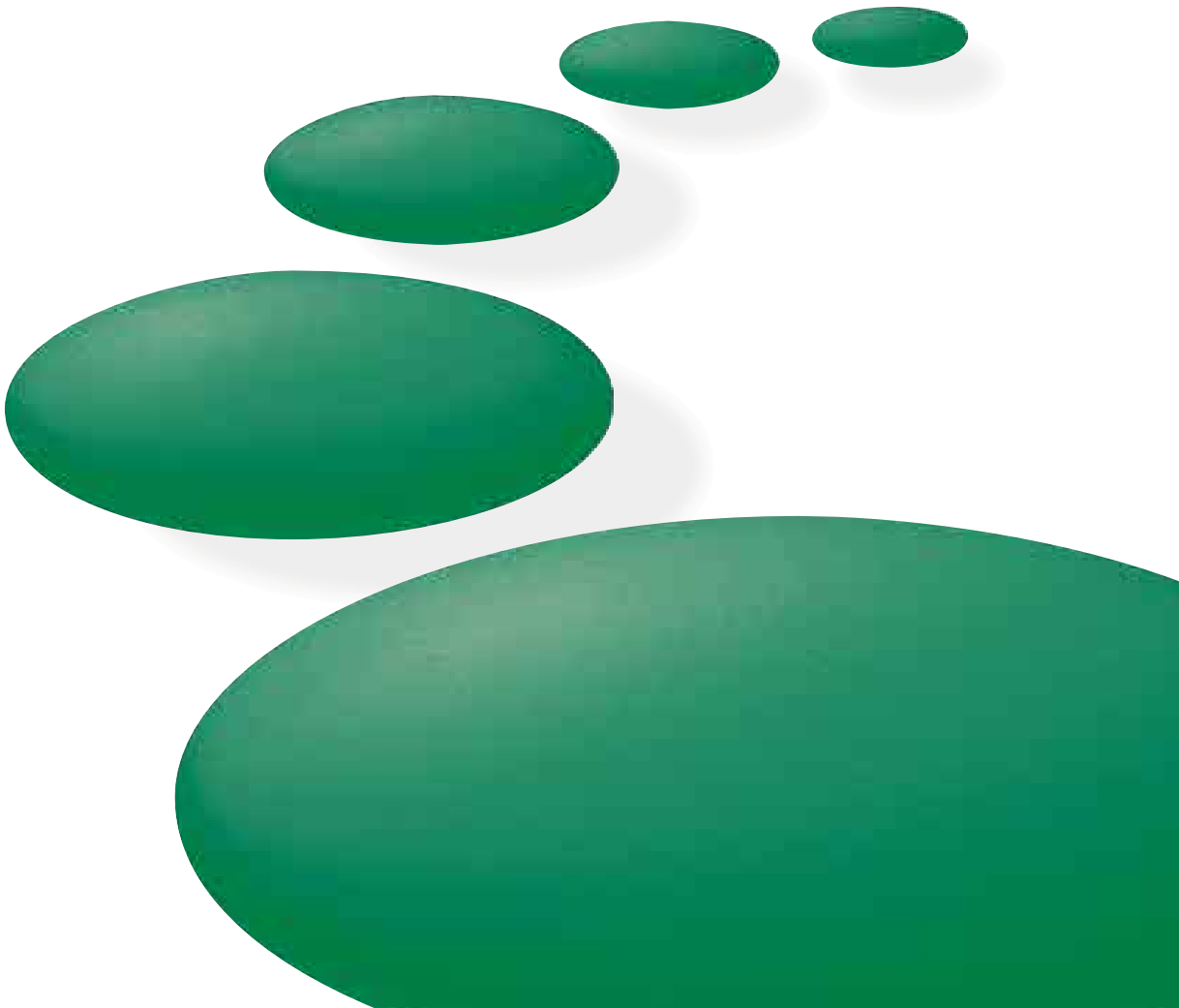
# nicorette®
## gum

## product monograph



# Contents

# Nicorette® Gum: summary

Nicorette® Gum provides relief of the craving and withdrawal symptoms associated with tobacco dependence. It is a sugar-free chewing gum formulation that provides user-controlled nicotine release for oral absorption. Nicorette® Gum can be chewed whenever there is an urge to smoke. It is available in original, mint and citrus flavours. The gum is also available in two strengths, low (2 mg) and full (4 mg) strength, the latter for highly dependent smokers or those who fail to stop smoking with the 2 mg gum.

## Characteristics

Each piece of Nicorette® Gum contains 2 mg or 4 mg of nicotine bound to an ion-exchange resin, which permits slow release of nicotine, and an alkaline hydrocarbonate buffer, which increases the oral absorption of nicotine by increasing salivary pH to 8.5. The chewing gum formulation of Nicorette® provides readily absorbed nicotine and some oral gratification.

## Dosage and administration

Nicorette® Gum should be chewed according to the instructions in the package leaflet whenever there is an urge to smoke. The dosage should be individualised according to the smoker's nicotine dependence. Highly dependent smokers (FTND ≥6 or smoking ≥20 cigarettes/day) and those who have failed to quit when using the 2 mg gum should use the 4 mg strength. Otherwise, subjects should use the 2 mg dosage.

Sufficient gum, usually 8–12 pieces, but no more than 24, should be used each day. Gum use should continue for at least 3 months, then be reduced gradually to 1–2 pieces per day, at which point treatment should be discontinued. Spare gum should be retained in the event of sudden cravings. Regular use of the gum beyond 12 months is generally not recommended, although some ex-smokers may require prolonged treatment in order to avoid relapse to smoking.

## Pharmacokinetics

Depending on the rate and intensity of chewing and the amount of saliva produced, approximately 75% of the nicotine contained in Nicorette® Gum is released during 30 minutes of chewing.

Individuals generally chew fewer pieces of Nicorette® Gum than the number of cigarettes they smoke, and thus plasma nicotine concentrations attained are approximately one-third (2 mg dose) and two-thirds (4 mg dose) of those achieved by smoking. However, chewing Nicorette® 4 mg gum on an hourly basis may result in plasma nicotine concentrations comparable to those attained by smoking. There is little risk of transferred dependence because there are no pronounced peaks in blood nicotine concentration.

## Clinical efficacy

**Craving and withdrawal symptoms**

Studies have shown that Nicorette® Gum reduces the incidence and severity of tobacco withdrawal symptoms, such as irritability, anger and impatience, more effectively than placebo. Nicorette® Gum has also been shown to markedly reduce the incidence and severity of hunger, which may persist for several weeks or months after quitting.

**Cessation rates**

A meta-analysis of 48 studies that compared smoking cessation rates with nicotine gum or placebo reported that 18% of subjects receiving nicotine chewing gum were abstinent at 12 months, compared to 11% in the group using placebo gum. The odds ratio of abstinence for nicotine gum was 1.63 compared to placebo. Trials that directly compared the 2 mg versus 4 mg gum in highly dependent smokers found a significant benefit in favour of the 4 mg strength (odds ratio 2.67, 95% confidence interval 1.69 to 4.22).

## Safety

Nicorette® Gum used at the recommended dose has not been found to cause any serious adverse events. Nicotine from the gum may sometimes cause slight throat irritation and increased salivation at commencement of treatment. Excessive swallowing of dissolved nicotine may cause hiccups.

