Background
In spite of an established safety and efficacy record, nicotine replacement therapy (NRT) is frequently used incorrectly, suboptimally, or not at all.

Objective
This article reviews practical evidence based strategies to optimise the use of NRT in clinical practice. The increasing role of combination therapies is explored and strategies to prevent relapse using NRT are examined.

Discussion
Misguided concerns about safety and efficacy undermine the use of NRT and should be addressed proactively with accurate information. It is also vital to give detailed instructions for the correct use of NRT products and to use an adequate dose to relieve symptoms.

Quit rates can be increased further, by starting the nicotine patch 2 weeks before quitting, combining a patch with an oral form of NRT (such as gum or lozenges) and continuing to wear the patch after a lapse. Oral forms of NRT relieve cue induced cravings and this may help prevent relapse.

Keywords
nicotine replacement products; smoking cessation

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Nicotine replacement therapy (NRT) has been available in Australia for nearly 30 years and is the most widely used pharmacotherapy to help smokers quit. Nicotine replacement therapy is available as a nicotine patch, gum, lozenge, inhalator and mouth spray.

Nicotine replacement therapy has an established safety and efficacy record in over 150 clinical trials and increases quit rates by about 60% compared to placebo. Ongoing research continues to find new ways of using NRT more effectively. However, in spite of this, studies show that there is considerable misinformation about the safety, effectiveness and correct use of therapeutic nicotine among both patients and health professionals.

There is good evidence that NRT products are frequently used incorrectly, suboptimally, or not at all. Nicotine patches are now available on the Pharmaceutical Benefits Scheme (PBS) and may be prescribed by the general practitioner as NRT.

This article reviews practical evidence based strategies to optimise the use of NRT in clinical practice. This includes how to improve patient compliance and the vital importance of adequate dosing and correct use of all types of NRT products. The increasing role of combination therapies is explored and strategies to prevent relapse using NRT are also examined.

Nicotine replacement therapy addresses only the physical component of smoking (ie. nicotine addiction). Counselling and support to break the psychological habit are an integral part of treatment, but will not be discussed in this review.

Patient compliance
Compliance with NRT is generally poor, especially in pregnancy. Most smokers use less than the prescribed dose of medication and do not complete the full course of treatment. However, studies consistently show that using more pieces of nicotine gum and nicotine lozenges, and more doses of nicotine inhaler, increase quit rates. For example, for each additional lozenge used per day, the odds of successful quitting increase by 10%.

Correct adherence with daily use of a nicotine patch also increases success. In one study, daily patch use in the first 3 weeks more than tripled abstinence at 6 weeks compared to less compliant use.

Most users discontinue treatment prematurely. For example, in one community study, fewer than 1 in 8 people used it for 8 weeks, which is the recommended minimum duration of treatment.

Misinformation about NRT is a common cause of poor compliance. Many smokers believe that NRT is unsafe. However, nicotine is not the major toxic ingredient in tobacco and NRT has a strong safety record.

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Misinformation about NRT is a common cause of poor compliance. Many smokers believe that NRT is unsafe. However, nicotine is not the major toxic ingredient in tobacco and NRT has a strong safety record.
A majority of smokers do not believe NRT is effective, in spite of extensive research conclusively demonstrating the opposite. A common fear is that NRT is addictive. In fact, all forms of NRT deliver nicotine much more slowly than cigarettes, and NRT has low or no abuse potential. In any case, the adverse effects of long term NRT are negligible compared to smoking. These beliefs may reduce the uptake of NRT and thereby undermine outcomes. If they are directly addressed with scientific information, approximately half of the misinformed smokers say they would be more likely to use NRT as part of a quit attempt. This would also be expected to increase compliance when using NRT. General practitioners could proactively discuss these issues with their patients, particularly concerns about safety (Table 1).

Ironically, one of the most common reasons for ceasing NRT prematurely is because it is effective. When craving and withdrawal are well controlled via treatment, patients may mistakenly assume that the treatment is no longer necessary. Other causes of poor compliance and strategies to address these are shown in Table 2.

