Chapter 2. Pharmacotherapy for smoking cessation

Key points

- Pharmacotherapy should be recommended to all people who smoke with nicotine dependence.
- The most successful approach to quitting for people who smoke with nicotine dependence is behavioural support combined with first-line pharmacotherapy and follow-up.
- Nicotine replacement therapy (NRT), varenicline and bupropion are licensed and available in Australia to assist smoking cessation.
- Varenicline is the most effective single-form pharmacotherapy for smoking cessation.
- Combination NRT is as effective as varenicline and more effective than single types of NRT.
- NRT may be considered in pregnancy if the patient is unable to quit without medication, but only after the risks and benefits have been carefully explained.
- Considerations guiding choice of pharmacotherapy for people who want to quit smoking are based on evidence of effectiveness, clinical suitability and patient choice.

Three forms of medicine – NRT, varenicline and bupropion – are licensed and available in Australia to assist smoking cessation. These medicines have been shown to assist smoking cessation in meta-analyses of randomised clinical trials.[1–4]

Pharmacotherapy should be recommended to all people who smoke with nicotine dependence.[5] However, an individual's choice to attempt to quit without assistance should be respected and supported.

The most successful quit approach for those who are nicotine dependent is behavioural support combined with first-line pharmacotherapy and follow-up.[5–10] Overall, varenicline or combination NRT almost triples the odds of quitting,[11] and bupropion and NRT alone almost doubles the odds of quitting versus placebo (dummy treatments plus brief counselling) at six months.[11,14]

First-line pharmacotherapy options

First-line pharmacotherapy options are medicines that have been shown to be effective and safe and are licensed for smoking cessation.[1,11–13] In Australia, these medicines include NRT,[11] varenicline and sustained-release preparations of bupropion hydrochloride. NRT is also licensed for smoking reduction as a step towards smoking cessation for people who are unable or not willing to stop smoking abruptly.

From current available evidence, varenicline is the most effective form of single pharmacotherapy (monotherapy) for smoking cessation.[1,11–13] A Cochrane collaboration analysis concluded that combination NRT is as effective as varenicline and more effective than single types of NRT.[11] Varenicline has been shown to be more effective than bupropion in a number of studies. Head-to-head comparisons between bupropion and NRT monotherapy have shown these medicines are equivalent to each other in efficacy.[11]

Efficacy of licensed smoking cessation medicine

All randomised controlled trials that examined and analysed smoking cessation pharmacotherapy include at least some behavioural support; for varenicline, this included intensive behavioural support (multiple sessions with at least two hours of total contact time).[15]

- Varenicline is effective, and can increase six- to 12-month continuous or sustained abstinence rates by 15% (95% confidence intervals [CI]: 13, 17) compared with placebo and 7% (95% CI: 4, 11) compared with bupropion. It is more effective than nicotine patches.[11]
- NRT is effective and can increase six- to 12-month continuous abstinence rates by 6% (95% CI: 6, 7) compared with placebo.
- Combining a nicotine patch with a faster-acting NRT (eg gum, lozenge) increases six- to 12-month abstinence rates by 5% (95% CI: 3, 7) compared with single-form NRT.
- Bupropion is effective. Its use can increase six- to 12-month continuous abstinence rates by 7% (95% CI: 6, 9) compared with placebo.
- Bupropion appears to be as effective as NRT monotherapy, but evidence from three randomised controlled trials suggests that it is less effective than varenicline.