The most frequently reported adverse events are gastrointestinal disturbances (including nausea and vomiting, borborygmus and hiccups), headache, dizziness, and local adverse events (sore mouth or throat and jaw ache). Less frequent adverse events include palpitations, erythema and urticaria.

# Other Nicorette® products

The adverse health consequences of smoking are increasingly being publicised.[1,2] In addition, legislation aimed at restricting smoking in public places is also increasing.[3,4] 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:[5,6]

- 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.[7] In addition to the gum, four other Nicorette® products are also available.

**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 less pronounced. 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.

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

**Nicorette® Inhaler** is a unique oral nicotine delivery form. Drawing air through a nicotine-impregnated porous polyethylene plug controls nicotine release. The air becomes saturated with vaporised nicotine, which is absorbed via the oral mucosa. Because of the oral absorption, the high plasma nicotine peaks that result from pulmonary nicotine absorption when smoking a cigarette do not occur with Nicorette® Inhaler. The Nicorette® Inhaler directly addresses the pharmacological and the behavioural (i.e. hand-to-mouth) activity associated with tobacco dependence. It is also extremely flexible, allowing the user to finely adjust the dosage.

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

**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® 2 mg and 4 mg sublingual tablets provide 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.

# 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.[8] 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.[8] 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.[2] 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:[8-11]

- 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:[9,10,12]

- 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.[13,14]

## 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.[15] 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.[16] 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.[16]

## 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).[17] 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.[18] 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).[19] 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.[18]

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.[18] There is also a complete or partial reversal of the risk of stroke within 5–10 years of stopping smoking.[20] 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.[20] Most of these risk factors improve within days of stopping smoking.[20]

*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.

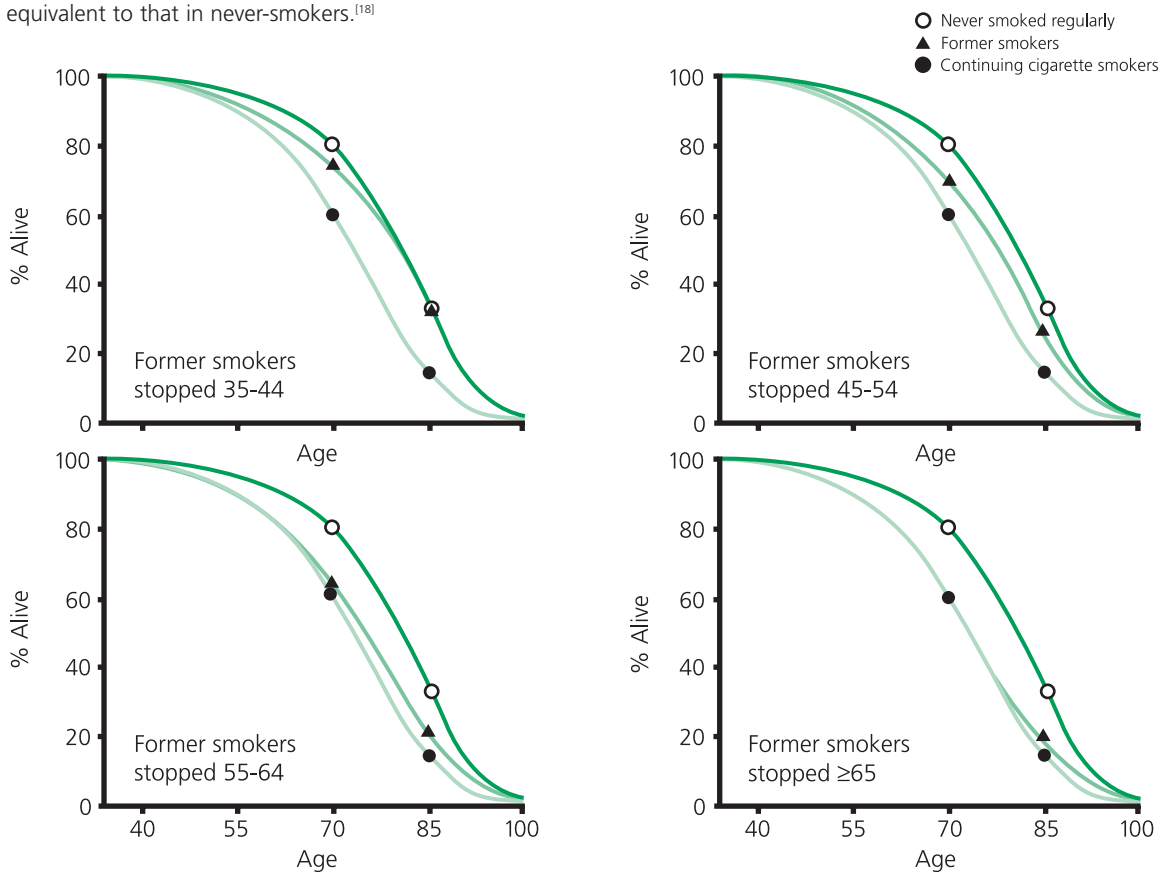



Figure 1. Effects on survival after ages 45, 55, 65 or 75 of stopping smoking during the previous 10 years.[19]
Br Med J 1994; 309:901-911, with permission from the BMJ Publishing Group.

# 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.[21] 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.[22,23] 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.[23] Nicotine has not been shown to cause cancer.[24,25]

*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).

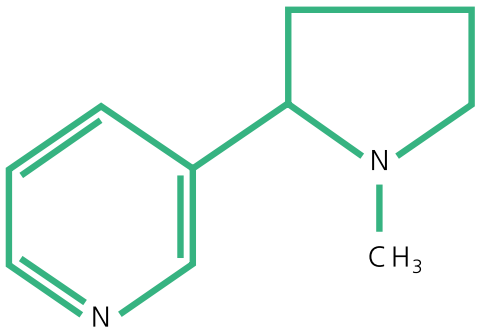



Figure 2. Structural formula of nicotine.

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.[26] Nicotinic receptor activation causes the release of neurotransmitters, including acetylcholine, noradrenaline, dopamine, serotonin, beta endorphin, and glutamate.[27] 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.[28-30]

## 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.[31] $Na^+$, $K^+$ and $Ca^{++}$ ions can permeate nicotinic receptors. The fact that $Ca^{++}$ can permeate nicotinic receptors reinforces the role that nicotine may play in modulating the release of neurotransmitters such as acetylcholine, noradrenaline, dopamine, serotonin, g-aminobutyric acid (GABA) and glutamate through presynaptic nicotinic receptors.[31] 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.[32]

## Cardiovascular system

The acute cardiovascular effects of tobacco smoking include:[26]

- 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.[27]

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.[33-35]

## 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.[26] 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.[26] Smoking is also associated with an earlier menopause and increased risk of osteoporosis in women.[26]

## 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.[31] 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.[32] 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.[36] Such observations have raised new interest in the use of nicotine as a therapeutic agent, particularly for individuals with neurological or psychiatric disease.[28,30]