**Correct usage of oral NRT**

The oral, quick acting forms of NRT (lozenges, gum, inhalator, mouth spray) are often used incorrectly, resulting in lower effectiveness and more side effects. It is vital to instruct patients on their correct use and to review their technique at follow up visits (Table 3).

Nicotine from all the oral products is absorbed through the lining of the mouth. A slow chewing and sucking technique is vital for nicotine gum and lozenges as swallowed nicotine is poorly absorbed and may cause nausea or hiccups. The inhalator requires shallow inhalations to deliver nicotine into the oral cavity, as, unlike cigarettes, it is not absorbed from the lungs. The mouth spray is sprayed into the side of the mouth or under the tongue.

Patients should be advised not drink or eat immediately before and while using any form

### Table 2. Improving patient compliance

<table>
<thead>
<tr>
<th>Common causes of poor compliance</th>
<th>What to discuss with patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerns about safety</td>
<td>NRT is always safer than smoking. Nicotine levels from NRT are much lower than smoking. Nicotine does not cause cancer, lung disease or heart attacks. It is the other chemicals in tobacco smoke that cause most of the health effects of smoking. NRT does not kill, it helps people stop smoking, and stopping smoking saves lives.</td>
</tr>
<tr>
<td>Concerns about the addictiveness of NRT</td>
<td>Cigarettes are far more addictive than NRT. You get less nicotine from NRT and it is delivered more slowly so the risk of becoming addicted is very small. Using NRT for a very long time is much less harmful to health than smoking</td>
</tr>
<tr>
<td>Lack of confidence in efficacy</td>
<td>Short term use of NRT is a proven aid to quitting. It makes quitting more comfortable by relieving cravings and withdrawal symptoms and significantly increases your chances of quitting</td>
</tr>
<tr>
<td>Not using enough pieces</td>
<td>NRT is more effective when higher doses are used. NRT is relatively harmless and is safer than smoking</td>
</tr>
<tr>
<td>Stopping NRT too early</td>
<td>The treatment is working but needs to be taken for at least 8 weeks to give you time to break the smoking habit. Don’t stop NRT until you feel you can resist cravings in situations that would have made you smoke in the past</td>
</tr>
<tr>
<td>NRT is not working</td>
<td>Have more doses of oral NRT, use combination therapy or add a second patch. Do not drink or eat for 15 minutes before or while using oral products so your mouth can absorb the nicotine. Boost behavioural support. Consider varenicline or bupropion</td>
</tr>
</tbody>
</table>

### Table 1. Safety of nicotine

<table>
<thead>
<tr>
<th>What nicotine does</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoactive effects: dependence, short term relief of anxiety and low mood, increased arousal and concentration</td>
</tr>
<tr>
<td>Minor haemodynamic effects: increased heart rate and cardiac contractility, transient increase in blood pressure, vasoconstriction</td>
</tr>
<tr>
<td>Fetal neurotoxicity, lung damage, hypoxia</td>
</tr>
<tr>
<td>Reduced insulin sensitivity</td>
</tr>
<tr>
<td>Delayed wound healing (vasoconstriction)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What nicotine does NOT do</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine does not cause cancer</td>
</tr>
<tr>
<td>Nicotine does not cause cardiovascular disease</td>
</tr>
<tr>
<td>Nicotine does not cause lung damage</td>
</tr>
</tbody>
</table>
of oral NRT as this reduces the absorption of nicotine in the mouth.14

Nicotine mouth spray is the latest oral form of NRT on the Australian market. In a recent phase 3 trial, mouth spray more than doubled the quit rate compared to placebo at 12 months (RR 2.48).15 Nicotine mouth spray may relieve cravings more quickly than lozenges and other nicotine products.16 The mouth spray is well tolerated and the discontinuation rate due to side effects is comparable to other NRTs.15 Adverse events include irritation of the mouth and throat, salivary hypersecretion, nausea, dyspepsia, headache and hiccups.15