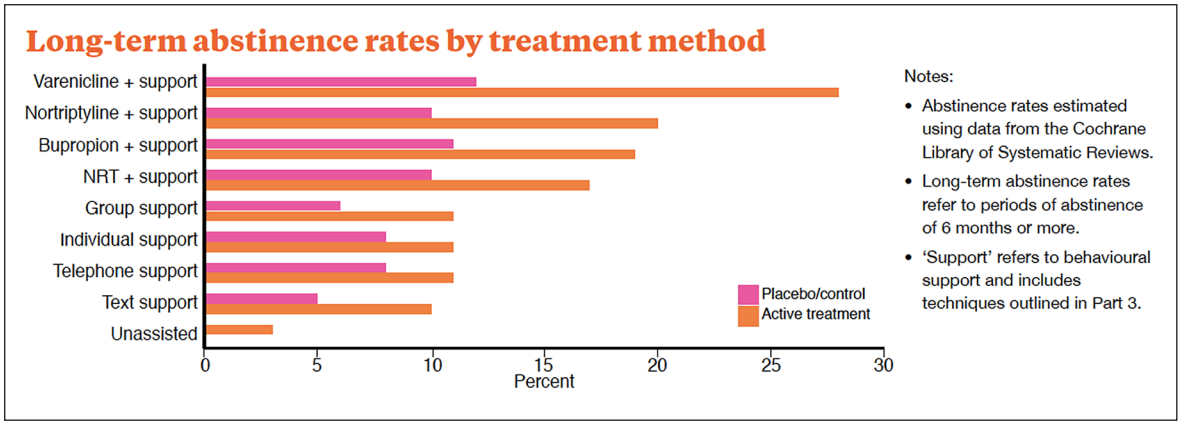

Figure 2.1 Long-term abstinence rates by treatment method[16]

Reproduced from New Zealand Government Ministry of Health. New Zealand guidelines for helping people to stop smoking. Wellington: Ministry of Health, 2014. Available at **www.health.govt.nz/publication/new-zealand-guidelines-helping-people-stop-smoking** [Accessed 8 March 2018].

The choice of pharmacotherapy most likely to assist people who are attempting to quit smoking is based on evidence of effectiveness (Figure 2.1), clinical suitability and patient choice (Figure 2.2). Considerations when helping an individual to select an appropriate form of pharmacotherapy to quit include:

- previous experience with pharmacotherapy
- cost and convenience
- adherence issues (eg individual preferences for a patch or gum, one or more forms of NRT, non-nicotine options)
- prescription medicine versus over-the-counter medicine
- potential for adverse events
- possible drug–drug interactions.

Patients who are quitting smoking using any method are at some risk of increased psychological stress during the process as a result of nicotine withdrawal symptoms, especially patients with a history of mental illness.[12] Clinicians should alert patients to this possibility and encourage them to return promptly if they experience neuropsychiatry symptoms (eg anxiety, depression, behaviour changes, suicidality). Patients can also be encouraged to inform family members about this possibility so they can be alert to any concerning changes. People with mental illness are at higher risk of neuropsychiatric symptoms during smoking cessation and must be carefully monitored during treatment.

It is important on medication cessation to reinforce the quitting process to prevent relapse.[17] Approximately 50% of those who have quit at the end of pharmacotherapy relapse to smoking;[5] therefore, combining pharmacotherapy and behavioural intervention is important.

Recommendation 5 – In the absence of contraindications, pharmacotherapy (nicotine replacement therapy, varenicline or bupropion) is an effective aid when accompanied by behavioural support, and should be recommended to all people who smoke who have evidence of nicotine dependence. Choice of pharmacotherapy is based on efficacy, clinical suitability and patient preference. *Strong recommendation, high certainty*

Key points

- Smoking cessation using NRT is always less harmful than continuing to smoke.
- When used correctly, all forms of NRT (at equivalent doses) are similarly effective in achieving long-term cessation.
- All forms of NRT monotherapy can increase the rate of quitting by 50–60%.
- More than one form of NRT (ie combination NRT) can be used concurrently with increased success rates and no greater safety risks.
- Higher dose forms of nicotine gum (4 mg) are more effective than lower dose forms (2 mg) for more people who smoke with nicotine dependence.
- Nicotine patches can be commenced several weeks before starting smoking cessation to help people who smoke prepare for quitting.
- NRT can be used by people with cardiovascular disease. Caution is advised for people in hospital for acute cardiovascular events, but NRT can be used under medical supervision if the alternative is active smoking.
- NRT may be considered in women who are pregnant if they were unsuccessful in stopping smoking without pharmacotherapy. If NRT is used, the benefits and risks should be explained carefully to the patient by a suitably qualified health professional. The clinician supervising the pregnancy should also be consulted.
- NRT accompanied by behavioural interventions can be used in those aged 12–17 years who smoke.

Nicotine is the main substance in tobacco that causes addiction as it makes people dependent on cigarettes. However, it is the other chemicals in combusted tobacco products that cause cancer, accelerate heart disease and affect other areas of health. While nicotine also has the potential for adverse effects in vulnerable developmental life stages, including pregnancy, childhood and adolescence,[18–20] it is considered to be a safer alternative to tobacco smoking.

