound to an ion-exchange resin (to prevent the drug from being released too quickly) soon entered clinical trials. The first NRT product, Nicorette® Gum, was launched on the market by Pharmacia in 1978. Continued clinical development resulted in the introduction of the Nicorette® Patch in 1992, Nicorette® Nasal Spray (1994), Nicorette® Inhalator (1996) and Nicorette® sublingual tablet (1998). The name Nicorette® derives from nicotine delivered in the 'right' (= rätt, in Swedish) way.

## Misunderstandings about NRT

Many smokers and health professionals remain unclear about some of the important differences between NRT and cigarettes, including safety, dependence potential and nicotine content.

### Health risks of nicotine

One of the most common misperceptions surrounds the effect of nicotine on health. Although nicotine addiction sustains tobacco use, it is the other components in tobacco smoke that cause lung cancer, chronic bronchitis and emphysema.<sup>[22]</sup> In other words, people smoke for nicotine but die from tar, carbon monoxide and other harmful gases taken in along with nicotine. Nicotine addiction *per se* does not cause the harm associated with smoking, but tobacco is an extremely contaminated way of obtaining the drug.<sup>[86]</sup> Nicotine has not been shown to cause cancer.<sup>[24,25]</sup> Nicotine does exert some cardiovascular effects, but cigarette smoke also contains numerous other cardiovascular toxins. Cigarette smoking appears to precipitate acute cardiac events by three mechanisms, the most important being production of a hypercoagulable state which promotes thrombosis.<sup>[87]</sup> This seems to be due to the bolus doses of nicotine in cigarette smoke, and does not occur with gradual delivery of nicotine via NRT.<sup>[87]</sup>

### Dependence potential

One frequent question is: "If nicotine is addictive, and cigarette smoking is addictive, won't smokers get addicted to NRT?" It is important to understand that the addictiveness of nicotine largely depends on the dose and the speed of delivery to the brain. Smoking is a uniquely effective form of systemic drug administration, because nicotine is delivered to the pulmonary (rather than the portal or systemic) venous circulation. It takes only 10–20 seconds for nicotine to pass from the cigarette to the brain.<sup>[37]</sup> Cigarettes also contain additives that maximise the rate of delivery, such as ammonia (which increases the pH of smoke, speeding delivery of free nicotine) and theobromine (which dilates the airways, facilitating inhalation).<sup>[88]</sup> Compared to cigarettes, NRT provides lower doses of nicotine, which are delivered more slowly, and NRT has low potential for abuse.<sup>[25,89]</sup>

*When tobacco use stops, the sudden lack of nicotine results in abnormal levels of neurotransmitters, which cause craving and withdrawal symptoms*

*Cancer and respiratory disease are caused by the tar and irritant gases in tobacco smoke*

*Compared to cigarettes, NRT provides lower doses of nicotine, which are delivered more slowly*

## NRT and weight gain after stopping smoking

Transferred dependence may occur, and long-term use of NRT has been reported in a small proportion of abstinent smokers.<sup>[72,90]</sup> Some smokers require prolonged treatment with NRT in order to prevent relapse to smoking, but long-term use of NRT is less harmful than continued tobacco use.<sup>[72]</sup>

### Nicotine content

At first glance, the dose of nicotine contained in NRT seems higher than that in cigarettes. However, there are two key factors to consider: the amount of nicotine in NRT that is actually absorbed, and the real dose of nicotine obtained from cigarettes. For example, although Nicorette® 2 mg chewing gum contains 2 mg nicotine, only half the dose (1.07±0.29 mg) is released on chewing.<sup>[91]</sup> Plus, some of the free nicotine gets swallowed and metabolised by the liver, so the total dose absorbed is less than 1 mg.<sup>[91]</sup> In contrast, the dose of nicotine obtained from a cigarette is often higher than that shown on the packet. Light cigarettes have tiny ventilation holes on the filter that dilute the smoke, and thus reduce nicotine delivery during laboratory machine tests, leading to low advertised nicotine levels.<sup>[92]</sup> But in real life, smokers often cover these holes with their fingers or lips, and/or inhale more deeply and more frequently or smoke more of the cigarette, all of which lead to inhalation of much higher levels of both nicotine and cancer-causing tar.<sup>[92]</sup> All widely marketed cigarettes contain 6–13 mg of nicotine, of which the smoker typically absorbs 1–3 mg, irrespective of the nicotine-yield rating on the pack.<sup>[5]</sup>

### Dosage and duration of treatment

NRT alleviates tobacco withdrawal symptoms by substituting some of the nicotine normally obtained from cigarettes. The degree of relief is related to the dose.<sup>[6]</sup> Many smokers underdose with NRT for various reasons: they may be afraid of becoming dependent on NRT, or falsely believe that nicotine causes tobacco-related disease. Others deny that they are addicted to tobacco, and fail to understand (or admit) that medical treatment is required in order to become abstinent. Whatever the reason, it is important that an adequate dosage of NRT is used to control craving and other withdrawal symptoms in order to prevent relapse to smoking. Similarly, the duration of treatment must be long enough to control symptoms that may persist for several weeks following quitting. Some smokers may require prolonged NRT to remain abstinent.<sup>[72,93]</sup>

Anxiety about weight gain is an important impediment to stopping smoking.<sup>[48]</sup> Many smokers, particularly women, are concerned about their weight and fear that stopping smoking will result in weight gain. Many also believe that the only way to prevent putting on weight after quitting is to start smoking again. However, NRT (particularly nicotine gum) appears to be effective in delaying weight gain following smoking cessation.<sup>[48]</sup> There appears to be a dose-response relationship between gum use and weight suppression; the more gum that a subject uses, the less weight gained.

Concerns about weight gain may prevent smokers from trying to give up. However, although most smokers who stop smoking will gain weight, the majority will put on less than 4.5 kg.<sup>[94]</sup> Smokers should also be reminded that the weight gain associated with stopping smoking represents a negligible threat to health compared to continued smoking.

## Long-term use

The side effects associated with long-term use of Nicorette® Gum 2 mg were investigated as part of the Lung Health Study, a 5-year, multicentre, randomised controlled trial which involved 3,094 smokers.<sup>[90]</sup> Participants (smokers aged 35–60 years with evidence of early stage COPD) were assigned to either intervention (a multicomponent smoking cessation programme, including Nicorette® Gum) or usual care. NRT use was monitored throughout the study.

