

# Pharmacotherapy for **smoking cessation**

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# Introduction

**This guide aims to be a practical, concise and evidence based resource to be used by a wide range of health professionals working with people who smoke.**

Smoking is the largest preventable cause of death and disease in Australia. Smoking cessation is both cost and clinically effective. Research shows that the cost per life year saved by smoking cessation interventions, makes it one of the most cost effective healthcare interventions.<sup>1</sup>

Health professionals should systematically identify smokers and provide brief advice to quit at every opportunity. Advice from a health professional is one of the most effective ways to encourage people to stop; one in every 33 conversations will lead to a patient successfully stopping smoking.<sup>2</sup>

# Pharmacotherapy for smoking cessation

Three medicines are available in Australia to help people who smoke to quit.

- **Nicotine replacement therapy** (NRT)- patches, intermittent formulations such as lozenges, gum, mouth spray and inhalator
- **Bupropion** (Zyban®)
- **Varenicline** (Champix®).

These medicines have been shown to assist smoking cessation in meta-analyses of randomised clinical trials.<sup>1</sup>

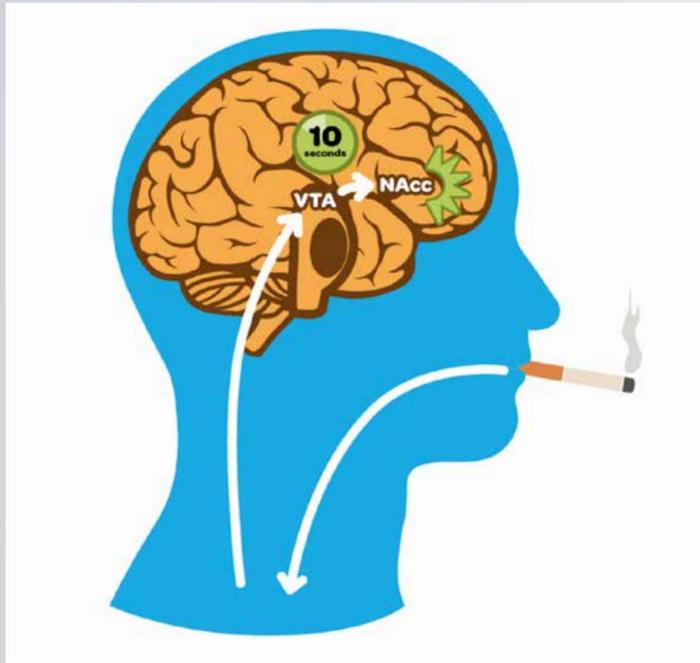
Nicotine patches, Bupropion and Varenicline are available on prescription and are subsidised through the Pharmaceutical Benefits Scheme (PBS).  
<http://www.pbs.gov.au/pbs/home>

All nicotine replacement therapy formulations are widely available through pharmacies and supermarkets.

The choice of pharmacotherapy should be based on clinical suitability and patient choice.

# Smoking is a complex process made up of:

**nicotine dependence** • behavioural connections • psychological connections



## Nicotine dependence

Most people who smoke become nicotine dependent and this can happen quickly.

When cigarette smoke is inhaled, nicotine is absorbed

via the lungs and travels to the brain through the bloodstream within 10 seconds.

Nicotine activates receptors in the brain triggering the release of dopamine and other neurochemicals which bring pleasurable effects.

Smoking (or nicotine dependence) is classified as a chronic medical disease.<sup>3</sup>

Nicotine dependence is under-recognised by health professionals. Assessment of nicotine dependence can help predict whether a

person who smokes is likely to experience symptoms of nicotine withdrawal upon stopping smoking and can direct the intensity and the type of support that may be required to assist quitting. Time to first cigarette after waking has been shown to be a reliable indicator of nicotine dependence.<sup>4</sup>

The Heaviness of Smoking Index ([HSI](#)), is a widely used tool to measure nicotine dependence.

Responses from two questions are summed and a score from 0 to 6 results. A higher score represents higher dependence. People who smoke who experienced withdrawal symptoms during previous quit attempts can be expected to experience them again in a future quit attempt.

