

# Recent developments in smoking cessation

**New research into nicotine replacement therapy (NRT) has delivered creative ways to enhance the use and effectiveness of existing products, such as pre-quit treatment with nicotine patches, combination NRT and the use of nicotine products in unmotivated smokers. The new drug varenicline is another potent tool for helping smokers quit.**



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Currently, 16.6% of Australians aged 14 years or older smoke daily.<sup>1</sup> This represents 2.9 million people in Australia, one in two of whom will die prematurely from a smoking-related disease if they continue to smoke.<sup>2</sup>

GPs are in a prime position to help address this major public health problem. There is strong evidence that even minimal advice from the GP has a significant impact on the patient.<sup>3</sup> The more time GPs can give to consultations, the better their skills in counselling and motivating patients, and the more knowledge they have about the effective use of smoking cessation medications, the more effective the interventions will be.

This article aims to update GPs on some recent developments in the field of smoking cessation to help enhance their interventions with their patients who smoke.

## Pharmacotherapy for all nicotine-dependent motivated smokers

The most popular method of quitting used by

Australian smokers is the 'cold turkey' method – that is, quitting abruptly with no medication or assistance. At their last attempt at quitting, 88% of former smokers used this technique.<sup>4</sup> However, only 3 to 5% of smokers who try to quit without treatment remain abstinent six to 12 months later.<sup>5</sup>

Australian and international guidelines now advise using medication to assist quitting in all smokers who are nicotine dependent, except where contraindicated, such as the use of bupropion in a smoker with an eating disorder.<sup>6,7</sup> First-line therapies consist of nicotine replacement therapy (NRT; Nicabate products, Nicorette products, Nicotinell products, QuitX products), varenicline (Champix) and bupropion (Clorprax, Prexaton, Zyban SR), which all increase quit rates by two to three times compared with placebo (Table 1). They mostly work by reducing cravings and easing withdrawal symptoms.

Although medication is effective on its own, the best results are achieved when it is provided with counselling and support.

### IN SUMMARY

- Pharmacotherapy should be offered to all motivated smokers who are nicotine dependent.
- Nicotine patches should be started two weeks before quitting in motivated smokers.
- Nicotine gum or a nicotine inhaler should be used to help unmotivated smokers quit.
- The most effective therapies are combination nicotine replacement therapy, varenicline and pre-quit nicotine patches.
- Nicotine replacement therapy should be continued after a lapse to prevent progression to a full relapse.
- The new drug varenicline is an effective and well-tolerated first-line smoking cessation therapy.

### Assess motivation

Medication should only be given to patients who are motivated or ready to quit (except in the new 'cut down then stop' strategy described below). According to recent research, 21% of Australian smokers are planning to quit in the next 30 days, 42% are unsure ('contemplators') and 36.5% are not thinking about quitting ('precontemplators').<sup>8</sup>

To assess motivation, the patient should be asked:<sup>9</sup>

- How do you feel about your smoking at the moment?
- Are you ready to quit now?

Most interventions for smokers are now matched to the stage of readiness of the smoker to quit. However, a meta-analysis of smoking cessation trials found limited effectiveness for this approach. Further high-quality trials are required to clarify the value of stage-based interventions.<sup>10</sup>

### Assess nicotine dependence

Pharmacotherapy is only appropriate if the smoker is nicotine dependent. To assess nicotine dependence the patient should be asked:

- Do you usually smoke within 30 minutes of waking?
- Do you smoke between 10 and 15 or more cigarettes per day?
- Have you had cravings or withdrawal symptoms during previous quit attempts?

Nicotine dependence is likely if there is a positive answer to any of these questions.

### Pre-quit treatment with nicotine patches

Conventional practice is to start using nicotine patches (Nicabate and Nicabate Clear, Nicorette Patch, Nicotinell Patches, QuitX Patches) on day one of quitting ('quit day'). This almost doubles the chance of quitting successfully compared with the use of placebo patches (risk ratio [RR] = 1.9).<sup>11</sup> However, a recent meta-analysis of four trials found that starting nicotine patches two or four weeks before quitting more than doubles the odds of quitting successfully at six months compared with patch use from quit day only (odds ratio [OR] = 2.17).<sup>12</sup>

When NRT was first introduced patients were warned to avoid smoking when using it; however, extensive research has failed to show any harm



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from smoking while on NRT.<sup>13</sup> Furthermore, there were no increased adverse events or safety concerns in the pre-quit trials.