Over the 5 years of the study, there was no correlation between rates of cardiovascular-related hospitalisation and either the use (or dose) of NRT or concomitant smoking and NRT. Moreover, a protective effect associated with nicotine gum use that dissipated with time was reported. There was no increase in side effects among patients who smoked and used NRT concomitantly. Most of the reported side effects were minor and transient. The authors concluded that long-term use of NRT as used in the Lung Health Study 'appears to be safe and unrelated to any cardiovascular illnesses or other serious side effects'. Although existing long-term data was gained with the gum, long-term use of other NRT products should be equally safe. It should be noted that long-term use of nicotine medications is far preferable to continued long-term tobacco use.<sup>[72]</sup>

## Use in patients with cardiovascular disease

Nicotine increases myocardial oxygen demand, and theoretically this may represent a hazard to patients with pre-existing cardiovascular disease. However, mounting evidence suggests that the low, gradual doses of nicotine supplied from NRT do not pose a risk, even in patients with cardiac disease. Studies of NRT in patients with cardiovascular disease have shown no evidence of increased risk. As part of the 5-year Lung Health Study, more than 3,000 patients with COPD received nicotine 2 mg gum.<sup>[90]</sup> There was no increase in either cardiovascular-related hospitalisation or death in the NRT group, including those who continued to smoke.

Similarly, in two double-blind, randomised, placebo-controlled studies of nicotine patch in cardiac patients, there was no significant increase in the incidence of cardiovascular events with NRT. In one study, 156 patients with coronary artery disease received either transdermal nicotine (14 mg/day) or placebo. After one week, the active dose was increased to 21 mg/day for those patients who had continued to smoke  $\geq 7$  cigarettes. Transdermal nicotine did not affect angina frequency, overall cardiac symptom status or the number of arrhythmias. Furthermore, the rate of withdrawal because of adverse events was greater in the placebo group than in the active treatment group (10% vs 4%;  $p=0.13$ ).<sup>[95]</sup>

In the second study, 584 high-risk outpatients with cardiovascular disease received either transdermal nicotine or placebo for 10 weeks. Over the 14-week monitoring period, cardiovascular-related hospitalisation or death was recorded in 5.4% of the active treatment group, compared to 7.9% of the placebo group.<sup>[96]</sup>

These trials suggest that NRT does not increase cardiovascular risk. The available evidence has been reviewed by Benowitz and Gourlay,<sup>[87]</sup> who concluded that 'the risks of NRT for smokers, even those with underlying cardiovascular disease, are small and are substantially outweighed by the potential benefits of stopping smoking'.

## Pregnancy and lactation

Pregnant smokers should be advised and encouraged to stop smoking completely without pharmacologic treatment.<sup>[94]</sup> However, many pregnant women continue to smoke.<sup>[72]</sup> Cigarette smoking during pregnancy substantially increases the risk of spontaneous abortion, prematurity, low birth-weight and perinatal mortality.<sup>[72]</sup> Although nicotine may have some potentially harmful effect on the foetus, NRT is less hazardous than continued smoking, which exposes the woman and foetus to numerous dangerous toxins.<sup>[72]</sup> Benowitz<sup>[97]</sup> reviewed the evidence and concluded that the benefits of NRT outweigh the risks of continued smoking, but suggests that NRT should only be offered to pregnant women if they are unable to stop smoking without treatment. Pregnant women should only use NRT if advised to do so by their physician, as part of a supervised programme to stop smoking. As nicotine passes into the breast milk, NRT products should be avoided by nursing mothers.

*The risks associated with NRT in patients with cardiovascular disease are small and outweighed by the benefits of stopping smoking*



# Pharmacokinetics of nicotine

## Absorption

Nicotine base is weakly alkaline and is highly soluble in both water and lipids. As nicotine is a weak base, its movement across cell membranes is pH-dependent. There are two principal routes of absorption in smokers, via the lungs and the oral mucosa. Cigarette smoke is acidic (pH around 5.5); at this pH nicotine is mostly ionised and little absorption occurs through the oral mucosa.<sup>[27]</sup> However, once the smoke reaches the large surface area of the small airways and alveoli it is buffered to physiological pH, resulting in much greater and faster absorption of nicotine.<sup>[29,85]</sup> Once nicotine enters the circulation, it distributes rapidly and reaches the brain within 10–20 seconds.<sup>[29]</sup> During cigarette smoking, arterial nicotine levels exceed venous levels by up to tenfold. As peak nicotine concentrations depend on the rate of absorption, the inhalation pattern and pH of smoke are major determinants of plasma nicotine levels in smokers.<sup>[98]</sup>

Because smokers consume many cigarettes during the day there are oscillations between peak and trough plasma nicotine levels, which typically range from 20–40 ng/ml.<sup>[27]</sup> The decline in nicotine levels in the brain between cigarettes provides an opportunity for resensitisation of receptors so that positive reinforcement may occur with successive cigarettes, despite the development of tolerance. Smokers absorb approximately 1 mg of nicotine per cigarette,<sup>[99]</sup> but there is significant interindividual variability in nicotine intake from cigarettes and plasma nicotine levels.

## Distribution

During smoking, nicotine is absorbed extremely rapidly via the pulmonary circulation and reaches the brain faster after inhalation than it would following intravenous administration.<sup>[85]</sup> Absorption is followed by distribution of nicotine to the brain and peripheral tissues.<sup>[29,85]</sup> Plasma protein binding of nicotine is low ( $\leq 5\%$ ) and the volume of distribution is large (2.6 L/kg).<sup>[32]</sup>

*Nicotine reaches the brain faster during cigarette smoking than it would following intravenous administration*

*The high arterial nicotine levels during smoking make cigarettes highly addictive*

## Metabolism

Nicotine is extensively and rapidly metabolised to a number of metabolites. The majority of nicotine (70–80%) is metabolised to cotinine via C-oxidation, and some (around 4%) is metabolised to nicotine N-oxide<sup>[29]</sup> (Figure 6).

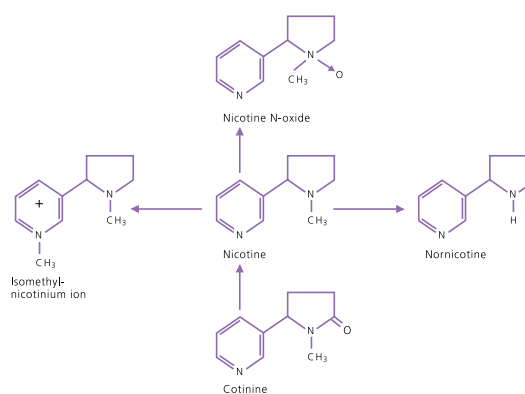


Figure 6. Primary metabolites of nicotine.