# Smoking is a complex process made up of:

nicotine dependence • behavioural connections • psychological connections

## Behavioural connections

People who smoke tend to develop behaviours and routines that are closely linked to their smoking such as drinking caffeinated or alcoholic beverages, taking a break at home or work, socialising, watching television, finishing a meal and talking on the phone. These connections tend to be strong and have built up over many years.

## Psychological connections

People who smoke may form psychological connections to cigarettes, because their smoking is related to how they feel, their moods and emotions. They often draw a connection between smoking and stress relief (especially in a time of crisis), relief of boredom or feelings of comfort and relaxation, especially with a sense of achievement or celebration.

# Nicotine withdrawal

Withdrawal from nicotine can be an uncomfortable experience, particularly within the first 24 hours when symptoms are most severe. These withdrawal symptoms fade significantly within two to four weeks of stopping smoking.

Symptoms commonly include cravings as well as the onset of any of the following shortly after stopping:

- **insomnia**
- **irritability**
- **restlessness**
- **frustration**
- **constipation**
- **mouth ulcers**
- **increased appetite**
- **weight gain**
- **anxiety**
- **difficulty concentrating**

# Nicotine replacement therapy (NRT)

## KEY POINTS

- Using NRT is always safer than smoking<sup>6</sup>
- NRT can increase quit rates by 50–70% compared to unassisted quitting<sup>7</sup>
- More than one form of NRT can be used at the same time with increased success rates and no significant increase in adverse effects<sup>8</sup>
- All forms of NRT at equivalent doses are similarly effective<sup>7</sup>
- Best results are achieved when NRT is combined with counselling and support<sup>9,10</sup>
- There is no evidence that weaning therapy is better than abrupt withdrawal<sup>7</sup>
- People need to use NRT for at least 8 weeks<sup>7</sup>

Smoking leads to a peak in plasma nicotine levels, activation of the reward system, followed by gradual fall into withdrawal, relieved by the next cigarette.

NRT aims to reduce motivation to smoke and the severity of withdrawal symptoms experienced by replacing the nicotine that would be otherwise derived from cigarettes without providing the harmful components of tobacco smoke. This enables people to better focus on addressing the behavioural and psychological aspects of their dependence.

It is important to remember that no formulation offers the

same rapid nicotine delivery of a cigarette. As NRT delivers nicotine slowly, it does not produce high plasma nicotine levels and therefore has minimal dependence potential.<sup>11</sup>

### **Combination therapy**

Combining two formulations of NRT (patch plus intermittent form of NRT) has been shown to have superior efficacy compared to using just one product.<sup>12</sup>

Combination therapy should be recommended for most people who smoke, especially those who are highly dependent, unable to quit using one product or experience cravings while using one product alone.

The patch delivers nicotine gradually and produces sustained nicotine levels throughout the day, whereas the intermittent forms provide flexible relief for breakthrough cravings. Intermittent forms should be taken in anticipation of a smoking trigger if possible, but can also be used when a craving arises.

Using a single type of NRT results in levels of nicotine in the blood that are approximately one third to one half of the nicotine levels reached by smoking.<sup>13</sup>

# Nicotine replacement therapy (NRT)

## Higher dose

Adding a second patch produces a modest increase in quit rates, around 14%.<sup>7</sup> Higher doses of intermittent formulations have been shown to be safe and significantly increase quit rates and should be used in those who smoke within 30 minutes of waking.<sup>6</sup>

## Longer durations

Some people may need NRT for longer than 8 weeks. A randomised controlled trial by Scholl et al. compared extended use of nicotine patches (30 weeks) with standard therapy (8 weeks).<sup>14</sup>

Point prevalence abstinence was two times greater for extended versus standard therapy at week 24. Moore and colleagues demonstrated that when NRT was used for 6–18 months, there was no statistically significant difference to placebo in terms of mortality or serious adverse events.<sup>15</sup>

## Cut down to stop

Unfortunately many people who smoke and cut down the number of cigarettes smoked, often smoke these fewer cigarettes in a different way (breathing in deeper and holding the smoke in their lungs

longer). Therefore they may inhale a similar dose of nicotine along with harmful components of tobacco smoke as they did from smoking their usual amount. This is called ‘titrating the nicotine dose’.

People who choose the ‘cut down to stop’ method should use intermittent formulations of NRT at the same time to help mitigate this ‘titration’.

This method may increase the number of quitters by engaging a broader population of people who smoke compared with traditional interventions.