There are several possible mechanisms to explain the successful quitting of patients using pre-quit treatment. These mechanisms include:

- possibly helping to reduce the anxiety associated with an abrupt quit
- possibly reducing dependence on cigarettes
- making cigarettes smoked while wearing a nicotine patch possibly less satisfying
- allowing smokers to become familiar with the patches before quit day.

Although only four trials of pre-quit treatment have been conducted, the results of the meta-analysis of these trials are robust, consistent and highly significant. GPs should feel confident in using this method as a first-line treatment.

**Table 1. First-line smoking cessation products available in Australia**

Medication	Brand names	Strength	Course length according to PI*	Efficacy† (risk ratio)	PBS listing
Varenicline	Champix	1 mg	12 weeks An additional 12-week course can be given to increase success rate	2.33	S4 (PBS Authority)
Bupropion	Clorprax, Prexaton, Zyban SR	150 mg	7 weeks	1.94	S4 (PBS Authority)
NRT patch	Nicabate and Nicabate Clear	7 mg, 14 mg, 21 mg per day	10 to 14 weeks	1.9	Unscheduled
	Nicotinell Patches, QuitX Patches	7 mg, 14 mg, 21 mg per day	12 weeks		
	Nicorette Patch	5 mg, 10 mg, 15 mg per 16 hours	16 weeks	1.9	Unscheduled
NRT gum	Nicabate Soft Gum, Nicorette Chewing Gum, Nicotinell Chewing Gum, QuitX Chewing Gum, QuitX Coated Chewing Gum	2 mg, 4 mg	16 weeks maximum	1.43 (2 mg and 4 mg gum combined)	Unscheduled
NRT lozenge	Nicabate Lozenges	2 mg, 4 mg	12 weeks initially and a further 12 weeks if tempted to smoke	2.02 (lozenges and tablets combined)	Unscheduled
NRT tablet	Nicorette Microtab	2 mg	2 to 6 months		Unscheduled
NRT inhaler	Nicorette Inhaler	10 mg	3 to 5 months	2.00	S2 (pharmacy medicine)

\* Please refer to full product information. †Efficacy figures taken from the Cochrane Database of Systemic Reviews.<sup>11,18,20</sup>  
 ABBREVIATION: NRT = nicotine replacement therapy.

One brand of nicotine patch (Nicabate Pre-Quit) has been approved in Australia as a pre-quit treatment for smokers of 15 cigarettes or more per day. The pre-quit patches are worn for two weeks before quit day. Nicotine patches are then continued for the full course of 10 to 14 weeks after quit day.

### Cut down then stop method

Cut down then stop is a new strategy for smokers who are not currently willing or able to stop smoking but are prepared to cut down. At any one time, about half of smokers are interested in cutting down

rather than stopping completely. The use of nicotine gum (Nicabate Soft Gum, Nicorette Chewing Gum, Nicotinell Chewing Gum, QuitX Chewing Gum, QuitX Coated Chewing Gum) or a nicotine inhaler (Nicorette Inhaler) in this group motivates some of them to make a quit attempt.

A meta-analysis of eight trials found that this strategy almost doubles the chance of the patient being abstinent one year later compared with placebo (RR=1.90).<sup>14</sup>

When attempting the cut down then stop method, smokers start using nicotine

gum or a nicotine inhaler while still smoking. They gradually cut down their cigarette use and stop smoking completely by six months. NRT is ceased by 12 months (Table 2).<sup>15</sup>

NRT boosts nicotine levels, making it easier for the smoker to have fewer cigarettes, reducing dependence and making it easier to finally quit. No serious adverse effects have been found when combining smoking with nicotine gum or an inhaler. Blood nicotine levels are mostly unchanged because smokers titrate their nicotine intake.<sup>13</sup>

Cutting down smoking by concurrent

use of NRT is only recommended as a precursor to quitting and progressing to complete abstinence remains the goal. There is uncertainty about the size of the health benefit achieved from simply reducing cigarette use, without actually quitting.<sup>14</sup>

The Therapeutic Goods Administration (TGA) has approved the use of nicotine gum and nicotine inhaler for the cut down then quit method.