## 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.

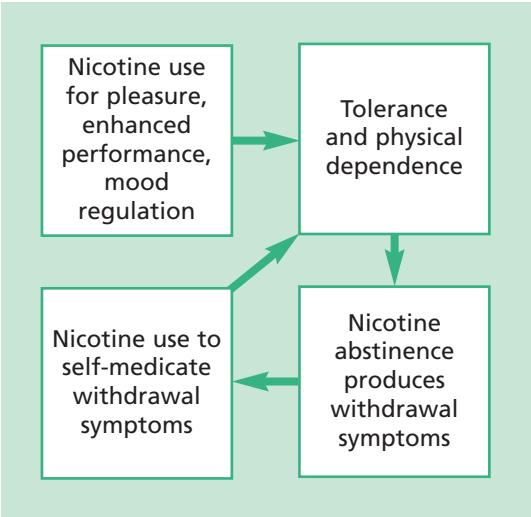



Figure 3. Classical model of addiction as applied to nicotine.[93]

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

- 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.[26] 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).[38] 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)[39] 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.[39] Reproduced with permission.

| Questions | Answers | Points |
|---|---|---|
| 1. How soon after you wake up do you smoke your first cigarette? | Within 5 minutes<br>6–30 minutes<br>31–60 minutes<br>After 60 minutes | 3<br>2<br>1<br>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<br>No | 1<br>0 |
| 3. Which cigarette would you hate most to give up? | The first one in the morning<br>all others | 1<br>0 |
| 4. How many cigarettes per day do you smoke? | 10 or less<br>11–20<br>21–30<br>31 or more | 0<br>1<br>2<br>3 |
| 5. Do you smoke more frequently during the first hours after waking than during the rest of the day? | Yes<br>No | 1<br>0 |
| 6. Do you smoke if you are so ill that you are in bed most of the day? | Yes<br>No | 1<br>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).[40] 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:

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

- 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.[40-42] However, craving for nicotine (the most characteristic feature of tobacco withdrawal), hunger and weight gain may continue for several months.[26,40,43]

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.[44,45]

# 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),[46] 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).

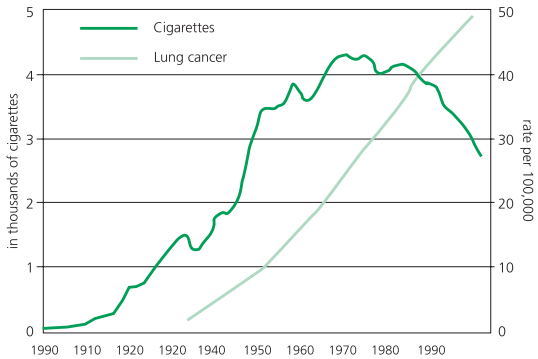



Figure 4. Change in *per capita* cigarette consumption and lung cancer death rate in the United States between 1900 and 1990, indicating the time lag between peak rates of smoking and peak incidence of lung cancer.
Source: US National Center for Health Statistics.

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.[37] Over the past decade, consensus statements and clinical guidelines have increasingly focused on the need to improve smoking cessation efforts.[47-51]

## 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.[52-54] 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).[53] These methods (alone or in combination) may be provided on an individual or group basis.[53] However, results from randomised, controlled trials do not support the use of behaviour modification therapy in smoking cessation.[53] Other methods such as hypnosis and acupuncture are also either unproven or ineffective.[53,55]

*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 $a_2$-noradrenergic agonist (clonidine), sensory stimulants (citric acid) and aversive treatment (silver acetate).[56,57] Bupropion, combined with counselling, has demonstrated efficacy in placebo-controlled trials.[58] 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.[56,57] In contrast, nicotine replacement therapy has consistently demonstrated efficacy in the treatment of tobacco dependence.[5,7,53]

*NRT doubles quit rates, irrespective of adjunctive support*

## Efficacy of NRT in smoking cessation

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

A landmark randomised, double-blind trial with biochemical validation reported in 1982 that nicotine chewing gum doubled abstinence rates compared to placebo,[59] 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).[7] All five existing NRT products (nicotine gum, transdermal patch, inhaler, nasal spray and sublingual tablet) have similar efficacy in smoking cessation.[7] The efficacy of Nicorette® Gum in treating tobacco dependence is detailed on pages 21 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.[48,49]

## Combination treatment with NRT for smoking cessation

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

Although NRT doubles quit rates, absolute success rates remain modest (generally 10–30% at 1 year).[60] 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,[61,62] one investigated nicotine 16 hour patch plus nasal spray[63] and one combined nicotine 16 hour patch plus nicotine inhaler.[64] In all four studies, combination treatment achieved higher 1-year abstinence rates than single NRT. The pooled results of the first three studies[61-63] give an odds ratio of 12-month abstinence for combination versus single treatment of 1.8 (95% confidence interval 1.2–2.8).[60] 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 (16 hour 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.[37] 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).[65,66]

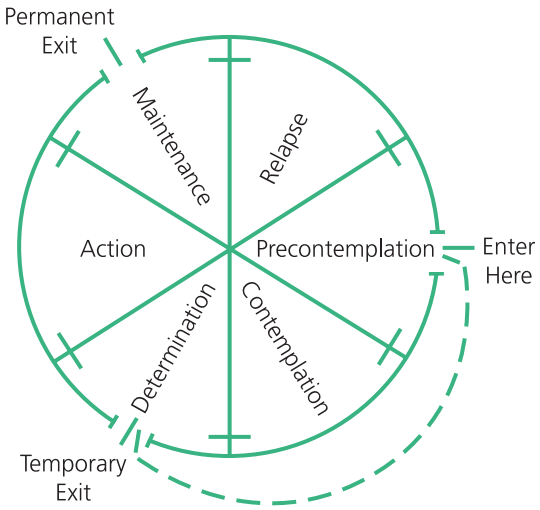



Figure 5. Stages of change model of smokers' behaviour according to readiness and motivation to stop smoking.

Given that only a small proportion of smokers are ready to quit at any one time,[67] 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.

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.[68] 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.[69] However, as NRT effectively controls tobacco withdrawal symptoms and craving, it can be used to reduce smoking.[70]

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.[70] A long-term study involving 400 smokers confirmed that NRT could achieve and sustain smoking reduction over a period of 2 years.[71] 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 ≥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.[70] 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.[72]

## 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.[25] Tobacco dependence is a medical condition, according to the World Health Organization *International Classification of Diseases*,[38] and the American Psychiatric Association lists nicotine withdrawal in the *Diagnostic and Statistical Manual (DSM-IV)*.[40] As nicotine withdrawal causes clinically significant symptoms that may occur within 2 hours of smoking the last cigarette,[73] 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 risk of tobacco-related disease is dose dependent. NRT can reduce smoking in individuals unable to quit*

The efficacy of NRT in relieving tobacco withdrawal symptoms is well documented[44,74] 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.[72] 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.

*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.[75] 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,[76] 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.[77] 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.[76,78]

## 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.[79] 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[75] and WHO[80] both support widening the access to effective treatments for tobacco dependence, such as NRT.

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

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.[81] 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.[82]

# 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.[83] 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.[84] 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.[85] 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.