Adequate dosing of nicotine

In general, patients using NRT receive too little nicotine, partly due to misguided concerns about safety.2,3 Smokers of 10 or more cigarettes per day should start with a full strength patch (21 mg/24 hours or 15 mg/16 hours).11 If cravings or withdrawal symptoms are not controlled, an oral form of NRT should be added (see below). Adding a second nicotine patch produces only a modest 14% increase in quit rates.1

The recommended doses of oral forms of NRT are shown in Table 3; 4 mg gum or lozenges are advised for more addicted smokers,11 such as those who smoke within 30 minutes of waking.17,18 Blood nicotine levels from the recommended doses of NRT are about half those of regular smoking,19 so the initial dose can be safely titrated upward if symptoms are not controlled. Higher doses of the oral products have been shown to be safe and significantly increase quit rates.6–8

Smokers who are more nicotine dependent or those who metabolise nicotine more quickly generally need larger doses than average.20 Lower strength nicotine patches (14 mg/24 hours and 7 mg/24 hours) are now listed on the PBS for smokers who require a dose reduction, for example due to side effects from the full strength patch. There is no evidence that weaning with lower strength patches at the end of treatment offers any benefit over abrupt cessation.1

Combination therapy

Combining the nicotine patch with an oral form of NRT (combination therapy) has been shown to increase quit rates by 34–54% compared to using the patch alone.1,21 The patch provides a steady protection against background cravings and the oral forms give quick, flexible relief for breakthrough cravings as a result of smoking triggers, such as the smell of smoke.

Combination therapy is well tolerated. Adverse effects and adherence are similar to monotherapy,21 but there is a greater financial cost to the patient.

In Australia, combinations of the nicotine patch and nicotine 2 mg gum, 2 mg lozenge, 1.5 mg mini lozenge and mouth spray are Therapeutic Goods Administration licensed for smokers who have relapsed in the past or who experience cravings using only one form of NRT. However, some smoking cessation experts now recommend combination therapy as first line treatment for most dependent smokers using NRT, rather than monotherapy.22

Combining NRT with bupropion increases quit rates by 24% compared to bupropion alone.1 There have been no randomised controlled trials of NRT combined with varenicline to date.

Pre-cessation use of a nicotine patch

There is evidence to support the use of nicotine patches before smoking cessation, with the Therapeutic Goods Administration licensing an approach of starting a patch 2 weeks before quit day.11 A Cochrane review found that starting a patch before quit day increases success rates by 35% over and above the traditional quit day application.1 The evidence does not support the use of oral forms of NRT before quit day.1

Smoking while using NRT is safe and is not associated with any additional adverse reactions.2,23 Patients need to be reassured about this.

Continue nicotine patch after a lapse

Studies show that even a single episode of smoking (‘lapsing’) almost inevitably leads to relapse.24

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Table 3. Correct use of oral forms of nicotine replacement therapy

<table>
<thead>
<tr>
<th>Product</th>
<th>Instructions</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gum</td>
<td>Chew slowly until taste becomes strong then rest between gum and cheek. Chew again several times slowly when taste fades. Try not to swallow excessively. Repeat for 30 minutes or until the taste fades</td>
<td>2 mg gum: 8–20 pieces 4 mg gum: 4–10 pieces</td>
</tr>
<tr>
<td>Lozenge</td>
<td>Allow to dissolve in mouth (about 20–30 minutes), moving from side-to-side from time-to-time. Try not to swallow excessively. Do not chew or swallow whole</td>
<td>2 mg and 4 mg lozenges: 9–15 pieces</td>
</tr>
<tr>
<td>Mini lozenge</td>
<td>Allow to dissolve in mouth (about 10–13 minutes), moving from side-to-side from time-to-time. Try not to swallow excessively. Do not chew or swallow whole</td>
<td>1.5 mg mini lozenges: 9–20 pieces 4 mg mini lozenges: 9–15 pieces</td>
</tr>
<tr>
<td>Inhalator</td>
<td>Take shallow puffs approximately every 2 seconds or alternatively take four puffs every minute. Continue for up to 30 minutes</td>
<td>3–6 cartridges</td>
</tr>
<tr>
<td>Mouth spray</td>
<td>Spray into the mouth, avoiding the lips. Do not inhale while spraying. Use when cigarettes would usually be smoked or if cravings emerge. Do not swallow for a few seconds after spraying</td>
<td>1–2 sprays every 30–60 minutes. Maximum four sprays per hour or 64 sprays per day Maximum two sprays per hour or 32 sprays per day if used with NRT patches</td>
</tr>
</tbody>
</table>

Note: The nicotine sublingual microtablet was recently discontinued in Australia.