Several cytochrome P-450 enzymes play a role in nicotine metabolism, but CYP 2A6 appears to be the principal enzyme involved in the conversion to cotinine.<sup>[29]</sup> The major biotransformation of nicotine occurs in the liver, but some metabolism also occurs in the lungs and brain.<sup>[27]</sup> Since nicotine undergoes extensive first-pass elimination, the drug has low oral bioavailability (around 44%).<sup>[99]</sup>

As the primary metabolite, cotinine, has a half-life of 15–20 hours,<sup>[27]</sup> and its concentration in the bloodstream of smokers is approximately 10 times that of nicotine,<sup>[85]</sup> measurement of plasma cotinine levels is a useful means of assessing abstinence in smokers. Cotinine has little pharmacological activity in humans at concentrations observed in heavy cigarette smokers.<sup>[85]</sup>

## Elimination

Plasma nicotine levels decrease in a bi-exponential manner, with a short distribution half-life of approximately 8 minutes<sup>[99]</sup> and an elimination half-life of around 2–3 hours.<sup>[29]</sup> Nicotine and its metabolites are excreted almost entirely in the urine. Renal excretion of unchanged nicotine is pH-dependent: nicotine clearance increases in acidic urine and decreases in alkaline urine.<sup>[85]</sup> In normal urine, renal clearance is 5–10% of total clearance.<sup>[100]</sup>

## Special populations

### Patients with renal impairment

Progressive severity of renal impairment is associated with decreased renal and non-renal clearance of nicotine. In one study, in which 9 healthy subjects and 13 patients with mild, moderate or severe renal failure received an intravenous infusion of nicotine (0.028 mg/kg) over 10 minutes, total clearance in patients with moderate (glomerular filtration rate  $\leq 36$  ml·min<sup>-1</sup>·1.73<sup>-1</sup>m<sup>2</sup>) or severe (glomerular filtration rate  $< 11$  ml·min<sup>-1</sup>·1.73<sup>-1</sup>m<sup>2</sup>) was approximately 75% and 50%, respectively, of that of the healthy controls.<sup>[101]</sup> Renal clearance of cotinine is also decreased in patients with renal impairment.

### Patients with hepatic impairment

A similar study involving intravenous administration of nicotine (0.028 mg/kg) over 10 minutes to 8 patients with liver cirrhosis and 8 healthy volunteers reported that the pharmacokinetics of nicotine is unaffected in patients with mild liver impairment (Child score 5). However, in patients with moderate liver impairment (Child score 7), total and non-renal clearance of nicotine are decreased by approximately 50% compared to healthy controls.<sup>[101]</sup>

### Elderly

A comparison of the pharmacokinetics of intravenous nicotine 0.028 mg/kg (administered over 10 minutes) to 20 healthy elderly subjects (65–76 years of age) and 20 healthy adults (22–43 years of age) indicated that total clearance and volume of distribution were reduced by approximately 20% in the elderly.<sup>[101]</sup> Changes in nicotine disposition of this magnitude do not necessitate any adjustment of dosage of NRT in the elderly.

# Nicorette® Inhaler

## Rationale

Cigarette smokers become accustomed to the regular hand-to-mouth activity and sensory stimuli provided by smoking. It has been noted that the intensity of nicotine addiction appears to be disproportionate to the subtle rewarding and psychological effects achieved by smoking.<sup>[102]</sup> This may be explained by considering cigarette smoking as a highly reinforced behaviour in which hand-to-mouth movement is rewarded by the stimulant and/or euphoric effects that result from bolus doses of nicotine.

The importance of the sensory component of smoking is illustrated by the observation that pulmonary absorption of nicotine, without accompanying sensory stimuli, is not necessarily effective at reducing craving for cigarettes.<sup>[103]</sup> Moreover, inhalation of dilute citric acid (which mimics the throat sensation of tobacco smoke)<sup>[104]</sup> or smoking nicotine-free cigarettes<sup>[105]</sup> has been shown to reduce the desire to smoke. The satisfaction gained from the citric acid aerosol correlated highly with the intensity of the throat sensations.<sup>[104,106]</sup>

Hand activity related to smoking forms part of an attentional skill; the act of smoking may be either a primary or secondary task, depending on the level of activity required by any accompanying task. In this context, the desire to smoke may be reduced when the hands are already occupied and increased when hand activity is absent.<sup>[107]</sup>

Thus, the wide variety of withdrawal symptoms that occur when smoking ceases result both from the sudden lack of nicotine and the interruption of reinforced smoking behaviour.<sup>[108]</sup> Ideally, both aspects should be addressed if high compliance is to be achieved with nicotine replacement.

Preliminary studies suggested that inhaled nicotine showed promise in the treatment of tobacco dependence.<sup>[109,110]</sup> The Nicorette® Inhaler was specifically designed both to treat the pharmacological dependence and to address the behavioural and sensory stimuli associated with smoking, in order to minimise the difficulties of transition to abstinence.

## Properties

The Nicorette® Inhaler consists of a plastic mouthpiece and a replaceable cartridge which contains a porous polyethylene plug that is impregnated with nicotine (Figure 7). Each plug contains 10 mg of nicotine, of which approximately 4 mg is released during repeated use. At room temperature, one puff on the inhaler releases approximately 13 µg of nicotine in 35 ml of air (compared with one puff of a cigarette, which releases 150–300 µg of nicotine).

The availability of nicotine from the inhaler depends on the volume of air passing through the plug and the environmental temperature.

Nicorette® Inhaler is a unique dosage form of NRT that addresses the behavioural hand-to-mouth component of smoking in addition to the pharmacological aspects of tobacco dependence. It may therefore be particularly useful for highly behaviour-dependent smokers who enjoy the hand activity provided by smoking.

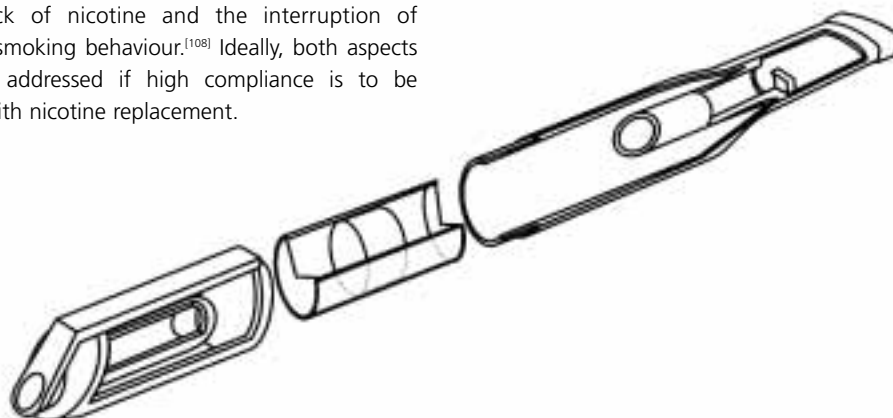


Figure 7. Diagrammatic representation of Nicorette® Inhaler.

*Nicorette® Inhaler was designed to treat tobacco dependence by reproducing the hand-to-mouth activity and sensory stimuli of smoking*

*Nicotine release depends on the volume of air passing through the plug and the environmental temperature*

## Acceptance

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A high level of clinical acceptance is important with nicotine replacement in order to ensure good compliance. Compliance with treatment translates into adequate control of withdrawal symptoms and craving, and effective treatment of tobacco dependence.