## Use of nicotine patches prior to quitting

Another application is the use of nicotine patches prior to quit date. This method has been shown to increase success rates over and above the traditional quit date application by 35%.<sup>7</sup> The person’s self-efficacy is increased as they feel confident that the NRT can minimise their withdrawal symptoms.

# Specific patient groups or settings

## Adolescents

It is estimated that more than 80% of people who smoke become nicotine dependent as teenagers.<sup>16</sup> All formulations of NRT can be used safely by people aged 12 years and over.

*Evidence-* NRT can be safely used, however there is little evidence that NRT alone is effective at promoting long term cessation and requires comprehensive counselling support.<sup>17</sup>

## Cardiovascular

NRT can be recommended to people with stable cardiovascular disease. There is also growing evidence for the safety of NRT

in smokers with acute coronary syndrome, and its use can be considered under medical supervision if patients are unable to abstain from smoking without it.<sup>18-20</sup>

*Evidence-* use of NRT after acute coronary syndrome was not associated with an increased risk of cardiovascular events.<sup>21</sup> The safety of NRT in smokers with stable cardiovascular disease has been firmly established. A number of studies have found no increased incidence of adverse cardiovascular events compared with placebo.<sup>22,23</sup>

## Pregnancy

Non-pharmacological strategies should be trialled if possible.

NRT may be considered in pregnant women who have failed to quit smoking using non-pharmacological strategies.

Use the lowest effective dose of NRT and where possible intermittent formulations are preferred.<sup>24</sup>

*Evidence-* although there is limited safety information (ADEC category D- <https://www.tga.gov.au/australian-categorisation-system-prescribing-medicines-pregnancy>), the risk to the fetus is probably less than to be expected with continued smoking due to lower plasma nicotine concentrations and no exposure to polycyclic

hydrocarbons and carbon monoxide.<sup>25</sup>

## Breast feeding

Non-pharmacological strategies should be trialled if possible. NRT may be considered in breast feeding mothers who have failed to quit smoking using non-pharmacological strategies. Use the lowest effective dose of NRT and where possible intermittent forms are preferred.

*Evidence-* limited information available. Allow approximately 2–3 hours following the use of intermittent forms of NRT before breast feeding to reduce nicotine exposure in the breast-fed infant.<sup>26,27</sup>

# Practical guide to NRT administration

## Transdermal formulation



### Nicotine patch

- Place patch on a clean, non-hairy site on the chest or upper arm, preferably at night
- Remove the old patch and apply new patch daily, alternating sites
- Skin irritation may occur, but it is usually transient
- Slow skin absorption – takes several hours to reach steady state
- Continue to use patch after a lapse- 4–5 times more likely to be abstinent at end of treatment period<sup>28</sup>
- This is the only formulation currently available on the PBS

## Intermittent formulations

Nicotine from all the intermittent products is absorbed through the buccal mucosa (lining of the mouth). Concurrent eating and drinking should be discouraged. Correct technique is important for all of these products as swallowed nicotine is poorly absorbed and may cause adverse effects such as nausea or hiccups.



### Nicotine lozenges

- Recommend regular use
- Suck gently to release the bitter taste, and then rest the lozenge in the side of the mouth (between cheek and gum). Suck again when the taste starts to fade.
- Move the lozenge from one side of the mouth to the other until completely dissolved
- Do not chew or swallow
- Each lozenge will take approximately 15–20 minutes to dissolve

# Practical guide to NRT administration

## Nicotine gum

- Recommend regular use
- Place gum in mouth and chew slowly until a tingly sensation or bitter taste appears
- Avoid chewing quickly or for too long
- 'Park' the gum under the tongue or between the cheek until tingling and/or taste subsides
- Resume chewing and repeat above process
- To extract all of the nicotine, the gum needs to be chewed for approximately 30 minutes using the correct technique



## Nicotine inhalator

- Recommend regular use
- Insert cartridge into mouthpiece
- Take shallow inhalations to deliver the nicotine into the oral cavity- deep inhalations should be avoided
- A puff of the inhalator delivers far less nicotine than a puff of a cigarette, therefore 8–10 times more puffs of an inhalator are required compared to a cigarette
- Each cartridge contains the same amount of nicotine as 7 cigarettes



