

Nicotine and nicotine replacement therapy

– the facts

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There are many misperceptions about the role of nicotine in the harmful effects of smoking on health. Surveys of Australian smokers suggest that these misperceptions result in a significant number of smokers both delaying quit attempts and avoiding quitting with clinically proven nicotine replacement therapy.

This review addresses the common myths or misperceptions surrounding nicotine by summarising the available evidence on the role of nicotine and the safety of nicotine replacement therapy.

Introduction

There are many misperceptions about the role of nicotine in the harmful effects of smoking on health.¹ A survey of Australian smokers found that 25% believed that nicotine replacement therapy (NRT) was just as harmful as smoking cigarettes and an additional 40% of smokers did not know whether this was true or false.¹ These misperceptions result in a significant number of smokers both delaying quit attempts and quitting unassisted,¹ which is less effective than quitting with proven aids like NRT.²

The effectiveness of NRT in aiding cessation is well established and is supported by the highest level of clinical evidence,^{2,3} systematic review of more than 90 randomised clinical trials.² Smoking cessation guidelines from Australia and overseas recommend that all smokers be offered pharmacotherapy to assist quitting, unless contraindicated, and recommend NRT as a first-line therapy.^{3,4} Guidance from the National Prescribing Service notes the equivalent efficacy of NRT and bupropion on current evidence but recommends NRT be used first, given its more extensive clinical experience and superior safety profile.⁵ By combining NRT with behavioural support, success rates can be further improved.⁶ Nicotine replacement therapy is not only effective it is also cost effective, at a daily cost that is approximately half that of smoking cigarettes, and when NRT is stopped the typical smoker will save in the order of \$3000 per year by not purchasing cigarettes.

This review addresses the common myths or misperceptions surrounding nicotine by summarising the available evidence on the role of nicotine and the safety of nicotine replacement therapy.

Myth 1: Nicotine is the most harmful ingredient in cigarettes

Fact: Cigarette smoke contains over 4000 compounds and it is these other toxins, not nicotine, that are responsible for tobacco-related diseases.

Smoking tobacco is the leading cause of preventable disease and death in Australia. Smoking harms nearly every organ in the body, causing many diseases including many cancers, chronic respiratory illnesses, and cardiovascular disease.⁷

The most important action of nicotine in cigarettes is the maintenance of addiction.⁸ It is the myriad of other toxins in cigarette smoke that are responsible for the majority of harmful effects of smoking.⁸

Nicotine has not been shown to be carcinogenic.⁸ It has not been implicated in the development of chronic respiratory diseases.⁸ Although nicotine has haemodynamic effects that may play some role in increasing the risk of heart disease, it is not a major cardiac risk factor.⁸ The use of nicotine replacement therapy (NRT) is not associated with increase risk of cardiovascular events.⁹⁻¹¹

Table: Nicotine myths and facts

Myth	Fact
1. <i>Nicotine is the most harmful ingredient in cigarettes</i>	Nicotine is not directly responsible for tobacco-related diseases. The only important actions of nicotine in cigarettes are the induction and maintenance of addiction. Nicotine is not carcinogenic, does not cause respiratory diseases and is not a major cause of cardiac risk associated with smoking.
2. <i>Nicotine causes cancer</i>	Nicotine is not carcinogenic. There is no clinical evidence that NRT is associated with an increased risk of developing cancer.
3. <i>Nicotine causes cardiovascular disease</i>	Nicotine does have haemodynamic effects however it is not the major cause of increased cardiac risk associated with smoking. NRT can be safely used as a cessation aid in patients with stable cardiac conditions, including angina and previous myocardial infarction.
4. <i>Smoking while using nicotine replacement therapy is unsafe and increases the risk of heart attack.</i>	Smoking whilst using nicotine replacement therapy does not increase the risk of a heart attack or related cardiovascular events as tolerance to the haemodynamic effects of nicotine develops acutely.
5. <i>Using more than one form of nicotine replacement is unsafe</i>	Combining more than one form of NRT can be used safely to assist people quit smoking. Clinical trials have demonstrated no significant increase in adverse events when more than one form of NRT is used concurrently in suitable smokers.
6. <i>Nicotine replacement therapy is as addictive as cigarettes</i>	Nicotine from cigarettes is addictive because it is delivered rapidly from smoke. All forms of NRT deliver nicotine slowly and have low or no abuse potential.
7. <i>Nicotine replacement therapy is just as harmful as smoking during pregnancy</i>	NRT is safer than continuing smoking during pregnancy and has the potential to improve birth outcomes.
8. <i>Nicotine replacement therapy is just as harmful as smoking while breastfeeding</i>	The use of NRT while breastfeeding is unlikely to be hazardous and is safer than continuing smoking as it reduces infant exposure to cigarette smoke.
9. <i>Nicotine replacement therapy is not safe for use by adolescent smokers</i>	NRT can be safely used by adolescent smokers to help them quit. The adverse event profile of NRT in adolescents is the same as in adults. NRT should be considered as a cessation aid by adolescent smokers who are daily smokers and who are motivated to quit.