Preliminary double-blind testing of Nicorette® Inhaler using menthol at concentrations of 0, 2, 5 or 10% (in relation to the nicotine content) as a flavouring agent was performed in 25 healthy volunteer smokers to determine the optimal concentration of menthol. Evaluation of acceptability showed that this was maximised with 10% menthol<sup>[101]</sup> and this concentration is used in the commercial product.

In summary, the advantages of the inhaler include:

- behavioural replacement through regular hand-to-mouth activity
- sensory characteristics that resemble those of smoking
- *ad libitum* dosage to meet individual needs
- highly acceptable route of administration.

# Pharmacokinetics of Nicorette® Inhaler

## Absorption and bioavailability

Two criteria were studied with regard to their effect on the bioavailability of nicotine from Nicorette® Inhaler:

- release of nicotine from the cartridge at various temperatures
- inhalation technique.

### Effect of temperature on release of nicotine

As it is likely that Nicorette® Inhaler will be used at various environmental temperatures, the effect of three different temperatures (20, 30 and 40°C) on nicotine release was investigated.<sup>[111]</sup> The maximal plasma concentrations were also determined at each temperature. In a three-way crossover study, 18 volunteer subjects (who smoked >10 cigarettes per day) inhaled deeply from an inhaler every 15 seconds for 20 minutes (a total of 80 inhalations). This was repeated every hour for 10 hours at each temperature. Pharmacokinetic parameters were determined during the last dosing interval.

The effects of temperature on maximal plasma nicotine concentrations ( $C_{max}$ ) and the area under the plasma concentration-time curve during the last dosing interval ( $AUC_{10-11}$ ) are shown in Figure 8. As the temperature increased, the AUC increased from 20.5 ng/ml-h at 20°C to 26.5 ng/ml-h at 30°C and to 30.3 ng/ml-h at 40°C. Despite these rises,  $C_{max}$  levels attained by this intensive use (22.5 ng/ml, 29.7 ng/ml and 34.0 ng/ml, respectively) were no higher than those achieved when smoking.

### Absolute bioavailability and effect of inhalation technique

The effects of pulmonary or buccal modes of inhalation on plasma nicotine levels were compared in a three-way crossover study.<sup>[112]</sup> Fourteen volunteer smokers inhaled nicotine vapour for 20 minutes, using either deep inhalations (pulmonary mode, 80 inhalations) or shallow puffing (buccal mode, 600 puffs), and repeated the procedure every hour for 11 hours. The volume of air inhaled was measured using a gas-volume meter. Following each inhalation method, the mean amount of nicotine released over the 20-minute period was calculated by weighing the cartridge before and after use. The mean dose of nicotine released was  $3.87 \pm 0.75$  mg during pulmonary inhalation and  $4.0 \pm 0.60$  mg during buccal inhalation. The AUC during the final dosing interval was 30.9 ng/ml-h (pulmonary) and 29.5 ng/ml-h (buccal), indicating an absolute bioavailability of 56% and 51%, respectively, for each mode of use. The intensive inhaler use in this study generated plasma nicotine levels similar to those observed with smoking. However, during normal use, the plasma nicotine levels attained with Nicorette® Inhaler are less than half those achieved during smoking (figure 8).

Another study estimated the dose of nicotine released during use to be 2.7 mg.<sup>[101]</sup> However, it is likely that the subjects in the study described above<sup>[112]</sup> were inhaling more efficiently because of increased focus on the importance of inhalation technique, which may explain the apparent discrepancy between the study results.

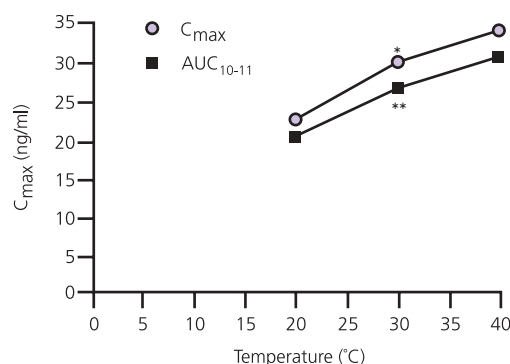


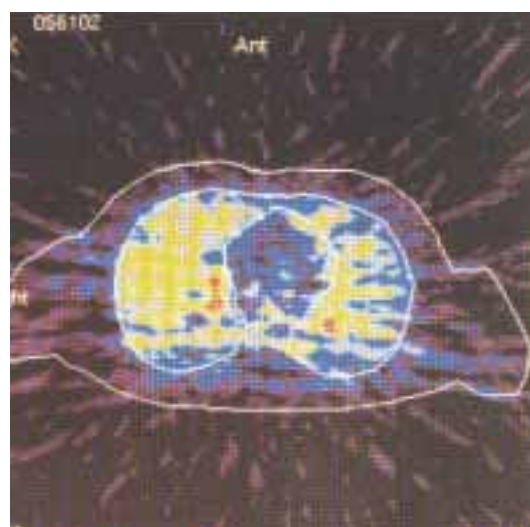
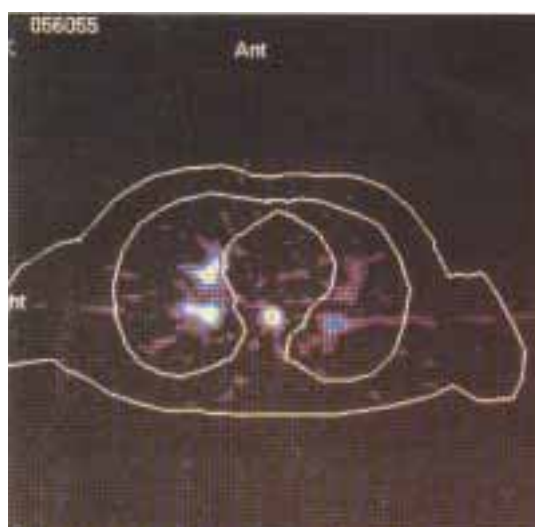
Figure 8. Effect of environmental temperature on maximum plasma nicotine concentration ( $C_{max}$ ) and area under the concentration-time curve (AUC) after administration of Nicorette® Inhaler 10 mg (deep inhalations every 15 s for 20 min, every hour for 10 h) in 18 volunteers; \* $p < 0.001$  vs 20°C,  $p = 0.032$  vs 40°C; \*\* $p < 0.002$  vs 20°C,  $p = 0.036$  vs 40°C.

*Inhalation technique (deep or shallow) does not affect either the bioavailability or deposition of nicotine*

### Effect of inhalation technique on site of absorption

The effect of different inhalation modes on the deposition and site of absorption of nicotine was investigated in a two-way crossover study.<sup>[113]</sup> Six healthy volunteers (who smoked >10 cigarettes/day) inhaled radio-labelled <sup>11</sup>C-nicotine for 5 minutes from Nicorette® Inhaler, either by deep inhalation (pulmonary mode) or shallow puffing (buccal mode).