### Combination nicotine replacement therapy

Combination NRT refers to the use of nicotine patches to provide steady background nicotine levels combined with a quick-acting form of NRT (such as chewing gum, lozenges [Nicabate Lozenges], inhaler or tablets [Nicabate Microtab]) for prompt relief of withdrawal symptoms or cravings as they arise.

**Table 2. Schedule for cut down then quit using nicotine gum or a nicotine inhaler\***

Time	Goal
0 to 6 weeks	Cut down the number of cigarettes smoked to 50%
6 weeks to 6 months	Continue to cut down; stop completely by six months
6 to 9 months	Stop smoking completely, continue NRT
Within 12 months	Stop using NRT

\* Data from Guidelines for healthcare professionals on using nicotine replacement therapy for smokers not yet ready to stop smoking. Action on Smoking and Health Australia, February 2007. <http://www.ashaust.org.au/pdfs/NRTguide0702.pdf><sup>5</sup>

A recent Cochrane meta-analysis of seven trials of combination NRT found that it increases the odds of quitting by more than one-third compared with using one product alone (RR=1.35).<sup>11</sup>

Australian and US guidelines suggest using combination NRT for highly

dependent smokers who experience relapse or withdrawal symptoms with monotherapy.<sup>6,7,16</sup> However, many experts now advise routine use of combination NRT for all patients, unless it is contraindicated.<sup>17</sup>

When using NRT, patients often fail

to follow the correct dosing instructions and receive inadequate levels of nicotine. Combination NRT delivers higher blood nicotine levels that are more effective in controlling symptoms.

There are no safety concerns with combination therapy and adverse effects are uncommon. Smokers self-regulate their nicotine intake and avoid excessive blood nicotine levels. Combination NRT has recently been approved by the TGA and is now included in the Australian product information of nicotine products.

Combination therapy with nicotine patches and bupropion is also a safe and effective combination treatment.

### Varenicline

Varenicline is the latest smoking cessation product and it became available as a PBS authority prescription on 1 January 2008. Varenicline reduces cravings and withdrawal symptoms as other treatments do, but also reduces satisfaction gained from smoking a cigarette.

A recent Cochrane meta-analysis found that varenicline increases rates of quitting by two to three times compared with placebo use at six months or longer (RR=2.33).<sup>18</sup> A head-to-head trial of varenicline and nicotine patches showed a 'modest' benefit of varenicline compared with the patches at one year (RR=1.31).<sup>19</sup> Varenicline was more effective than bupropion (RR=1.52).<sup>18</sup>

Varenicline is taken as a 12-week course of 1 mg tablets twice daily after an initial one-week titration phase. The patient should quit smoking between seven and 10 days after the first dose.

Nausea occurs in up to 30% of patients taking varenicline, but it is usually mild and responsible for discontinuation of treatment in less than 3% of cases. Other side effects include headache, insomnia, disturbed dreams and drowsiness. Varenicline is excreted unchanged in the urine and the dose should be halved in patients with severe renal impairment.

There have been postmarketing reports of patients taking varenicline experiencing depressed mood, agitation, changes in behaviour and suicide ideation, and some suicides; however, there is no scientific evidence of a causal relation. Smoking cessation itself causes these symptoms and exacerbates underlying psychiatric illness. All patients using varenicline should be monitored for mood or behaviour changes. Special care should be taken with patients with a history of psychiatric illness. The studies on varenicline excluded patients with serious psychiatric conditions, so there is a lack of evidence about the efficacy and safety of varenicline in these patients.

### Bupropion

Bupropion is an effective first-line therapy that almost doubles the odds of quitting (OR=1.94).<sup>20</sup>

There is a one in 1000 risk of seizures in patients taking it and it is contraindicated in patients with predisposing risk factors for seizures. In 2001, there were postmarketing reports of deaths while taking bupropion, although subsequent analysis revealed no increased risk of death from the drug.<sup>21</sup> Although it is generally well tolerated, bupropion is now prescribed infrequently as a result of these concerns.