The aim of NRT is to reduce craving and withdrawal symptoms by providing some of the nicotine that would normally be obtained from cigarettes, without providing the harmful components of tobacco smoking. NRT provides lower doses of nicotine at a slower rate than tobacco smoking; none of the available forms of NRT (ie transdermal patch, gum, inhalator, lozenge, mouth spray) offer the same rapid nicotine delivery of a cigarette.[21]

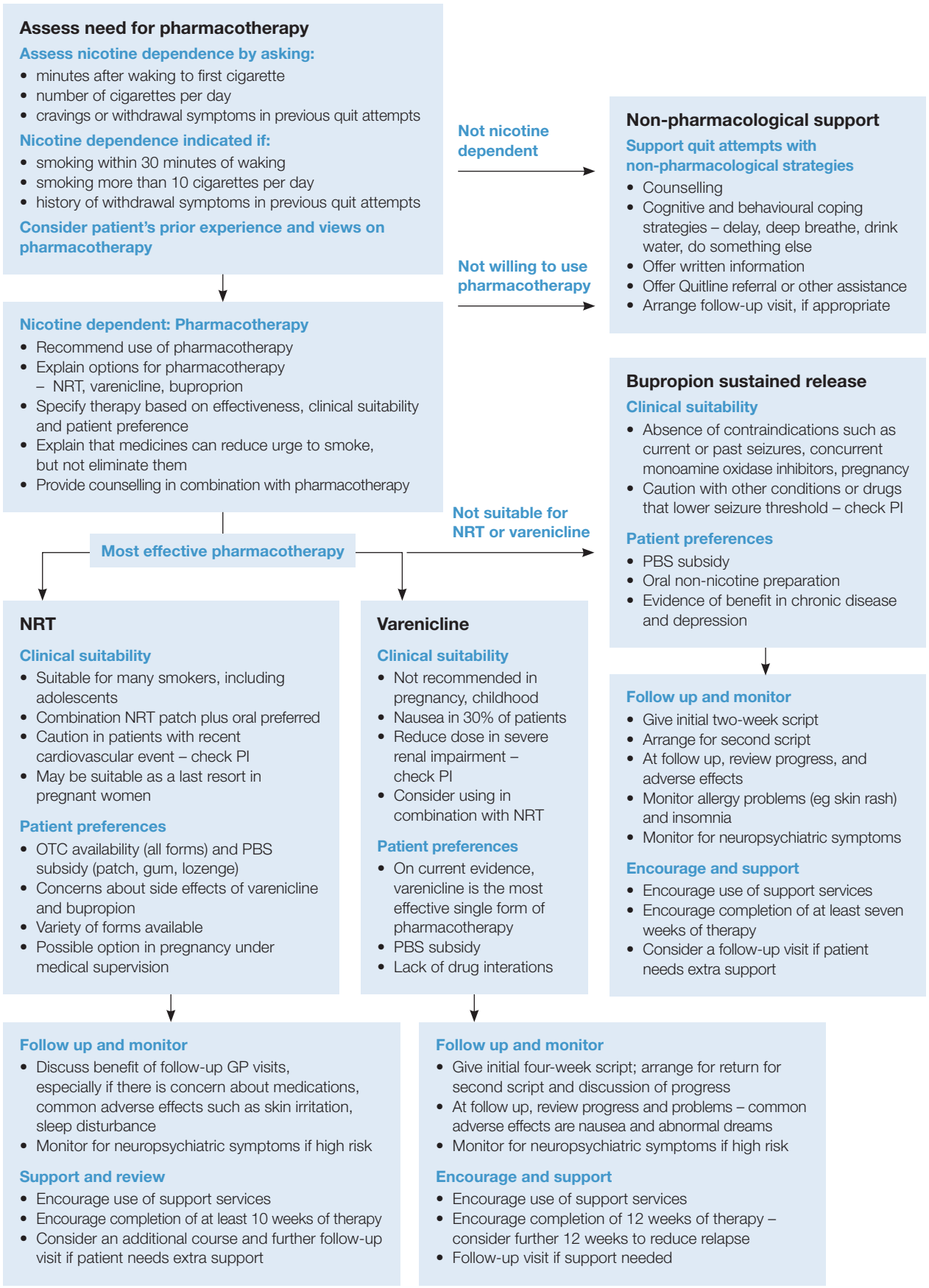

Figure 2.2 Pharmacotherapy treatment algorithm

GP, general practitioner; NRT, nicotine replacement therapy; OTC, over the counter; PBS, Pharmaceutical Benefits Scheme; PI, product information

Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate, while other nicotine products are acute dosing forms of nicotine. Other nicotine products provide relief for general craving and breakthrough craving with faster release of nicotine than the patch. The main advantage of nicotine patches over acute NRT formulations is that patient adherence is simple despite its slow delivery.[22] The advantage of acute-dosing NRT is that both the amount and timing of doses can be titrated by the person who smokes.