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

### 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.[22] 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.[86] Nicotine has not been shown to cause cancer.[24,25] 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.[87] 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.[87]

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

### 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.[37] 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).[88] Compared to cigarettes, NRT provides lower doses of nicotine, which are delivered more slowly, and NRT has low potential for abuse.[25,89]

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

Transferred dependence may occur, and long-term use of NRT has been reported in a small proportion of abstinent smokers.[72,90] 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.[72]

**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, of the 2 mg of nicotine contained in Nicorette® 2 mg chewing gum, approximately 75% (1.5 mg) is released during 30 minutes of chewing (depending on the rate and intensity). Most of the extracted nicotine is absorbed via the oral mucosa. Some of the nicotine gets swallowed and metabolised by the liver, so the total dose absorbed is 1.2 mg (approximately 60% of nominal dose).[91] 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.[92] 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.[92] 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.[5]

**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.[6] 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.[72,93]

## NRT and weight gain after stopping smoking

Anxiety about weight gain is an important impediment to stopping smoking.[48] 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.[48] 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.[94] 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.[90] 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.[72]

## 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.[90] 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 ≥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).[95]

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.[96]

These trials suggest that NRT does not increase cardiovascular risk. The available evidence has been reviewed by Benowitz and Gourlay,[87] 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.[94] However, many pregnant women continue to smoke.[72] Cigarette smoking during pregnancy substantially increases the risk of spontaneous abortion, prematurity, low birth-weight and perinatal mortality.[72] 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.[72] Benowitz[97] 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 reaches the brain faster during cigarette smoking than it would following intravenous administration*

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.[27] 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.[29,85] Once nicotine enters the circulation, it distributes rapidly and reaches the brain within 10–20 seconds.[29] 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.[98]

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

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.[27] 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,[99] 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.[85] Absorption is followed by distribution of nicotine to the brain and peripheral tissues.[29,85] Plasma protein binding of nicotine is low (≤5%) and the volume of distribution is large (2.6 L/kg).[32]

## 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[29] (Figure 6).

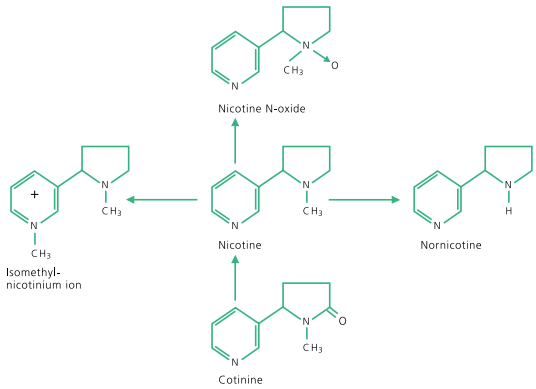



Figure 6. Primary metabolites of nicotine.

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.[29] The major biotransformation of nicotine occurs in the liver, but some metabolism also occurs in the lungs and brain.[27] Since nicotine undergoes extensive first-pass elimination, the drug has low oral bioavailability (around 44%).[99]

As the primary metabolite, cotinine, has a half-life of 15–20 hours,[27] and its concentration in the bloodstream of smokers is approximately 10 times that of nicotine,[85] 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.[85]

## Elimination

Plasma nicotine levels decrease in a bi-exponential manner, with a short distribution half-life of approximately 8 minutes [99] and an elimination half-life of around 2–3 hours.[29] 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.[85] In normal urine, renal clearance is 5–10% of total clearance.[100]

## 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 ≤36 $ml \cdot min^{-1}.1.73^{-1}m^2$) or severe (glomerular filtration rate <11 $ml \cdot min^{-1}.1.73^{-1}m^2$) was approximately 75% and 50%, respectively, of that of the healthy controls.[101] 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.[101]

**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.[101] Changes in nicotine disposition of this magnitude do not necessitate any adjustment of dosage of NRT in the elderly.

# Nicorette® chewing gum

## Rationale for development

*Stopping smoking with Nicorette® Gum involves a two-step process*

Pharmacologically, the regular smoker is dependent upon nicotine, the chemical reinforcer of smoking. Nicotine substitution can reduce the characteristic withdrawal symptoms and craving for cigarettes associated with tobacco dependence. The chewing gum formulation permits oral absorption of nicotine and thereby minimises extensive first-pass metabolism.

Use of Nicorette® Gum treats tobacco dependence by reducing nicotine-specific withdrawal symptoms. The user adjusts to the loss of common smoking sensory reinforcers and learns to eliminate ritual reinforcers. After adjusting to non-smoking lifestyle changes, a gradual reduction in nicotine intake is indicated.

## Formulation

Each piece of Nicorette® Gum contains 2 or 4 mg of nicotine bound to an ion-exchange resin, which permits slow release of the nicotine, and an alkaline hydrocarbonate buffer, which increases the oral absorption of nicotine by increasing salivary pH to about 8.5. Nicorette® Gum also contains gum base and flavour, and is sugar-free, using either sorbitol or xylitol as sweeteners. Nicorette® 4 mg gum contains quinoline yellow.

Nicorette® 2 and 4 mg gum formulations are available in original, mint and citrus flavours (this varies between countries). Nicorette® is formulated as a gum for several reasons:

- nicotine is readily absorbed via the oral mucosa
- gum chewing provides a degree of behavioural substitution in terms of oral gratification
- the risk of addiction is low because there are no pronounced peaks in blood nicotine concentration
- the risk of toxicity from accidental or unintentional swallowing is low because nicotine is tightly bound to the ion-exchange resin.

The process of quitting smoking using Nicorette® Gum is divided into two distinct phases. First, after giving up cigarettes, the smoker minimises tobacco withdrawal symptoms through self-administration of Nicorette® Gum. During this time the smoker learns not to respond to cues previously associated with smoking and develops other methods to relax, cope with stress and deal with anger or boredom. Once the psychological dependency associated with smoking has been adequately overcome, the second phase of cessation begins: this involves a gradual reduction in Nicorette® Gum use.

# Pharmacokinetics of Nicorette® Gum

## Absorption and bioavailability

Most of the nicotine contained in Nicorette® Gum is released after 30 minutes of chewing, although this varies greatly depending on factors such as rate and intensity of chewing and the amount of saliva produced during chewing. As nicotine is a weak base, absorption into the systemic circulation is influenced by salivary pH. Depending on the rate and duration of chewing, 2.5–3 mg of nicotine is extracted from one piece of nicotine 4 mg gum.[91,102] However, approximately 80% of the nicotine extracted from the gum reaches the bloodstream.[91]

Formulations using various flavours have been developed to further increase consumer choice. Pharmacokinetic studies conducted in healthy smokers given each of the different flavour gums determined that the formulations were bioequivalent at steady state.[101]

## Plasma concentration

Although smoking cigarettes and chewing nicotine gum result in ingestion of similar amounts of nicotine, plasma nicotine levels are lower while chewing nicotine 2 mg or 4 mg gum than during normal *ad libitum* smoking.[91] The rate of absorption of nicotine is also much lower from the gum than from cigarettes (Figure 7).