- Opened cartridges should only be used for a maximum of 12 hours or until empty

# Practical guide to NRT administration

## Nicotine mouth spray

- Recommend regular use
- Press the top of the dispenser to release one spray into the side of the cheek or under the tongue, being sure to avoid the lips
- If the spray is being used for the first time or it has not been used for several days, the spray should be primed
- Priming involves pointing the spray away from you and depressing the dispenser with the index finger several times until a fine mist appears. This ensures the correct dosage is dispensed
- Do not spray directly into the throat, directly onto the tongue or inhale while spraying
- Do not swallow for a few seconds after spraying for best results (this is so the nicotine can be absorbed through the lining of the mouth)



# Varenicline (Champix®)

## KEY POINTS

- Varenicline can increase the chances of successful long term smoking cessation between two to three-fold compared with pharmacologically unassisted quit attempts<sup>29,30</sup>
- Superior efficacy of varenicline compared to single type NRT or bupropion; it is as effective as combination NRT<sup>31</sup>
- Meta-analysis of randomised controlled trials (RCTs) suggest a longer course increases long-term quit rates<sup>32</sup>
- Closely monitor use in patients with underlying cardiovascular or psychiatric illness
- The EAGLES study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo in patients with or without a history of psychiatric disorders\*<sup>33</sup>
- Nausea is common, but can be minimised by taking with food and having adequate daily fluid intake. If persistent, dose reduction can be considered
- Varenicline may also be helpful for those who are less committed to smoking cessation<sup>34</sup>

Varenicline is a partial agonist at nicotinic acetylcholine receptors where it binds to these receptors alleviating the symptoms of craving and withdrawal. At the same time, when a cigarette is smoked, it prevents this nicotine from activating the receptor sufficiently to cause the pleasure and reward response. It is recommended that treatment is started while the patient is still smoking and a 'target stop date' set within the first two weeks of treatment, preferably in the second week.

A longer pre-loading period prior to the quit date may be more effective in achieving abstinence.<sup>35</sup>

It is available on prescription only (PBS- authority). If smoking cessation is successful in the first 12 weeks, the person is eligible for a further 12 week supply.

To view product information for any of the formulations visit the Clinicians Health Channel at:  
<https://www2.health.vic.gov.au/clinicianshealthchannel>

\*The EAGLES study included people who smoke with psychiatric disorders who were stable and treated or who had previous psychiatric conditions that were in remission<sup>33</sup>

# Bupropion (Zyban®)

## KEY POINTS

- Clinical trials have shown that bupropion increases long-term quit rates when compared to placebo, but it is not as effective as varenicline (may be a useful option when varenicline is not appropriate)<sup>36</sup>
- Bupropion is contraindicated in patients with a history of seizures, eating disorders and those taking mono-amine oxidase inhibitors
- Bupropion should be used in caution in patients taking medications that lower the seizure threshold<sup>29</sup>
- Insomnia is common but can be minimised by bringing the evening dose forward (provided there is at least eight hours between doses). If persistent, dose reduction may be considered
- Bupropion should be taken for at least 12 weeks. A longer duration therapy may prevent relapse in successful quitters<sup>37</sup>
- Bupropion may be a good choice for use in those people who smoke who are especially concerned about post-cessation weight gain, which bupropion blunts temporarily<sup>38</sup>

Bupropion is a non-nicotine oral therapy; originally developed as an antidepressant.

It works by increasing brain levels of dopamine and noradrenaline which reduces nicotine withdrawal symptoms and urges to smoke. It is recommended that treatment is started while the patient is still smoking and a 'target stop date' set within the first two weeks of treatment, preferably in the second week.

It is available on prescription only (PBS- authority).