It is important to advise those who smoke on the correct use of the different forms of NRT and ensure an adequate dose is taken to relieve cravings and withdrawal symptoms (Figure 2.3).[23,24] Under-dosing is a recognised problem with current NRT, whereby those who want to quit often do not use enough NRT to obtain the best clinical effect.[25] Standard dosing references and product information guides for NRT tend to recommend more conservative doses.

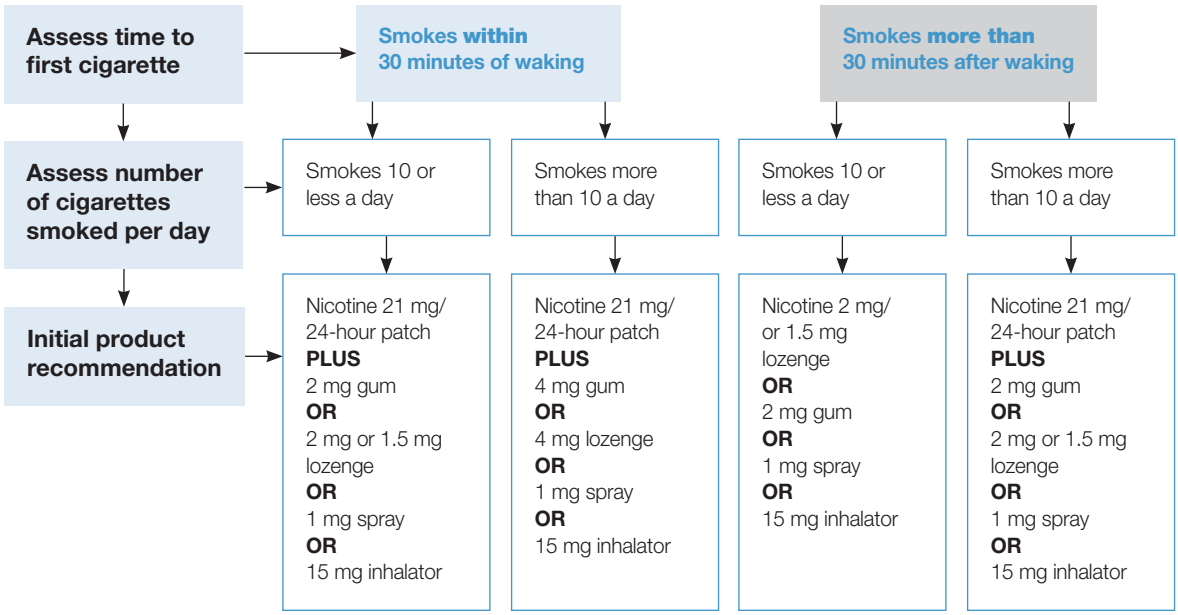

Figure 2.3 NRT initial dosage guideline[24]

Adapted with permission from Ministry of Health, New Zealand. Guide to prescribing nicotine replacement therapy (NRT). Wellington: Ministry of Health, 2014. Available at www.health.govt.nz/system/files/documents/publications/guide-to-prescribing-nicotine-replacement-therapy-nrtv2.pdf [Accessed 9 September 2019].

Patients should be reassured about the safety, efficacy and low addictive potential of NRT, as misinformed concerns are a major cause of poor adherence.[23,26]

Regular use of NRT beyond 12 months is not generally recommended as there is no evidence of efficacy beyond 24 weeks.[27] At the 24-week point, the prospect of stopping NRT can be confronting for some who do not feel ready to stop treatment. An extended but not limitless period of treatment may be reasonable for such patients, although there are no data to support this approach. Current scientific evidence does not support an association between long-term NRT exposure and serious adverse health effects;[25,28] a longer period of NRT may help some people remain abstinent[29] and it is less harmful than tobacco smoking.