Table 2. Almost half of the dose was deposited in the oral cavity, and a further 10% in the oesophagus. Only a small amount (5%) was deposited in the lung. Although there was large interindividual variation, the general pattern was consistent, with no difference between the two inhalation techniques.



*Nicotine from the Nicorette® Inhaler is absorbed in the mouth and upper airways*

Figure 9. Cross-sectional tomographic images of the chest at heart level obtained after inhalation of <sup>11</sup>C-nicotine, average of the first 15 minutes. *Left image* shows the radioactivity distribution after inhalation from the vapour inhaler; *right image* shows the radioactivity distribution after smoking a cigarette. With the vapour inhaler only deposition in the large bronchi and oesophagus can be identified, whereas with the cigarette a uniform distribution over the lungs is seen.<sup>[113]</sup>

The deposition of <sup>11</sup>C-nicotine in the upper airways and lung was visualised using positron emission tomography (Figure 9). An average of 15% (range 6.0–25.1%) of the total radioactivity was released over a 5-minute period. The deposition of <sup>11</sup>C-nicotine following pulmonary and buccal inhalation is shown in

This study demonstrates that during use of Nicorette® Inhaler nicotine absorption takes place in the mouth and upper airways, with less than 5% occurring in the lungs. Consequently, the rapid, high arterial nicotine levels observed after smoking do not occur with the inhaler (see *below*).

Table 2. Deposition of radioactivity after inhalation of <sup>11</sup>C-nicotine in different organs and tissue compartments, expressed as a percent of radioactivity.<sup>[113]</sup>

Mode of inhalation	Deposition of radioactivity (%)							
	Oral (6.5 min)	Whole body soft tissue (6.5 min)	Trachea (10 min)	Oesophagus (10 + 15 min)	Bronchi (10 min)	Lungs (15 min)	Oral (50 min)	Whole body soft tissue (50 min)
Pulmonary	40.1 ± 9.0	15.2 ± 9.8	1.6 ± 0.4	10.6 ± 4.4	2.3 ± 1.7	6.2 ± 4.0	7.0 ± 5.1	64.3 ± 26.7
Buccal	49.4 ± 9.9	12.1 ± 21.7	0.7 ± 0.3	9.2 ± 2.9	1.0 ± 1.2	4.5 ± 3.1	8.4 ± 5.2	55.7 ± 23.6
Total	44.8 ± 10.3	13.7 ± 16.1	1.1 ± 0.6	9.9 ± 3.6	1.7 ± 1.6	5.4 ± 3.5	7.7 ± 4.9	60.0 ± 24.4

### Comparison of Nicorette® Inhaler vs cigarettes

A single-dose, crossover trial was used to investigate whether inhaled nicotine from Nicorette® Inhaler is absorbed into the pulmonary circulation.<sup>[114]</sup> Seven volunteers inhaled nicotine every 15 seconds for 5 minutes (20 inhalations) and smoked one cigarette over 5 minutes. Serial arterial (from brachial artery) and venous blood samples taken before, during and after each treatment showed that arterial plasma nicotine concentrations increased rapidly after cigarette smoking, reaching a peak of 49.2 ng/ml within 5 minutes (Figure 10).

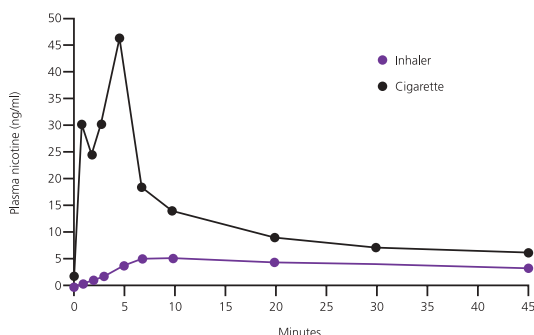


Figure 10. Mean arterial plasma nicotine concentrations in 7 subjects who used a nicotine inhaler every 15 sec for 5 min (20 inhalations) and smoked one cigarette for 5 min with evenly spaced puffs.<sup>[114]</sup>

In contrast, following inhaler use, arterial plasma nicotine rose much more slowly and peaked at 5.9 ng/ml. These results also indicate negligible pulmonary absorption with the Nicorette® Inhaler.

### Comparison of Nicorette® Inhaler vs Nicorette® Gum

Plasma nicotine concentrations achieved with Nicorette® Inhaler were compared with those using the Nicorette® Gum 2 mg in an open, randomised crossover study.<sup>[101]</sup> On two separate occasions, 18 volunteer smokers (>10 cigarettes/day) underwent repeated, intensive dosing with the inhaler (deep inhalation every 15 seconds for 20 minutes, repeated every hour for 10 hours) and the nicotine 2 mg gum (chewing every 2 seconds for 20 minutes, repeated every hour for 10 hours). The mean  $C_{max}$  and AUC achieved with the inhaler were more than double those with the gum ( $C_{max}$ , 26 ng/ml vs 11 ng/ml; AUC<sub>10-11</sub>, 24 ng/ml·h vs 10 ng/ml·h), but the  $t_{max}$  was comparable for both formulations.

### Degree of nicotine substitution

One randomised, placebo-controlled crossover study of *ad libitum* use of Nicorette® Inhaler during 2 consecutive days (19 volunteer smokers were instructed to use 5–15 cartridges per day) reported that pulmonary and buccal modes of inhalation resulted in comparable steady-state plasma nicotine concentrations (6.6 and 6.8 ng/ml, respectively).<sup>[108]</sup> During 2 days of normal smoking, the mean plasma nicotine concentration was 20.4 ng/ml, indicating that the degree of nicotine substitution with the inhaler was approximately 30%.

Similar results were obtained in an open, multiple dose study which compared *ad libitum* inhaler use with normal smoking.<sup>[101]</sup> Mean plasma nicotine levels were 16–18 ng/ml during smoking, compared to 5–6 ng/ml during inhaler use, confirming that the inhaler achieves approximately 30% of the plasma nicotine levels produced by smoking.

Nicorette® Inhaler does not produce the rapid, high arterial nicotine levels observed with cigarette smoking

During *ad libitum* use, nicotine substitution with Nicorette® Inhaler is approximately one-third that during smoking

# Clinical efficacy

## Abstinence rates

The clinical efficacy of Nicorette® Inhaler has been evaluated in six randomised, double-blind, placebo-controlled studies, involving a total of 1,440 nicotine-dependent smokers in Denmark, Sweden and the United States (Table 3). Active and placebo inhalers were identical in appearance. In each study, treatment could be used *ad libitum* for up to 3 months, after

instructed regarding optimal use of the inhaler and the need for adequate use (i.e. sufficient cartridges per day to control craving and withdrawal symptoms) was emphasised. The high compliance rate in the Tønnesen study (more than 80% of subjects used >2 cartridges per day) compared to the US studies probably explains the differences in study outcome.