Bupropion is available on authority prescription and should be considered for smokers who prefer an oral, non-nicotine and inexpensive medication.

### Therapies for highly dependent smokers

Many smokers are highly dependent on nicotine. These patients experience more severe withdrawal symptoms and cravings when trying to quit and are less likely to succeed than patients who are less dependent on nicotine. These smokers should be given the most potent medical therapies available, as well as additional counselling and support.

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Varenicline, combination NRT and pre-quit treatment with nicotine patches are the most effective medications to help smokers quit and are especially useful for more dependent smokers.<sup>7,12</sup> However, there have been no head-to-head trials of these therapies to make direct comparisons.

For highly dependent smokers, 4 mg nicotine gum is significantly more effective than 2 mg gum (RR=1.85).<sup>11</sup> Similarly, 4 mg nicotine lozenges appear to be more effective than 2 mg lozenges and are recommended for more dependent smokers who choose to use lozenges.<sup>22</sup>

Standard 21 mg nicotine patches have been compared with nicotine patches of up to double the standard dose in a meta-analysis of seven trials, which showed only a marginal benefit from the higher dose patch (RR=1.15).<sup>11</sup>

### Nicotine misconceptions

There are many misconceptions held by both patients and doctors about nicotine and its effects on health (Table 3).<sup>23</sup> Unfortunately, these may lead to the underutilisation of NRT. However, the safety of nicotine is now well established and NRT can be used more freely.

Nicotine is not one of the toxic ingredients in cigarettes and is not responsible for tobacco-related disease. It is not carcinogenic and does not cause respiratory disease.

Nicotine causes minor haemodynamic effects but is not a major cause of cardiac disease and can be safely used in stable cardiac conditions. Even smoking while using NRT does not increase the risk of cardiovascular events.

Nicotine from cigarettes is highly addictive because of the rapid method

of delivery of the drug. In comparison, it is delivered slowly from NRT formulations and the risk of addiction is low, especially from nicotine patches.

NRT has recently been approved for use in pregnancy for women unable to quit on their own. Quick-acting forms of NRT, such as the nicotine gum or lozenges, are preferred in pregnancy. If nicotine patches are used, they should be removed at bedtime.

Quick-acting forms of NRT are also now approved for use in women who are breastfeeding. Although nicotine may be harmful to the fetus, the risk of harm from NRT is less than that from smoking.

NRT is safe and well tolerated in adolescents, although its efficacy has not been clearly demonstrated. Use in this age group has recently been approved by the TGA.

**Table 3. Nicotine misconceptions and facts**

Misconception	Fact
Nicotine is the most harmful ingredient in cigarettes	Nicotine is not directly responsible for tobacco-related diseases. Its important action is induction and maintenance of addiction
Nicotine causes cancer	Nicotine is not carcinogenic
Nicotine causes cardiovascular disease	Nicotine does cause haemodynamic effects; however, it is not the major cause of increased cardiac risk associated with smoking
Smoking while using nicotine replacement therapy (NRT) is unsafe and increases the risk of having a heart attack	Smoking while using NRT does not increase the risk of having a heart attack or any related cardiovascular events
Using more than one form of NRT is unsafe	Using more than one form of NRT can be used safely to assist people to quit smoking
NRT is as addictive as cigarettes	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
NRT is just as harmful as smoking during pregnancy	NRT is safer than continuing smoking during pregnancy and has the potential to improve birth outcomes
NRT is just as harmful as smoking while breastfeeding	The use of NRT while breastfeeding is unlikely to be hazardous and is safer than continuing smoking because it reduces infant exposure to cigarette smoke
NRT is not safe for use by adolescent smokers	NRT can be used safely by adolescent smokers to quit. The adverse event profile in adolescents is the same as in adults

Adapted from Zwar N, Bell J, Peters M, Christie M, Mendelsohn C. Nicotine and nicotine replacement therapy – the facts. *Aust Pharm* 2006; 25: 969-973.<sup>23</sup>

## Weight gain

A recent review of the literature found that persistent quitters had gained an average of 7 kg in weight at a follow up of four to eight years.<sup>24</sup> This is about double the amount of weight gain seen at short-term follow up of six to 12 months, which is generally accepted to be about 2 to 4 kg.<sup>25</sup> It also challenges the traditional advice to smokers that weight gain is only temporary.