While there is evidence that NRT can increase quit rates with or without counselling,[8,9] research suggests over-the-counter NRT appears to be associated with reduced success rates. More research is needed on the effectiveness of NRT in this context.[7]

Combination NRT

Combining two forms of NRT (eg patch plus an acute form, such as spray, gum, inhalator or lozenge) has been shown to be more efficacious than a single form of nicotine replacement.[11,30] The patch provides a steady background nicotine level while the oral forms provide additional protection for breakthrough cravings. Oral doses (eg gum, lozenge, inhalator, mouth spray) can be taken on a regular basis (eg hourly) in anticipation of triggers or when cravings occur. Combination NRT, rather than monotherapy, has been recommended for those who smoke and are nicotine dependent, including use of higher dose forms of oral products for those who need them.[3]

Combination NRT can be recommended:

- as first-line treatment for those who smoke and are nicotine dependent (Figure 2.3)[4,5]
- for those unable to quit using NRT monotherapy alone
- for those who experience cravings using NRT monotherapy alone.

The evidence review conducted by the Joanna Briggs Institute (JBI) on the use of combination NRT identified 12 randomised controlled trials with a total of 6318 participants. The relative effect was 1.28 (95% CI: 1.15, 1.42). The Expert Advisory Group (EAG) rated the certainty of the evidence as moderate. The EAG concluded that there is a small but not trivial improvement in smoking cessation for combination NRT compared with single NRT. The reviewed studies only included those who smoke with at least low-to-moderate nicotine dependence.

Recommendation 6 – Combination nicotine replacement therapy (NRT) (ie patch and oral form) accompanied by behavioural support is more effective than NRT monotherapy accompanied by behavioural support, and should be recommended to people who smoke who have evidence of nicotine dependence. *Strong recommendation, moderate certainty*

Higher dose NRT

Higher dose oral NRT (ie 4 mg gum and lozenge) and higher dose patches (21 mg/24-hour patch and 25 mg/16-hour patch) are recommended for those who smoke with nicotine dependence. Higher dose NRT should also be considered for those who smoke with less nicotine dependence but who continue to report cravings when using the weaker form.[31] Higher dose therapy with the patch is also possible by adding a second patch. While this approach seems to be safe, a Cochrane review of five randomised controlled trials found no clear evidence of superiority of dual patching over single patch (risk ratio [RR]: 1.09; 95% CI: 0.93, 1.29).[32]

Pre-cessation nicotine patch

There is evidence to support the use of nicotine patches before smoking cessation, commonly known as preloading. A meta-analysis found that nicotine patches used before quit day increased success rates when compared with standard therapy.[33] A Cochrane review also found a 34% increase effect from the use of pre-cessation patches.[3] The Therapeutic Goods Administration (TGA)-approved approach involves using either a 21 mg/24-hour patch or 25 mg/16-hour patch for two weeks before quitting, then continuing to use the nicotine patch in the usual way for the quit attempt and adding intermittent oral NRT if needed.

Reduce to quit

There is also evidence for the use of NRT to help those who are not willing to quit immediately to reduce their tobacco use and then progress to quitting.[34] The TGA-approved approach (cut down then stop or reduce to quit) involves patients using NRT to prevent compensatory smoking (inhaling deeper on fewer cigarettes) when reducing the number of cigarettes they smoke before stopping completely within six months.[35] A meta-analysis found that reducing cigarettes smoked before quit day versus quitting abruptly with no prior reduction produced comparable quit rates.[32,36] Further research is needed to investigate those categories of people who smoke who would benefit the most from each approach.[37]

Tapering off NRT

Advice to wean off NRT over a period of weeks is included in the product information of NRT products, but it is not something that is supported by the evidence. The main issue is sufficient duration of NRT, not whether tapering occurs before the medicine is ceased.[23]

Longer treatment duration

There is limited evidence of benefit from longer term NRT. Two randomised controlled trials compared longer (up to 52 weeks) and standard courses (eight weeks) of NRT, but found no convincing effect from the longer course.[25,38]

Another use of longer term NRT is for relapse prevention in those who are abstinent at the end of a standard course of treatment or who have abstained unassisted. A systematic review of four trials found that prolonged NRT use was effective for the medium term (12- to 18-month follow-up).[39] The evidence review conducted by JBI on the longer term NRT found only one trial that met inclusion criteria, which included abstinence confirmed by exhaled carbon monoxide concentration <8 ppm. The relative effect was 2.17 (95% CI: 0.85, 2.17). The EAG rated the certainty of the evidence as low. There was a lack of evidence on the rate or severity of adverse effects associated with longer term NRT.