*Adequate use of Nicorette® Inhaler is important for quit attempts to succeed*

Table 3. Complete, sustained abstinence rates from week 2 onwards in six randomised, placebo-controlled studies of the Nicorette® Inhaler

Dosage	Country (no. of study participants)	Abstinence rates (%)											
		6 weeks			3 months			6 months			12 months		
		N	PI	p	N	PI	p	N	PI	p	N	PI	p
2-10 cartridges per day, <i>ad libitum</i>	USA (n=223) <sup>[101]</sup>	33	33	NS	22	30	NS	14	20	NS	12	18	NS
	USA (n=241) <sup>[101]</sup>	28	25	NS	21	18	NS	17	15	NS	13	14	NS
	Denmark (n=286) <sup>[115]</sup>	28	12	0.001	21	9	0.007	17	8	0.02	15	5	0.004
4-20 cartridges per day, <i>ad libitum</i>	USA (n=222) <sup>[116]</sup>	45	14	<0.005	31	8	<0.005	21	6	0.003	11	5	NS
	USA (n=223) <sup>[117]</sup>	29	14	0.01	24	10	0.005	17	9	NS(0.08)	13	8	NS
	Sweden (n=247) <sup>[118]</sup>	46	33	<0.05	37	23	<0.05	35	19	<0.005	28	18	<0.05

Abbreviations: N = nicotine inhaler; PI = placebo inhaler; p = significance value; NS = not significant

which subjects had the option to gradually reduce the dosage over a period of 3 months. Follow-up was performed at 12 months. Complete, sustained abstinence from smoking was measured using investigators' case reports, subjects' diaries and expired carbon monoxide (<10 ppm).

In the first three studies, treatment consisted of *ad libitum* usage of 2–10 cartridges per day (Table 3).<sup>[101,115]</sup> However, this restriction on dosage resulted in underdosing in the two US studies, with many subjects in one of the trials reporting that they only used 1 inhaler cartridge per day. Treatment use was higher in the Danish study, which showed Nicorette® Inhaler to be significantly superior to placebo at all time points up to and including 12 months.<sup>[115]</sup> In the Tønnesen study, all subjects were

Based on the experience of inadequate treatment use and ensuing results from these three studies, subsequent study protocols stipulated the following criteria:

- use of a minimum of 4 cartridges per day in order to adequately control craving and withdrawal symptoms
- correct use of Nicorette® Inhaler to be emphasised.

Three studies were subsequently performed using a higher recommended dosage than that used in the early studies.<sup>[116-118]</sup> The studies were identical in design. Subjects were instructed to use at least 4 cartridges regularly throughout the day for at least 6 weeks.



The 6-month complete, sustained abstinence rates were more than doubled in the Nicorette® Inhaler treatment groups (17–35%) compared to placebo (6–19%). Abstinence rates were also consistently higher at the 12-month follow up (active 11–28%, placebo 5–18%) [Table 3]. The 6-month complete, sustained abstinence rates were significantly greater with Nicorette® Inhaler than placebo in two of the three studies ( $p < 0.05$ ). At one year, the Nicorette® Inhaler remained significantly superior to placebo in one of the studies (Figure 11).<sup>[118]</sup> Although 12-month abstinence rates with Nicorette® Inhaler were also greater than placebo in the other two studies, the difference was no longer significant,<sup>[116,117]</sup> however, these two studies were powered to detect significant difference at 6 weeks.

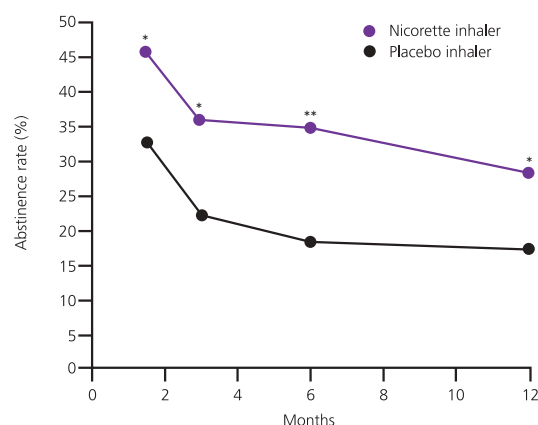


Figure 11. Comparison of the abstinence rates achieved at various time points up to 12 months in subjects who used either a nicotine inhaler ( $n=123$ ) or placebo inhaler ( $n=124$ ) *ad libitum* for 6 months; \*  $p < 0.05$ , \*\*  $p < 0.005$ , vs placebo.<sup>[118]</sup>

### Efficacy summary

A meta-analysis of all six placebo-controlled studies, in which the main outcome measure was complete abstinence from week 2 onwards, showed that Nicorette® Inhaler was significantly superior to placebo inhaler at all time points up to 1 year.<sup>[101]</sup> Analysis of the three later studies, which used the currently recommended dosage,<sup>[116-118]</sup> showed that use of Nicorette® Inhaler increased the Odds Ratio at 12 months of complete abstinence to 1.79 (95% Confidence Interval 1.15–2.78,  $p=0.009$ ). In a recent review, Silagy *et al.*<sup>[7]</sup> also concluded that Nicorette® Inhaler doubles successful quit rates compared to placebo.

### Effects on craving and withdrawal symptoms

Craving for nicotine plays an important role in maintaining tobacco dependence and causing relapse even when pharmacological withdrawal has been overcome.<sup>[119]</sup> One study therefore addressed the efficacy of Nicorette® Inhaler in controlling craving and tobacco withdrawal symptoms.

Fifteen volunteer smokers (smoking 12–30 cigarettes/day) participated in a randomised, placebo-controlled, crossover study to assess the effect of Nicorette® Inhaler on craving and withdrawal symptoms.<sup>[108]</sup> The study comprised three 2-day treatment periods: pulmonary inhalation using the inhaler, buccal inhalation using the inhaler and normal cigarette smoking. The inhaler could be used *ad libitum* (5–15 cartridges/day). Craving (urge to smoke, missing cigarettes) and withdrawal symptoms (irritability, impatience, difficulty concentrating and dizziness) were rated nine times over each 2-day period on a visual analogue scale.

Compared to placebo, Nicorette® Inhaler significantly reduced total craving scores at all time points ( $p < 0.005$ ). Both inhalation techniques (pulmonary or buccal) were equally effective at controlling craving (Figure 12). Active treatment was also superior to placebo at reducing withdrawal symptoms.