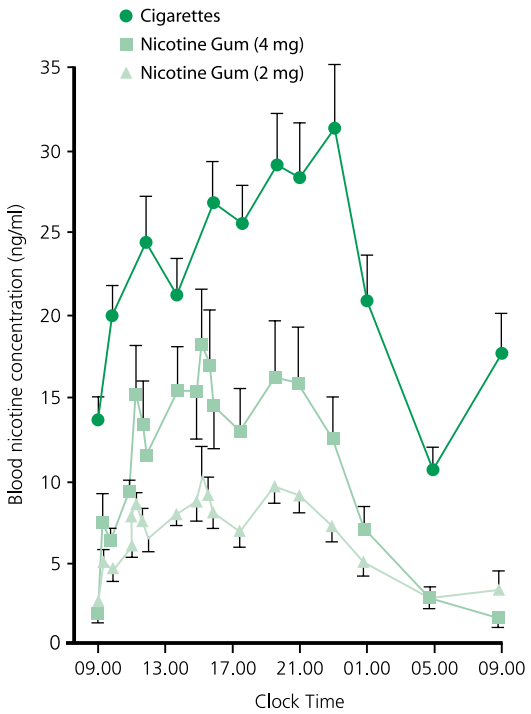



Figure 7. Mean blood nicotine concentrations throughout the day while smoking cigarettes *ad libitum* (n=14) or chewing nicotine 2 mg (n=7) or 4 mg (n=7) gum. One piece of nicotine gum was chewed for 20 minutes every hour from 0900 to 2100, a total of 12 pieces/day.[91] Reproduced with permission.

Theoretically, regular chewing of the 4 mg gum should produce trough plasma nicotine concentrations similar to those attained while smoking, but in practice subjects chew fewer pieces of Nicorette® Gum than they smoke cigarettes. Therefore, plasma nicotine concentrations attained are approximately one-third (with the 2 mg gum) and two-thirds (with the 4 mg gum) of those achieved by smoking.[103,104]

# Clinical efficacy

## Effects on craving and withdrawal symptoms

*Nicorette® Gum has been shown to increase the odds ratio of achieving abstinence compared to placebo in a variety of clinical settings*

Several placebo-controlled studies have shown that Nicorette® Gum effectively reduces the incidence and severity of tobacco withdrawal symptoms such as irritability, anxiety, impatience, difficulty in concentrating and restlessness.[59,105-108] During quit attempts, regular use of Nicorette® Gum for the recommended period helps control these symptoms and lowers the risk of relapse.

In a double-blind crossover study by Fagerström *et al*., 28 smokers received four different 3-day treatments: (i) placebo; (ii) Nicorette® 15 mg patch applied for 16 hours; (iii) Nicorette® 2 mg gum used *ad libitum*; and (iv) Nicorette® Patch and 2 mg gum combined.[44] Each treatment phase was separated by at least 4 days during which participants smoked as normal. Withdrawal symptoms were recorded using several visual analogue scales (VAS). The number of pieces of gum used during each treatment period varied from 4 to 6 pieces.

The results showed that placebo treatment was associated with significantly greater withdrawal symptoms than all active treatments ($p<0.001$). All three Nicorette® treatments significantly reduced withdrawal symptoms, but there was no significant difference between the patch or gum used alone.

Unlike most withdrawal symptoms, which subside within 3–4 weeks after quitting smoking, craving and increased appetite may persist for several weeks or even months. One 6-month study by Hughes *et al*. in 315 outpatients reported that Nicorette® markedly reduced the incidence and severity of craving and hunger in these individuals.[43]

## Abstinence rates

Nicorette® Gum has been extensively investigated, and numerous clinical studies have demonstrated that it aids smoking cessation. The Cochrane Tobacco Addiction Group conducted a meta-analysis of 48 randomised placebo-controlled studies investigating smoking cessation rates with nicotine gum.[7] At 12 months, 18% of those receiving nicotine gum remained abstinent, compared to 11% in the control group. Nicotine gum increased the odds ratio of abstinence to 1.63 (95% confidence interval 1.49–1.79) compared with placebo. In an earlier analysis, abstinence rates among nicotine gum users varied from 15% in hospital trials to 36% in smoking cessation clinic trials, compared to 11% and 23%, respectively, for placebo groups in these settings.[109]

In earlier reviews, Tang *et al*.[110] and Law *et al*.[53] analysed the results of 28 randomised trials of nicotine 2 mg gum. Overall efficacy, defined as the difference in abstinence rates between the active-treatment and control groups, was 6% (95% confidence interval (CI): 4–8%; $p\leq0.001$). When trials of nicotine 2 mg gum in family practice (n=15) and in self-referred smokers (n=13) were compared, differences between the active and placebo groups were 3% and 11%, respectively ($p\leq0.001$ for each comparison with placebo).

Individual study results vary widely depending on the study design and degree of sophistication. In addition, the outcome or success of treatment with Nicorette® Gum may be influenced by several factors, including:

- degree of patient motivation
- level of nicotine dependence
- dosage used
- follow-up procedure
- concomitant use of behavioural therapy and advice
- therapist experience.

## Short-term placebo-controlled studies

The short-term efficacy of Nicorette® Gum in stopping smoking has been investigated in several large double-blind, placebo-controlled trials (Table 2). Most of these studies also provided subjects with some form of behavioural therapy. After treatment periods of 3–6 weeks' duration, abstinence rates (verified by analysis of expired carbon monoxide) in subjects treated with Nicorette® 2 mg gum ranged from 27% to 89%, compared to 11–72% in those treated with placebo.

Table 2. Selected double-blind clinical trials (n=≥90 subjects) comparing the short-term efficacy of Nicorette® 2 mg gum and placebo in achieving abstinence.

| Study | Additional Therapy | No. of subjects | Timepoint (weeks) | Abstinence rates (% of subjects) | |
|---|---|---|---|---|---|
| | | | | Nicorette® 2 mg | Placebo |
| British Thoracic Society 1983[111] | None | 802 | 4 | 27 | 26 |
| Christen *et al*. 1984[112] | Phone and group | 208 | 6 | 34*** | 11 |
| Fagerström 1982[113] | Individual | 96 | 4 | 90* | 60 |
| Fee & Stewart 1982[114] a | Lecture | 352 | 5 | 46* | 33 |
| Hall *et al*. 1987[115] | Group | 139 | 3 | 82 | 72 |
| Hjalmarson 1984[116] | Group | 205 | 6 | 77*** | 52 |
| Hughes *et al*. 1989[117] | Individual | 315 | 4 | 54* | 41 |
| Jamrozik *et al*. 1984[118] | Individual | 200 | 4 | 29 | 24 |
| Jarvis *et al*. 1982[59] | Group | 116 | 2 | 67** | 45 |
| Malcolm *et al*. 1980[119] | Individual | 210 | 4 | 34 | 37 |
| Tønnesen *et al*. 1988[120] | Group | 113 | 6 | 73*** | 41.5 |
| Herrera *et al*. 1995[121] | Group | 322 | 6 | 70*** | 38 |

[a] Abstinence claims not verified by carbon monoxide analysis

Symbols: * p<0.05, ** p<0.01, *** p<0.001 vs placebo

## Long-term placebo-controlled studies

Table 3 summarises results of 21 double-blind trials which evaluated the long-term efficacy of Nicorette® 2 or 4 mg gum with respect to abstinence rates. Compared to placebo, Nicorette® increased long-term abstinence rates in almost all studies reviewed. The only exceptions were the British Thoracic Society study[111] which reported a slightly lower abstinence rate for participants randomised to Nicorette® Gum (but the methodology of this study has been criticised), and the study by Campbell *et al.*[124] which documented a 20% success rate for both treatment regimens. Overall, Nicorette® Gum produced 6- or 12-month abstinence rates of 3–48%, whereas placebo was associated with long-term success rates of 2–37%.