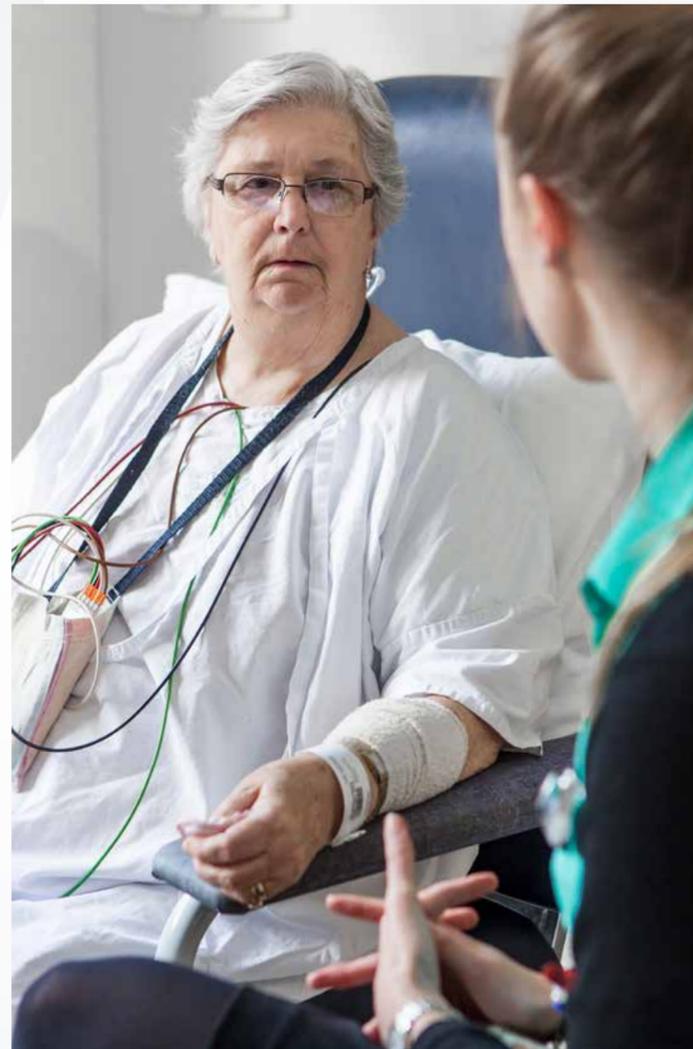
To view product information for any of the formulations visit the Clinicians Health Channel at:  
<https://www2.health.vic.gov.au/clinicianshealthchannel>

# Behavioural management strategies

A nicotine craving is short term and will usually fade within a few minutes. Ideally, the chosen pharmacotherapy will minimise the experience of cravings.

The following behavioural management strategies can be useful for coping with nicotine withdrawal symptoms and the behavioural and psychological connections associated with smoking:

- practice the 4Ds
  - delay
  - deep breathe
  - drink water
  - do something else
- undertake relaxation and breathing exercises
- exercise
- focus on specific reasons to quit



# Drug interactions

Many interactions between tobacco smoke and medications have been identified. In most cases it is the tobacco smoke, not the nicotine that causes these drug interactions.

Tobacco smoke may interact with medications through either pharmacokinetic or pharmacodynamic mechanisms.

The majority of pharmacokinetic interactions with smoking are the result of polycyclic aromatic hydrocarbons of cigarette

smoke stimulating the hepatic enzymes, in particular the cytochrome (CYP) P450 iso-enzymes 1A1, 1A2 and 2E. Induction of these enzymes may result in an increase in the metabolism of many medications that are substrates of these enzymes, and cause a subsequent decrease in plasma concentrations of these medications. This enzyme induction is rapidly reversed when patients completely stop smoking, with a new steady state of CYP activity reached after approximately one week.<sup>39</sup>

Pharmacodynamic interactions alter the expected response or actions of other drugs. Nicotine can counter the pharmacological actions of certain drugs, because it activates the sympathetic nervous system. The amount of tobacco smoking needed to have an effect has not yet been established and therefore the assumption is that any smoker is susceptible to the same degree of interaction.

The majority of interactions are not considered to be of clinical significance but the potential for interaction should be borne in mind if a person stops smoking. Those of greatest significance include caffeine, chlorpromazine, clozapine, insulin, olanzapine, theophylline and warfarin.

Since the majority of interactions are due to components of cigarette smoke other than nicotine, these interactions are not expected to occur with Nicotine Replacement Therapy (NRT).

# Drug interactions

Dose adjustments may therefore be required based on clinical presentation and according to medical review. In certain situations, it may be appropriate to liaise with a specialist team prior to dose adjustment e.g. for patients prescribed antipsychotic medications such as clozapine.

Drug information resources contain varying reports of the effect of smoking. The following references are useful for common medications which may need a reduction upon smoking cessation:

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