A meta-analysis of six comparative clinical studies shows that Nicorette® Inhaler significantly improves abstinence rates compared to placebo

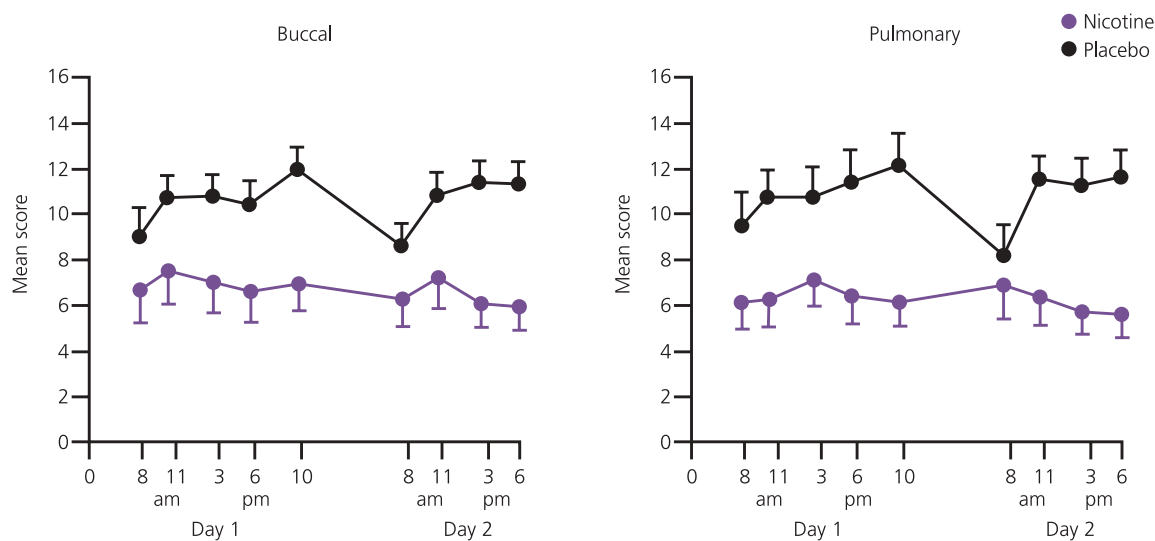


Figure 12. Comparison between the effect of inhaled nicotine or placebo on total craving score (mean  $\pm$  SEM), measured on a visual analogue scale, in 15 volunteers who used either buccal or pulmonary modes of inhalation.<sup>[108]</sup>

*Buccal and pulmonary inhalation are equally effective at controlling craving and withdrawal symptoms*

Plasma nicotine levels were similar with both the pulmonary and buccal modes of inhalation. There was a strong correlation between plasma nicotine levels and relief of craving, with a significant inverse relationship between plasma nicotine concentration and 'urge to smoke' (buccal mode  $p=0.006$ , pulmonary mode  $p=0.001$ ) and 'missing cigarettes' (buccal  $p=0.008$ , pulmonary  $p=0.048$ ). Thus, craving and withdrawal symptoms can successfully be controlled using either method of inhalation.

One of the large clinical studies also evaluated the effect of Nicorette® Inhaler on craving and withdrawal symptoms.<sup>[118]</sup> The results showed that total withdrawal symptoms were significantly reduced among the active treatment group during the first 2 days of treatment ( $p=0.01$  vs placebo). Similarly, the 'urge to smoke' was also significantly lower in those receiving the active inhaler ( $p=0.006$  vs placebo).

## Compliance

Treatment acceptability was measured in all six comparative clinical trials and was shown to be significantly greater with Nicorette® Inhaler than placebo in each study ( $p<0.005$ ). For example, in the study by Hjalmarsen *et al.*,<sup>[118]</sup> Nicorette® Inhaler was rated more highly than placebo as an aid to stopping smoking ( $p<0.001$ ). At 3 months, only 10% of subjects were still using the placebo inhaler, compared to 33% using the active inhaler ( $p=0.001$ ); 6-month usage rates were 3% and 16%, respectively. Treatment use during weeks 1 to 6 remained constant among those receiving the active treatment (mean number of cartridges per day  $6.4\pm 2.9$  and  $6.0\pm 2.9$ , respectively), whereas there was a significant decrease in consumption from week 1 to week 6 among those using placebo inhalers ( $6.3\pm 2.7$  and  $4.9\pm 2.5$ , respectively;  $p<0.001$ ).

# Safety

## Transferred dependence and abuse potential

### Adverse events

No serious systemic treatment-related adverse events have been reported to date with Nicorette® Inhaler. In clinical trials, the most common systemic adverse events were headache (nicotine inhaler 26%, placebo 20%), gastrointestinal discomfort (14% vs 8%) and nausea (10% vs 7%).<sup>[101]</sup>

Local adverse events are common during the first few days of treatment, but these are generally mild and diminish during repeated use. The most frequent are cough and irritation in the mouth and throat.<sup>[116-118]</sup> The mode of inhalation does not appear to influence the incidence of local adverse events; one study which compared pulmonary and buccal modes reported a similar incidence of sore throat (27%) in both groups.<sup>[108]</sup>

Existing post-marketing surveillance data support a favourable safety profile for Nicorette® Inhaler, which was first launched in 1996. A review of spontaneous adverse events reported has not revealed any change in the adverse event profile or the incidence of adverse events compared to that reported during clinical studies.<sup>[101]</sup>

The abuse potential of nicotine is closely linked to the route of administration and resulting pharmacokinetic profile. Important factors include the speed of onset of drug effect, peak plasma level and arterial/venous plasma ratio.<sup>[120]</sup> In contrast with cigarettes, Nicorette® Inhaler does not produce rapid, high arterial plasma nicotine concentrations, and the potential for abuse is low. One expert on the use of NRT recently concluded that 'evidence of nicotine replacement product abuse is essentially non-existent'.<sup>[121]</sup>

In clinical studies to date, the number of cartridges used per day has declined over the study period, indicating a low potential for transferred dependence with Nicorette® Inhaler.<sup>[115-118]</sup> Although 10% of subjects were still using the inhaler at 6 months, this is not necessarily a reflection of dependence on the treatment – some ex-smokers may require extended treatment with nicotine replacement in order to prevent relapse to smoking.<sup>[121]</sup>

*Local adverse events are generally mild and decrease during continued use of Nicorette® Inhaler*

# Product information

The local product information should be consulted for full information.

## Characteristics of Nicorette® Inhaler

The Nicorette® Inhaler comprises a mouthpiece containing a cartridge with a porous polyethylene plug, impregnated with 10 mg of nicotine plus a flavouring agent (menthol). As air is drawn through the plug it becomes saturated with nicotine. Each puff releases approximately 13 µg of nicotine at room temperature.

## Instructions for use

Nicorette® Inhaler acts by relieving craving and withdrawal symptoms and is indicated in the treatment of tobacco dependence.

In order to assemble the inhaler for use, the shaped mouthpiece is separated into two parts and a sealed cartridge (a tube containing the nicotine-impregnated plug) is inserted into the mouthpiece. When the mouthpiece is re-assembled, the seals on both ends of the unit are broken. Nicorette® Inhaler is then ready for use. The mouthpiece can be reused with new cartridges, and each blister tray contains 6 cartridges. Open cartridges should be used within 12 hours.