Recommendation 7 – For people who have stopped smoking at the end of a standard course of nicotine replacement therapy (NRT), clinicians may consider recommending an additional course of NRT to reduce relapse. *Conditional recommendation for the intervention, low certainty*

Contraindications and precautions

There is no safe level of smoking. Using therapeutic nicotine is always less harmful than continuing to smoke.

Contraindications

There are few contraindications associated with NRT use.[23,33] These include:

- children aged <12 years
- people with known hypersensitivity to nicotine or any other component of the NRT product.

It is important to note that those weighing <45 kg can use NRT, but may require the lower dose (eg 14 mg/24-hour patch).

Precautions

NRT should be used with caution for patients in hospital for acute cardiovascular events, but if the alternative is smoking, NRT can be used under medical supervision.

Side effects

Minor side effects are common with NRT use.[23,40] Common adverse effects with NRT depend on the delivery system. Patches can cause skin irritation, redness, itch and rash, which are usually mild but can be treated with 1% hydrocortisone cream if troublesome.[23] It is important to rotate the application site each day to reduce irritation. Insomnia and vivid dreams can also occur.[38] However, if irritation or sleep disturbance is severe, patients can remove the patch at bedtime or a couple of hours before and re-apply a new patch in the morning.[23]

For NRT gum and lozenges, minor side effects include dyspepsia and nausea; for NRT inhalator and mouth spray, mouth and throat irritation may occur.[23,41]

Use of NRT in cardiovascular disease

All forms of NRT can be used safely in stable cardiovascular disease;[38,42] however, these should be used with caution in people with recent (six weeks) myocardial infarction, unstable angina, severe arrhythmias and recent cerebrovascular events. NRT can be used in this situation under medical supervision.[39]

Recommendation 8 –

a) Nicotine replacement therapy (NRT) is safe to use in patients with stable cardiovascular disease. *Strong recommendation, high certainty*

b) NRT should be used with caution in patients who have had a recent myocardial infarction, unstable angina, severe arrhythmias or recent cerebrovascular events. *Strong recommendation, moderate certainty*

Use of NRT in pregnancy

Given the importance of smoking cessation in pregnancy, every effort should be made to support the expectant mother to quit. Behavioural counselling is recommended as the first-line treatment for quitting smoking in pregnancy. Behavioural intervention can:[43]

- increase the proportion of women who stop smoking during pregnancy
- decrease the proportion of infants born with low birthweight
- increase smoking cessation after birth.

Refer to Chapter 4, 'Smoking cessation for high-prevalence groups: Pregnant and breastfeeding women' for more information.

Pregnant women should be encouraged to use Quitline. In some jurisdictions, there are special programs of support that extend into the postpartum period when risk of relapse to smoking is high.

There is inconclusive evidence of the effectiveness and safety of NRT during pregnancy, and other forms of pharmacotherapy are contraindicated.[44,45] A Cochrane review and meta-analysis of eight studies and 2199 participants found that NRT as an adjunct to behavioural support was effective for smoking cessation in pregnancy (RR: 1.41; 95% CI: 1.03, 1.93). However, there was no significant difference in cessation rates in a sub-group analysis of placebo-controlled studies. Some observational studies

suggest effectiveness in clinical practice.[46,47] The modest effect of NRT could be due to inadequate dosing, as nicotine clearance is increased by 60% in pregnancy.[48] Poor adherence is also likely to cause reduced cessation outcomes.[49]

Although nicotine has been linked to harmful effects on the fetus in animal studies, clinical trials have not reported adverse effects from NRT in humans. The Cochrane meta-analysis found no significant difference in health and safety outcomes in four studies.[43] Several studies found no adverse effect on birth weight.[46,50] One study found that infants born to mothers who received NRT had a significantly higher rate of unimpaired development when assessed two years after delivery.[51] However, because of the small number of studies, further evidence is needed before firm conclusions on safety can be made.[52,53]