The available evidence can be summarised under the following statement:

Using nicotine replacement therapy to quit is always safer than continuing to smoke.

Myth 2: Nicotine causes cancer

Fact: Nicotine is not carcinogenic. There is no clinical evidence that NRT is associated with an increased risk of developing cancer.

Smoking tobacco is a leading cause of cancer.⁷ Tobacco smoke contains more than 50 known carcinogens including nitrosamines.⁷ There is substantial evidence that nitrosamines cause many human cancers.⁸

Nicotine has not been shown to be carcinogenic in animals and to date there is no evidence that NRT causes cancer in humans.⁸ Nicotine could theoretically contribute to an increased cancer risk via metabolism to form carcinogenic nitrosamines¹² or by promoting tumour growth,¹³ however it appears extremely unlikely that nicotine is capable of stimulating cancer under normal conditions.¹⁴

Evidence supporting the long term safety of nicotine comes from epidemiological studies of Swedish snus use, an oral smokeless tobacco product. These studies found no increased risk of lung cancer,¹⁵ oral cancer,¹⁴⁻¹⁷ gastric cancer,^{15,17} kidney cancer¹⁴ or head and neck cancers.¹⁸ One study of snus use has found an increased risk of pancreatic cancer, however the authors attributed this excess risk to nitrosamine content and not nicotine.¹⁷

Myth 3: Nicotine causes cardiovascular disease (e.g. myocardial infarcts and strokes)

Fact: Smoking is a leading cause of heart disease and strokes. Nicotine does have haemodynamic effects however it is not the major cause of increased cardiac risk. NRT is safe to use as a cessation aid in patients with stable cardiac conditions, including angina and previous myocardial infarction.

Smoking is a leading cause of heart disease and strokes.⁷ Nicotine has pharmacological effects on the cardiovascular system resulting in increased heart rate and blood pressure and it can cause coronary artery vasoconstriction.^{19,20} However cigarette smoking is more hazardous as, unlike smoking, nicotine alone does not lower oxygen carrying capacity, activate coagulation or lead to arterial disease.^{19,20}

The safety of NRT in patients with cardiovascular disease is well supported by evidence from meta-analysis,¹⁰ clinical trials,^{11,21-25} observational²⁶⁻²⁸ and physiological studies.²⁹⁻³² The evidence is that NRT is not associated with an increased risk of myocardial infarct or adverse cardiovascular outcomes.^{9,10,27} Cardiovascular risk factors improve overall with smoking cessation that is accomplished with NRT,²¹ and NRT appears safe even when used with high doses of transdermal patch,³² combination NRT²¹ or whilst continuing smoking.^{11,30}

NRT has not been well studied in acutely ill cardiac patients and patients with unstable cardiac conditions. The studies that have been done have not shown an increase in risk of vascular events.^{11,33} The slower delivery rates and lower levels of nicotine with NRT suggest that NRT is safer than continuing smoking in these patients.¹⁹

Myth 4: Smoking while using nicotine replacement therapy is unsafe and increases the risk of heart attack.

Fact: Smoking whilst using nicotine replacement therapy does not significantly increase the risk of a heart attack or related cardiovascular events.

It is advised that people using NRT cease smoking while using NRT to minimise the risk of adverse events associated with high doses of nicotine, such as nausea

and vomiting, as well as to increase the rate of successful quitting rather than any specific cardiovascular risk.

Smoking whilst using NRT does not pose a significant additional cardiovascular risk than that posed by smoking alone. Physiological studies, including one study of wearing up to three 21mg nicotine patches whilst smoking, have demonstrated that tolerance develops acutely to the haemodynamic effects of nicotine, such that further increases in nicotine concentrations from the use of NRT does not further increase heart rate, blood pressure or other cardiovascular effects compared to smoking alone.^{30,32}

Myth 5: Using more than one form of nicotine replacement is unsafe

Fact: Combining more than one form of NRT can be used safely to assist people during a quit smoking attempt.

There are only a small number of clinical trials of the combined use of more than one form of NRT.² These clinical trials indicate that combination therapy can be more effective than a single form of NRT for some patients. These trials have not shown any significant increase in adverse events to suggest that this practice is unsafe.^{21,32,34,35}

Myth 6: Nicotine replacement therapy is as addictive as cigarettes

Fact: Nicotine replacement therapy has a low abuse potential. Nicotine patches have negligible addictive potential and oral forms of NRT are significantly less addictive than cigarettes.