Table 3. Selected clinical studies (n=≥90 subjects) comparing the long-term efficacy of Nicorette® 2 mg or 4 mg gum and placebo in smoking cessation.

| Study | No. of subjects | Time to follow-up (months) | Abstinence rates (% of patients) | |
|---|---|---|---|---|
| | | | Nicorette® | Placebo |
| **Nicorette® 2 mg** | | | | |
| Areechon & Punnotok 1988[122] | 199 | 6 | 57** | 37 |
| British Thoracic Society 1983[111] | 802 | 12 | 10 | 14 |
| Campbell *et al.* 1987[a][123] | 985 | 12 | 3 | 2 |
| Campbell *et al.* 1991[124] | 219 | 12 | 20 | 20 |
| Fee & Stewart 1982[a,b][114] | 352 | 12 | 13 | 9 |
| Fagerström 1982[113] | 96 | 12 | 49 | 37 |
| Fagerström 1984[c][125] | 151 | 12 | 27* | 15c |
| Fortmann *et al.* 1988[126] | 299 | 12 | 26** | 18 |
| Hall *et al.* 1987[115] | 139 | 12 | 42** | 21 |
| Herrera *et al.* 1995[121] | 322 | 12 | 49*** | 22 |
| Hjalmarson 1984[116] | 205 | 12 | 29* | 16 |
| Hughes *et al.* 1989[117] | 315 | 12 | 10 | 7 |
| Jamrozik *et al.* 1984[118] | 200 | 6 | 10 | 8 |
| Jarvis *et al.* 1982[59] | 116 | 12 | 47** | 21 |
| Malcolm *et al.* 1980[119] | 210 | 6 | 23* | 5 |
| Quílez García *et al.* 1989[127] | 106 | 6 | 35* | 13 |
| Russell *et al.* 1983[c][128] | 1938 | 12 | 9** | 4c |
| Salvador *et al.* 1988[129] | 216 | 12 | 48** | 27 |
| Tønnesen *et al.* 1988[120] | 113 | 12 | 38 | 23 |
| **Nicorette® 4 mg** | | | | |
| Blöndal 1989[130] | 182 | 12 | 40* | 27 |
| Puska *et al.* 1979[131] | 160 | 6 | 35 | 28 |

a Abstinence claims not verified by carbon monoxide analysis

b Only 18% of subjects were followed up

c In the Fagerström 1984 and Russell 1983 studies, the control group received no intervention

Symbols: * p<0.05, ** p<0.01 vs placebo, ***p<0.001

## Nicorette® Gum vs other treatments

Several studies have compared Nicorette® 2 mg Gum with other smoking cessation methods such as acupuncture and various types of behavioural treatment, either therapist-administered or self-administered (Table 4).

Table 4. Clinical studies comparing the long-term efficacy of Nicorette® 2 mg Gum and other active therapy in the treatment of tobacco dependence.

| Study | Comparative treatment | Abstinence rates (% of subjects) | | Relative difference in percentage efficacy |
|---|---|---|---|---|
| | | Nicorette® | Other | |
| Clavel & Benhamou 1985[132] | Acupuncture | 12 | 8 | +50 |
| Harackiewicz *et al.* 1988[133] | Self-help manual | 13 | 15 | –13 |
| Killen *et al.* 1984[134] | Skills training | 23 | 30 | –23 |
| Raw *et al.* 1980[135] | Behavioural counselling and rapid smoking | 38 | 14 | +171 |

Abstinence rates indicate that Nicorette® alone is at least as effective as these other methods, which are frequently more time- and resource-consuming to administer. Nevertheless an optimum approach to the treatment of tobacco dependence may involve using a combination of pharmacological and behavioural therapy.

## Relative effect of Nicorette® 2 mg and 4 mg gum on treating tobacco dependence

Studies have indicated that in highly nicotine-dependent smokers, a 4 mg dosage of Nicorette® Gum is more effective than a 2 mg dosage. Of the six smoking cessation trials that compared the efficacy of nicotine 4 mg and 2 mg gum in highly dependent smokers, four found that the higher dose achieved significantly higher success rates (Table 5).

Table 5. Success rates[a] at 1-year of follow-up in highly dependent smokers receiving Nicorette® 2 mg or 4 mg gum (reproduced with permission) [Balfour & Fagerström 1996].

| Study | 2 mg | 4 mg | Relative difference |
|---|---|---|---|
| Tønnesen *et al.* 1988[120] | 33% | 37% | 1.1 |
| Kornitzer *et al.* 1987[136] | 18% | 33%* | 1.8 |
| Tønnesen *et al.* 1988[137] | 12% | 44%* | 3.6 |
| Herrera *et al.* 1995[121] | 16% | 39%* | 2.4 |
| Sachs 1995[b][138] | 30% | 59%* | 1.9 |
| Mean of all trials | 22% | 42% | 2.1 |

a Results are expressed as the percentage of subjects entering each trial

b Success rates at 6 weeks

Symbol: * $p<0.05$

Silagy *et al*. reported a pooled odds ratio of 2.67 (95% CI: 1.69–4.22) in favour of the higher dose with regard to abstinence rates in trials comparing the efficacy of 4 mg versus 2 mg gum in highly dependent smokers.[7] There was no evidence of a dose effect on abstinence in low-dependent smokers. The recent US clinical practice guideline also states that health professionals should recommend 4 mg, rather than 2 mg, gum to highly dependent smokers.[48]

In the first comparative study of different gum strengths, subjects who smoked ≥15 cigarettes per day were randomised to receive either 2 mg (n=101) or 4 mg (n=98) gum.[136] At 1 year, there was no significant difference in abstinence rates overall with the 2 mg and 4 mg gum (36% vs 45%). However, subanalysis of abstinence rates according to the participants' baseline degree of nicotine dependence, as assessed by the FTND, showed that highly dependent smokers did significantly better with nicotine 4 mg gum than with 2 mg gum (33% vs 18.5%; p=0.05).

Tönnesen *et al*. also found that long-term abstinence rates were higher in highly dependent smokers who used 4 mg gum.[120] The degree of nicotine dependence among patients was assessed prior to randomisation; among highly nicotine-dependent smokers, cessation rates after 1 and 2 years were 44% and 33%, respectively, in the 4 mg group, compared to 12% and 6%, respectively, in the 2 mg group. Among subjects with medium or low nicotine dependence, quit rates after the same periods were 38% and 28%, respectively, in the 2 mg group, compared to 23% and 9%, respectively, in the placebo group.