When a lapse occurs, about half of patch users stop using their patches within 2 days, usually due to misguided concerns about safety. However, smokers who continue to use the nicotine patch after a lapse are 4–5 times more likely to be abstinent at the end of treatment than those using a placebo patch.26,27

When prescribing the patch, advise patients to continue using it if a lapse occurs, and emphasise that concurrent patch use and smoking are safe.23

Cue induced cravings

Most lapses are triggered by situations and moods associated with smoking, such as exposure to alcohol, coffee or stress (cue induced cravings). Oral forms of NRT, such as nicotine gum and lozenges, significantly reduce the intensity and duration of cue induced cravings and help to prevent lapses. Oral therapies should be taken in anticipation of a smoking trigger if possible, or otherwise when cravings are experienced. Faster acting therapies such as the nicotine mouth spray are likely to be most effective. Long acting therapies, such as nicotine patches, varenicline and bupropion relieve background cravings but do not prevent or relieve cue induced cravings.28

Many patients will benefit from carrying a quick acting nicotine product with them during treatment and after quitting to them help cope with smoking triggers.

Summary

Smoking kills more Australians than any other preventable cause. Nicotine replacement therapy is a safe and effective treatment to help smokers quit. However, it is misunderstood and underused and there is the potential to increase its impact. See Table 4 for a checklist for NRT prescribing.

Compliance with NRT is undermined by myths and misinformation, particularly around safety, efficacy and addictiveness. Proactively addressing these issues will improve uptake and promote more effective use of NRT.

Simple, proven strategies to increase quit rates should be used more widely. These include pre-cessation use of a nicotine patch, combination NRT, and continuing the patch after a smoking lapse.

Quick acting forms of NRT relieve cue induced cravings and can be useful for long term relapse prevention.

Key points

- Proactively address misguided concerns about NRT safety as they undermine compliance.
- Provide detailed instructions on the correct use of all nicotine therapies.
- Titrate the dose of nicotine to relieve cravings and withdrawal symptoms and encourage a minimum of 8 weeks of treatment.
- Combining a nicotine patch with an oral form of NRT can increase quit rates.
- Starting the nicotine patch 2 weeks before quit day increases success rates compared to starting patch treatment on quit day.
- Advise patients to continue the nicotine patch after a lapse to prevent a full relapse.
- Use quick acting oral forms of NRT to prevent and treat cue induced cravings.

Author

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Competing interests: Colin Mendelsohn has received honoraria for teaching, consulting and travel from Pfizer, GlaxoSmithKline and Johnson & Johnson Pacific. He is on Pfizer Australia’s Champix Advisory Board and has served on GlaxoSmithKline’s Nicotine Replacement Therapy Expert Panel.

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Table 4. Checklist for prescribing nicotine replacement therapy

- Explain the rationale for NRT
- Emphasise that nicotine is safe, effective and has a low risk of addiction (Table 1)
- Start the nicotine patch 2 weeks before quit day
- Give detailed instructions on the correct use of oral forms of NRT (Table 3)
- Emphasise the importance of using an adequate dose of oral forms – number of pieces, puffs or sprays per day. If in doubt, use more
- Choose combination therapy for most smokers, especially if cravings or withdrawal symptoms persist with monotherapy
- Discuss possible side effects
- Encourage a full course of treatment – at least 8 weeks
- Continue the nicotine patch if a lapse occurs
- Arrange follow up visits

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References

Optimising nicotine replacement therapy in clinical practice

Clinical