This is bad news for many smokers and may discourage a quit attempt. However, smokers should be advised that the health benefits of quitting far outweigh the harm from any weight gain. Nevertheless, for some it will seem to be an insurmountable barrier.

Dieting while trying to quit worsens smoking outcomes. It is best to delay food restrictions until several months after stopping.<sup>26</sup>

Bupropion and NRT, in particular

4 mg gums and 4 mg lozenges, delay but do not prevent weight gain.<sup>7</sup>

## Use of nicotine replacement therapy after a lapse

Many smokers using NRT will have a lapse or slip (i.e. smoke one or two cigarettes) during a quit attempt. When this happens it is important to quickly refocus on quitting to prevent the lapse becoming a full relapse (i.e. a return to regular smoking), as is often the case.

The traditional advice to smokers has been to stop NRT after a lapse because of cardiovascular concerns with higher levels of nicotine from concurrent NRT and smoking. However, it is now known that this does not significantly increase the risk of adverse events. Smoking while using NRT appears to be safe.<sup>13</sup>

Furthermore, NRT has a powerful role in preventing a lapse from becoming a

full relapse. In one study, nicotine patches reduced progression from a lapse to a full relapse by seven-fold.<sup>27</sup> As a result, NRT should continue to be used during the lapse period to assist in the return to non-smoking.

## Gradual or abrupt cessation

It has been standard practice to advise smokers to quit abruptly or go 'cold turkey' rather than gradually reducing the number of cigarettes smoked before quitting. However, this recommendation is not based on evidence, because four of the five randomised controlled trials comparing gradual with abrupt cessation found higher quit rates were associated with gradual cessation.<sup>28,29</sup>

Many, if not most, smokers would prefer to reduce the number of cigarettes they smoke before quitting<sup>28,29</sup> and, given the evidence, should not be discouraged from doing so. One approach that has

## Patient resources

- Quitline 137 848
- Quit Now: [www.quitnow.info.au](http://www.quitnow.info.au)
- Quit Victoria: [ww9w.quit.org.au](http://ww9w.quit.org.au)

been suggested is to advise smokers to set a quit day three to four weeks in the future and to reduce their cigarette use by 50% in that time using one of two methods:

- hierarchical reduction – individual cigarettes are ranked from the hardest to give up to the easiest, and the easiest ones are eliminated first.
- scheduled reduction – the time between cigarettes is gradually increased.

Gradual reduction in the number of cigarettes smoked can be supported with quick-acting forms of NRT, such as the nicotine gum or inhaler, as for the cut down then stop method for unmotivated smokers. Some useful patient resources are given in the box on this page.

## Conclusion

Rates of unassisted quitting are very low. NRT, varenicline or bupropion should be used to boost quit rates in all motivated smokers who are nicotine dependent.

Research has now established the safety of therapeutic nicotine and delivered creative new ways of using it. Better results can be achieved by starting to use nicotine patches two weeks before quit day and by the more widespread use of combination therapy. NRT should be continued during lapses and can assist smokers who wish to quit gradually.

Nicotine gum and a nicotine inhaler also have a proven role in smokers who are not yet ready to quit, motivating them to make a quit attempt. Varenicline is a potent and well-tolerated first-line pharmacotherapy and is a valuable addition to the GP's armamentarium.

With these new tools and strategies,

GPs will make more of an impact when helping their smoking patients. **MT**

## Acknowledgements

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*A list of references is available on request to the editorial office.*

## Further reading

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**COMPETING INTERESTS:** Dr Mendelsohn has received honoraria for teaching, consulting and travel from Pfizer, and is on the Champix Advisory Board.

He has also received honoraria for consulting from GlaxoSmithKline and as a member of the Nicotine Replacement Therapy Expert Panel. Both companies have sponsored articles in *Your Health* newsletter, of which Dr Mendelsohn is the editor.

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