Nicotine can be highly addictive with its addictive potential varying according to the rate and route of administration.⁸ Inhalation of nicotine through cigarettes is the most addictive method of nicotine delivery as:

- It takes only 10-19 seconds for the nicotine absorbed from the lungs to reach the brain.⁸
- Peak blood nicotine levels are achieved within seconds and then decline rapidly; and this pattern is repeated and reinforced with every inhalation.⁸

Nicotine replacement therapy does not produce the rapid, high levels of nicotine in the blood as obtained from smoking. The rise in blood nicotine levels is slower and the level of fluctuation is decreased. Oral forms of NRT, e.g. gum, deliver nicotine at a rate faster than patch but much slower than from a cigarette. Nicotine gum and lozenges have a low addictive potential although it is higher than for NRT patches which has almost no addictive potential.⁸

Myth 7: Nicotine replacement therapy is just as harmful as smoking during pregnancy

Fact: Nicotine replacement therapy is safer than continuing smoking during pregnancy and has the potential to improve birth outcomes.

The harmful effects of smoking during pregnancy are well-established and include an increased risk of miscarriage, premature births and low-weight babies.³⁶ While nicotine may play a part with some of the risks to the foetus by contributing to foetal ischemia, hypoxia^{36,37} and potentially influencing CNS development,³⁷ overall NRT is considered to be safer than continuing to smoke as cigarette smoke contains other known foetal toxins as well as nicotine.^{36,38}

Systematic reviews of smoking cessation during pregnancy have clearly demonstrated that smoking cessation is associated with improved birth outcomes including a reduction in preterm birth and an increase in birth weight.^{39,40}

Experience with NRT in pregnant women is limited. To date, NRT use has not been associated with significant clinical problems for the mother or child,^{37,41,42} however its effectiveness to assist quitting has also not been established.⁴³⁻⁴⁵ Given the need to protect the unborn baby from cigarette smoke and the proven effectiveness of NRT in the general population,² NRT should be considered for use by pregnant smokers who don't believe they would be able to quit without its assistance.

Myth 8: Nicotine replacement therapy is just as harmful as smoking while breastfeeding

Fact: The use of nicotine replacement therapy while breastfeeding is unlikely to be hazardous and is safer than continuing smoking as it reduces infant exposure to cigarette smoke.

The risks of smoking to babies is well documented and includes an increased risk of neonatal mortality and sudden infant death syndrome (SIDS).⁷

Nicotine from smoking and NRT can pass to the baby through breast milk,^{37,46} however infant exposure to nicotine is estimated to be about 50 times less than maternal exposure and is unlikely to be hazardous.³⁷ The use of NRT whilst breastfeeding could reduce infant exposure to cigarette smoke that is known to be hazardous.³⁷

There is no evidence to favour one form of NRT in preference to another for women breastfeeding, hence the selection of which form of NRT to quit with should be based on patient preference and previous quitting experience.

Myth 9: Nicotine replacement therapy is not safe for use by adolescent smokers

Fact: Nicotine replacement therapy can be safely used by adolescent smokers to help them quit.

Most people commence smoking whilst they are teenagers; however there have been very few studies on how to assist adolescent smokers to quit.

To date there are only four published studies on the use of NRT amongst adolescent smokers. The data suggests that NRT patches and gum are well tolerated by adolescent smokers with adverse events reported matching those seen amongst adult smokers.⁴⁷⁻⁵⁰

The efficacy of NRT amongst adolescent smokers from these studies has not been well established in part due to the limited size of the studies. Six month abstinence rates of 5% were observed in the two open-label trials.^{49,50} In a placebo controlled trial, Hanson, *et al.* demonstrated that nicotine patches reduced cravings and withdrawal symptoms, however the quit rate of 28% at 10 weeks was not significantly different to placebo.⁴⁸ In contrast Moolchan, *et al.* demonstrated higher abstinence rates for nicotine patches (17.7% vs 2.5% placebo, $p=0.043$), however the abstinence rate for nicotine gum (6.5%) was not statistically different to placebo.⁴⁷ A potential secondary benefit of using NRT was the reduction in the number of cigarettes smoked per day even amongst those adolescents who failed to achieve total abstinence.⁴⁸

Given that the effectiveness of NRT is well established amongst adult smokers,² and that NRT appears to be well tolerated amongst adolescent smokers, NRT should be considered as a cessation aid by adolescent smokers who are daily smokers and who are motivated to quit.

Conclusion

The safety profile of nicotine replacement therapy is well established and the available evidence can be summarised under the following statement: using nicotine replacement therapy to quit is always safer than continuing to smoke.

Nicotine replacement therapy continues to be a first-line smoking cessation therapy and it has an expanding role in assisting previously considered special patient populations to quit smoking.

Conflict of interest

This review was developed by an expert panel convened by GlaxoSmithKline Consumer Healthcare. The authors would like to thank George Krassas of Scius Solutions Pty Ltd for assistance in the preparation of this manuscript; whose contribution has been funded by an unrestricted educational grant from GlaxoSmithKline Consumer Healthcare.

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