## Dosage and administration

Nicorette® Inhaler should be used whenever there is an urge to smoke. The inhalation technique is not important; shallow puffing (similar to using a pipe) or deep inhalation (like smoking a cigarette) result in similar plasma nicotine levels, provided the same amount of air has been drawn through the plug. The frequency and duration of inhalations and the inhalation technique can be varied according to individual preference. In order to provide adequate nicotine replacement, it is recommended that 6–12 cartridges are used per day.

The amount of nicotine obtained from the inhaler depends on the temperature; in colder temperatures, the inhaler has to be used for a longer period of time to achieve the same effect as a shorter period of use at a higher temperature.

For smoking cessation it is recommended that the full dosage of Nicorette® Inhaler should be continued for at least 3 months. The dose should then be tapered by gradually reducing the total number of inhaler cartridges per day, and treatment should be stopped once the dose is reduced to 1–2 cartridges/day. Any spare cartridges should be retained as craving may occur after treatment has been discontinued.

For temporary abstinence, the inhaler should be used during smoke-free periods, such as smoke-free areas or other situations when the smoker wishes to avoid smoking.

For smoking reduction, the inhaler should be used between smoking episodes to prolong smoke-free intervals, with the intention of reducing smoking as much as possible. If a reduction in the number of cigarettes per day has not been achieved within 6 weeks, the smoker should consider seeking advice from a health professional. Individuals who reduce their smoking should make a quit attempt as soon as they feel ready, and not later than 6 months after commencing treatment. Smokers who are unable to make a serious quit attempt within 9 months should seek professional advice.

It is not generally recommended that regular inhaler usage continues beyond 6 months. However, some ex-smokers may require extended treatment in order to avoid relapse to smoking.

Nicorette® Inhaler should not be administered to children or adolescents under 18 years of age without recommendation from a physician.

## Contraindications and warnings

The product should not be used by individuals with a known hypersensitivity to nicotine or menthol. Other contraindications include use in patients with recent (in the preceding 3 months) myocardial infarction, unstable or progressive angina pectoris, Prinzmetal's variant angina, severe cardiac arrhythmias or stroke in the acute phase.

It should be used with caution in patients with severe cardiovascular disease (e.g. occlusive peripheral arterial disease, cerebrovascular disease, stable angina pectoris, uncompensated heart failure), vasospasms, active duodenal or gastric ulcers, uncontrolled hypertension, severe/moderate hepatic impairment, severe renal impairment, chronic throat diseases or asthma. However, the risk of using NRT should be weighed against the risk of continued smoking.

As nicotine (both from NRT and tobacco) causes the release of catecholamines from the adrenal medulla, Nicorette® Inhaler should also be used with caution in patients with hyperthyroidism or phaeochromocytoma.

Patients with diabetes mellitus may need to reduce their dose of insulin as a result of stopping smoking.

As nicotine passes to the foetus and may affect its breathing movements and circulation, pregnant smokers should always be advised to stop smoking completely without using NRT. However, the risk of continued smoking may pose a greater hazard to the developing foetus than the use of NRT in a supervised treatment programme. Use of Nicorette® Inhaler by the pregnant highly nicotine-dependent smoker should only be initiated following advice from a physician. The product should be avoided by nursing mothers as nicotine passes into the breast milk and may affect the infant.

Transferred dependence may occur, but use of pure nicotine is less harmful than use of tobacco.

If a child swallows, chews or sucks the nicotine plug (used or unused), there is a risk of poisoning the child.

## Interactions

Smoking (but not nicotine) increases the activity of CYP 1A2, and clearance of some drugs metabolised by this enzyme may be reduced after stopping smoking. This may result in an increase in plasma levels, with clinical implications for drugs that have a narrow therapeutic window, such as theophylline, clozapine, tacrine. Plasma concentrations of other drugs partially metabolised by CYP 1A2, such as imipramine, olanzapine, clompiramine and fluvoxamine, may also increase following smoking cessation. The metabolism of flecainide and pentazocine may also be induced by smoking.

## Adverse effects

Nicorette® Inhaler may cause adverse reactions, which are mainly dose-dependent. Up to 40% of users may initially experience mild local reactions such as cough and irritation in the mouth and throat, but these decrease during continued use. Common (>1/100) adverse effects comprise headache, gastrointestinal discomfort, hiccups, nausea, vomiting, cough, irritation in the mouth and throat and nasal congestion. Less common effects (1/100-1/1,000) include palpitations. Rare adverse events (<1/1,000) comprise reversible atrial fibrillation.

Some symptoms e.g. dizziness, headache and sleeplessness, may actually be withdrawal symptoms associated with abstinence from smoking. The incidence of aphthous ulcers may increase after stopping smoking, although the reason is unclear.

## Overdose

Excessive ingestion of nicotine from either NRT and/or smoking may result in symptoms of overdose. Doses of nicotine that are tolerated by adult smokers during treatment with NRT may produce symptoms of poisoning in young children and may be fatal.

Symptoms of nicotine overdose include nausea, salivation, abdominal pain, diarrhoea, sweating, headache, dizziness, disturbed hearing and marked weakness. High doses may result in hypotension, weak and irregular pulse, breathing difficulties, prostration, circulatory collapse and general convulsions.

Any overdose should be managed by immediately stopping administration of nicotine and treatment of symptoms. Tachycardia causing circulatory impairment may require treatment with a beta-blocker. Excitation and convulsions may be treated with diazepam. Mechanically assisted ventilation should be instituted if necessary.

## Advice for health professionals

Quitting smoking involves personal motivation and a commitment from smokers, and this may be combined with input from health professionals, including physicians and pharmacists. NRT products such as Nicorette® Inhaler should be supported with comprehensible patient information leaflets as well as counselling and treatment follow-up in order to help stop smoking.

Health professionals have an important role in explaining the concept of nicotine replacement, outlining treatment goals and instructing patients on the correct use of Nicorette® Inhaler. Advice should include:

- explanation of the role of nicotine in tobacco dependence and the reasons why pharmacological addiction makes it difficult to quit smoking
- the rationale behind the use of NRT in the treatment of tobacco dependence
- a description of the various tobacco withdrawal symptoms and how these may be overcome, both pharmacologically and psychologically.

By evaluating baseline nicotine dependence, health professionals can determine the appropriate dosage of Nicorette® Inhaler for individual smokers. Guidelines for the optimal use of Nicorette® Inhaler include:

- explaining the objectives of the inhaler and demonstrating how to use it correctly
- emphasising the need for adequate nicotine substitution in order to control tobacco withdrawal symptoms and craving
- explanation of the most common local adverse events and that these are likely to decline during repeated use
- stressing the importance of continued treatment use throughout the treatment period
- an explanation of how to taper the dosage after completing 3 months' treatment
- stressing that it is not easy to achieve abstinence and that smokers must be highly motivated in order to succeed.

Further information and guidance for health professionals on the use of NRT can be obtained from the comprehensive smoking cessation guidelines recently published in England<sup>[49]</sup> and the United States.<sup>[48]</sup>

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