Herrera *et al*. stratified smokers into highly dependent (FTND ≥7; n=168) and moderate- or low-level dependence groups (FTND <7 (low dependent)) in a randomised, double-blind study of the efficacy of nicotine gum in combination with a behaviour-modification programme.[121] Highly dependent smokers received Nicorette® 4 mg (n=87) or 2 mg gum (n=81) and smokers with low or moderate levels of nicotine dependence received Nicorette® 2 mg gum (n=76) or placebo gum (n=78). Smokers from both groups were also randomised to either familiarise themselves with medication 1 week before quit day (n=122) or to start gum use on the quit day (n=122); all groups were placebo controlled (n=78). In the highly dependent group, abstinence rates at 6 weeks, 1 year and 2 years for those receiving nicotine 4 mg gum were 60%, 39% and 34%, respectively, compared to 41%, 16% and 16% for those receiving nicotine 2 mg gum. Among the low/moderately-dependent smokers, abstinence rates at 6 weeks, 1 year and 2 years were 70%, 49% and 39%, respectively, for smokers receiving nicotine 2 mg gum and 38%, 22% and 17% for those receiving placebo (Figure 8).

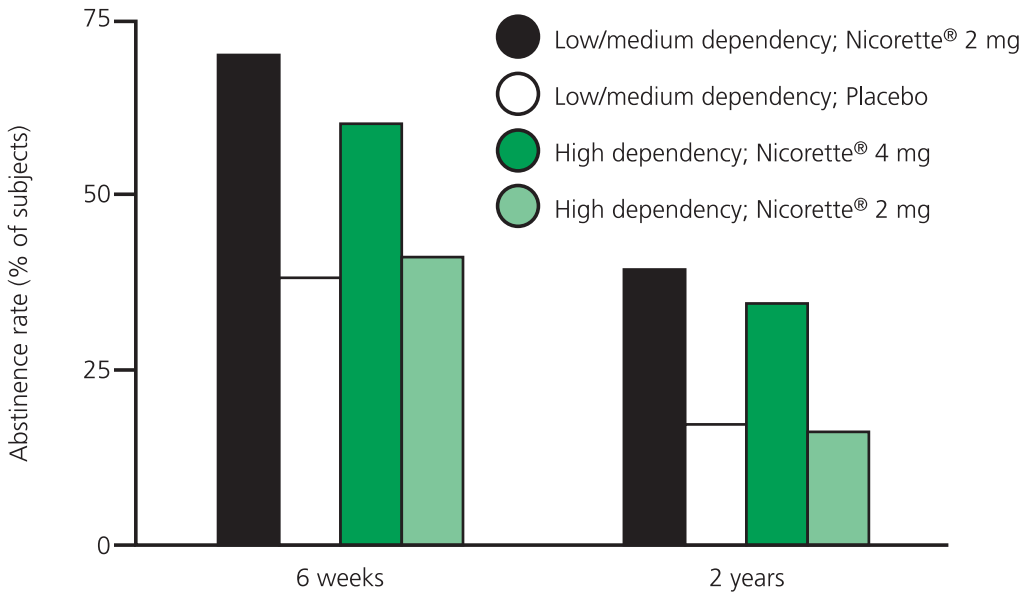



Figure 8. Smoking cessation rates at 6 weeks and 2 years in high- or low/medium-dependency smokers randomised to Nicorette® 2 mg or 4 mg gum or placebo.[121]

There was a non-statistically significant trend in favour of familiarisation with the product, reflected in better success rates at 6 weeks (61% vs 52%). It was concluded that highly dependent smokers require higher doses of NRT (nicotine 4 mg rather than 2 mg gum) and that nicotine 2 mg gum is superior to placebo in less-dependent smokers.

*Smokers should have their level of nicotine dependence assessed and the appropriate strength of gum should be recommended*

The largest and most recent comparative study also reported higher 1 year abstinence rates in highly dependent smokers who received 4 mg gum.[139] In this community-based study, 608 smokers were classified into low (n=263; mean FTND score 3.6±1.6, smoking a mean of 16±5.4 cigarettes/day) or high (n=345; mean FTND score 7±1.5, smoking a mean of 29.3±11 cigarettes/day) dependence groups. Subjects were then randomised to receive either placebo or nicotine 2 mg or 4 mg gum plus brief behavioural counselling. The 1-year abstinence rates in those receiving placebo, 2 mg or 4 mg gum were 11.2%, 19.5% and 18.4%, respectively, in the low-dependence group, and 6.1%, 15.7% and 20.7% in the high-dependence group. Although the relationship between dose and abstinence at 1 year did not reach significance for low- and high-dependence smokers, there was a significant linear trend for the higher strength gum to be related to increased abstinence among high-dependence smokers.

## Long-term use

Treatment with Nicorette® Gum should be tailored according to the needs of the individual, with the recommended duration of treatment being at least 3 months. Although a proportion of users continue with nicotine gum for longer, only a small minority continue to use it at 1 year (Table 6). The 5-year Lung Health Study assessed nicotine gum use in 3,094 participants with chronic obstructive pulmonary disease (COPD). Nicotine gum was supplied free of charge during the study period, and 1,042 (31%) were still using nicotine gum at 1 year; approximately 10% of participants used the gum for the entire 5-year study period. Extended use of nicotine gum was not found to be related to any serious side effects.[90]

*The efficacy of Nicorette® Gum 2 mg or 4 mg in smoking cessation is maintained over the longer term*

Longer-term use of nicotine gum may be appropriate for highly nicotine-dependent smokers who would otherwise be at risk of relapse.

Table 6. Long-term use of Nicorette® Gum in selected clinical studies (n=≥90 subjects).

| Study | No. of Subjects | Subjects using Nicorette® Gum at long-term follow-up (%) | | |
|---|---|---|---|---|
| | | 1 year | 2 years | 5 years |
| British Thoracic Society 1983[111] | 400 | 10 | | |
| Fagerström 1982[113] | 96 | 0 | | |
| Fortmann *et al*. 1988[126] | 299 | 0 | | |
| Harackiewicz *et al*. 1988[133] | 90 | 9 | | |
| Hjalmarson 1984[116] | 106 | 5 | 3 | |
| Kornitzer *et al*. 1987[136] | 199 | 17 | | |
| Salvador *et al*. 1988[129] | 101 | 5 | | |
| Tønnesen *et al*. 1988[137] | 120 | 6 | 3 | |
| Westling 1976[140] | 810 | 7 | 1.5 | |
| Murray *et al*. 1996[90] | 3,094 | | | 14% (ex-smokers)<br>5% (smokers) |

# Safety

## Adverse events

Compared with the constituents of cigarette smoke, Nicorette® Gum delivers only nicotine, generally at a lower dose and at a considerably slower rate of release than smoking. This clearly makes Nicorette® Gum safer than smoking. In addition, the potential adverse events of Nicorette® Gum are generally mild:

- gum chewing may cause problems such as jaw pain or dental problems
- excipients in the gum may cause allergic reactions such as pruritus, dermatitis or itching; the risk is similar with the 2 mg and 4 mg strengths, except that 4 mg nicotine gum contains quinoline yellow
- nicotine itself can produce a broad range of pharmacological effects, particularly with respect to the cardiovascular system
- heavy smokers using Nicorette® Gum may develop tobacco withdrawal symptoms because their nicotine intake is too low; this is more likely to occur with the 2 mg than the 4 mg strength.

*No serious treatment-related adverse events have been reported with Nicorette® Gum*

Use of Nicorette® Gum at the recommended dose has not been found to cause any serious adverse events. A slight throat irritation and increase in salivation may occur on commencing treatment, which is related to the nicotine contained in the gum, and excessive swallowing of dissolved nicotine may cause hiccups. The most frequently reported systemic adverse events include headache, dizziness, gastrointestinal discomfort, nausea and vomiting, while local adverse events include sore mouth or throat. Less frequent adverse events include palpitations, erythema and urticaria. Atrial fibrillation and allergic reactions have also been reported, but these are rare.[101]

The unusual taste and several other effects associated with Nicorette® Gum are sometimes found to be unpleasant. These effects are largely related to chewing technique, and the frequency and severity of such problems can be reduced with proper instruction. Patient acceptability may also be limited by other factors such as throat irritation, an unwillingness to chew gum in a social or work environment, and the effort required to chew gum for several hours each day.

## Long-term use

Side effects associated with long-term use of Nicorette® 2 mg gum were investigated as part of the Lung Health Study, a 5-year, multicentre, randomised, controlled study involving 3,094 smokers.[90]

Participants in the study (smokers aged 35–60 years with evidence of early-stage COPD) were assigned to either Nicorette® Gum and special intervention, a multicomponent smoking cessation programme or their usual care with minimal instruction and monitoring of nicotine gum use. Over the 5 years of the study, the rates of hospitalisation and death related to cardiovascular conditions were unassociated with either use or dose of nicotine gum or concomitant smoking and gum use. The frequency of side effects did not increase in those who smoked concomitantly. Most side effects were minor and transient. Importantly, some symptoms were 2–3 times more frequent in the usual-care group, suggesting that intensive instruction and monitoring may not only increase the effectiveness of nicotine gum in the treatment of tobacco dependence but may also reduce the rate of reported side effects. The authors concluded that long-term use of Nicorette® Gum, 'as used in the Lung Health Study, appears to be safe and unrelated to any cardiovascular illnesses or other serious side effects'.

## Post-marketing surveillance

Post-marketing surveillance indicates that the most common adverse events reported with Nicorette® Gum are:

- headache and dizziness
- slight throat irritation and excessive salivation
- gastrointestinal symptoms such as nausea, vomiting, hiccups and flatulence
- jaw muscle ache, aphthous ulcers, denture damage.

Sources of information for post-marketing surveillance include spontaneous reports, reports from national regulatory authorities and case reports documented in the medical literature. Since the nature, quality and quantity of this information varies widely, and the strength of Nicorette® Gum is frequently not indicated in any one report, it is not possible to determine separate adverse reaction profiles for the 2 mg and 4 mg strengths of Nicorette® Gum.

## Toxicity of Nicorette® Gum

With Nicorette® Gum, nicotine intoxication is unlikely even if several pieces are swallowed in rapid succession. The slow rate of release from the ion-exchange resin and the extensive first-pass metabolism of the drug prevent the development of nicotine toxicity. Indeed, simultaneous ingestion of 10 unchewed pieces of Nicorette® 4 mg gum produced peak blood nicotine concentrations of <10 ng/ml.[101] Furthermore, intentional poisoning by chewing several pieces of Nicorette® Gum is unlikely because severe nausea and vomiting would discourage further ingestion.

## Transferred dependence and abuse potential

Transferred nicotine dependence may occur with NRT. However, the potential for physical dependence on nicotine is related to various factors, including:[117]

- rapid onset of action
- attainment of high plasma nicotine levels
- lack of adverse events associated with treatment
- social acceptability
- frequent use.

*The risk of abuse and/or dependence with the Nicorette® Gum is low*

In contrast with cigarette smoking, administration of Nicorette® Gum does not result in rapid, high arterial plasma nicotine concentrations. The gum therefore has a low potential for dependence and/or abuse. In common with other nicotine replacement products, Nicorette® Gum should only be used for the recommended period, followed by a weaning-off period during which the dose is gradually reduced.

There have been several reports of long-term use of nicotine gum, but this may be due to abstinent ex-smokers prolonging treatment in order to prevent relapse to smoking.[141] Even if extended treatment is required in certain individuals, the risks associated with the use of Nicorette® Gum are substantially outweighed by the risks of continued or renewed smoking.

# Product information

The local product information should be consulted for full information.

## Characteristics of Nicorette® Gum

Nicorette® Gum is a sugar-free chewing gum containing either 2 mg or 4 mg of nicotine bound to an ion-exchange resin. The gum is available in three flavours: original, mint and citrus. Chewing the gum gradually releases free nicotine, which is absorbed through the oral mucosa.

## Instructions for use

Nicorette® Gum acts by relieving craving and withdrawal symptoms and is indicated in the treatment of tobacco dependence. To obtain maximum benefit from Nicorette® Gum, it is important that a proper chewing technique is used:

- approximately 15 chews are required to release some nicotine
- when a strong taste or tingling sensation begins, the gum should be parked between the cheek and teeth or gums
- when the taste or tingling has almost gone, chewing should begin again
- each piece of Nicorette® Gum should be chewed intermittently for approximately 30 minutes.

## Dosage and administration

Nicorette® Gum should be used whenever there is an urge to smoke. Two strengths are available, containing nicotine 2 or 4 mg. The initial dosage should be individualised according to the smoker's nicotine dependence. Smokers with low nicotine dependence should use the 2 mg gum, whereas highly dependent smokers (defined as those who smoke >20 cigarettes/day or score ≥6 on the FTND) should use the 4 mg gum. This higher dosage should also be used in those smokers who fail to stop smoking while using the 2 mg gum.

In order to provide adequate nicotine replacement, most smokers require 8–12 gums of the appropriate strength per day. The maximum dose should not exceed 24 gums per day.

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

For temporary abstinence, the gum 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 gum 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 gum usage continues beyond 12 months. However, some ex-smokers may require extended treatment in order to avoid relapse to smoking.

Nicorette® Gum 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 any other component of the gum. 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 or severe renal impairment. 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® Gum 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® Gum 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.

Smokers who wear dentures may experience difficulty in chewing nicotine gum. The chewing gum may stick to, and in rare cases damage, dentures.

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

## 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® Gum may cause adverse reactions, which are mainly dose-dependent. Most of the adverse effects occur during the first 3–4 weeks of starting treatment and decrease during continued use. Common (>1/100) adverse effects comprise headache, nausea/vomiting, gastrointestinal discomfort, hiccups, sore mouth or throat, and jaw ache. Less common effects (1/100-1/1,000) include palpitations, erythema and urticaria. Rare adverse events (<1/1,000) comprise reversible atrial fibrillation and allergic reactions, such as angioedema.

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. The risk of poisoning from swallowing nicotine gum is low, since absorption of nicotine in the absence of chewing is slow and incomplete. However, 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® Gum 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® Gum. 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® Gum for individual smokers. Guidelines for the optimal use of Nicorette® Gum include:

- emphasising the need for adequate nicotine substitution in order to control tobacco withdrawal symptoms and craving
- explanation of the most common adverse events and that these are likely to decline during repeated use
- explanation of the correct 'chew and rest' technique required in order to obtain maximum benefit from the gum
- 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 can be obtained from the comprehensive smoking cessation guidelines recently published in England [142] and the United States.[48]

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