The evidence review conducted by JBI examined the outcome of smoking cessation in later pregnancy. This work by JBI focused on the studies within the Cochrane systematic review by Coleman and colleagues.[45] Eight randomised controlled trials involving 2199 participants met entry criteria. The relative effect was 1.41 (95% CI: 1.03, 1.93), and the EAG rated the certainty of the evidence as low. The review found no evidence of an increase in adverse effects (ie miscarriage, stillbirth, pre-term birth, low birthweight, neonatal care unit admission, neonatal death) in women who used NRT during pregnancy. In fact, all comparisons found lower rates of these effects in the women who used NRT during pregnancy. However, it should be noted that the 95% CI for all RR were analysed to have no effect (ie RR: 1). On current evidence, the EAG concluded that there are important improvements in smoking cessation outcomes associated with use of NRT in pregnancy, while there does not appear to be an increase in harms.

Given this evidence, if quit attempts are unsuccessful without the use of pharmacotherapy, and the patient is motivated to quit:

- pharmacotherapy (usually oral forms of NRT) should be considered
- if NRT is used, the benefits and risks should be considered and explained carefully to the patient by a suitably qualified healthcare professional, and the clinician supervising the pregnancy should be consulted[49,54,55]
- intense behavioural support and close clinical surveillance of the pattern of any continuing smoking should be provided.

Recommendation 9 – For women who are pregnant and unable to quit smoking with behavioural support alone, clinicians might recommend nicotine replacement therapy (NRT), compared with no NRT. Behavioural support and monitoring should also be provided. *Conditional recommendation for the intervention, low certainty*

Use of NRT in breastfeeding

Nicotine passes from the mother to child through breastmilk. Depending on the concentration of nicotine in the maternal blood, it is likely to be less harmful than continued smoking.[56,57] NRT (ie patch, intermittent) is considered an option for breastfeeding mothers.[58] Infant exposure to nicotine can be reduced further by taking intermittent NRT immediately after breastfeeding.

Women who smoke should be encouraged to continue breastfeeding and provided with strategies to minimise the potential harm to their child through breastmilk and second-hand smoke.[52]

Varenicline

Key points

- Varenicline is a nicotinic receptor partial agonist drug for smoking cessation that relieves symptoms of craving and withdrawal.
- The use of varenicline can more than double the chances of long-term quitting.
- In a Cochrane review meta-analysis, varenicline was found to be more effective than bupropion, more effective than NRT monotherapy and similar in effect to combination NRT.
- A second course of varenicline can be considered to reduce relapse.
- Combining varenicline with NRT may improve quit rates.
- Varenicline can be used in those who smoke with mental health problems, but must be monitored during quit attempts. These patients should be advised to report unusual mood changes, depression, behaviour disturbance and suicidal thoughts, and stop using the medicine if these occur.
- Varenicline is not recommended for pregnant and breastfeeding women, nor for adolescents.
- There are two options for quitting with varenicline, both equally effective but chosen by preference:
  - fixed option, which involves the person who smokes setting a date to stop smoking – varenicline should start one to two weeks before this date
  - flexible approach, when the person who smokes begins varenicline dosing, then quits smoking between days 8 and 35 of treatment.

Varenicline was developed specifically for smoking cessation. It acts at the nicotinic acetylcholine receptors (nAChRs) in the reward centre in the brain. Varenicline binds with high affinity at the alpha-4 beta-2 (α4β2) nAChRs, where it acts as a partial agonist to alleviate symptoms of craving and withdrawal. If a cigarette is smoked, the varenicline prevents inhaled nicotine from activating the α4β2 nAChRs agonist activity, and so blocks the pleasure and reward response. This mechanism may explain why quitting can occur later in a course of treatment with varenicline.

Efficacy

At the standard dose, varenicline can more than double the chances of successful long-term smoking cessation when compared with pharmacologically unassisted quit attempts.[59] A Cochrane meta-analysis of 27 trials of varenicline found it more than doubled sustained abstinence rates at six-month follow-up.[1] Varenicline monotherapy was also more effective than NRT monotherapy at 24 weeks;[1] however, it was of similar efficacy to combination NRT (patch and oral form).[11] Varenicline improves smoking cessation rates two-fold over bupropion and is well tolerated.[60,61]

Recommendation 10 – Varenicline should be recommended to people who smoke and who have been assessed as clinically suitable for this medication; it should be provided in combination with behavioural support. *Strong recommendation, high certainty*

Two randomised controlled trials have examined varenicline as an aid to relapse prevention in those who smoked and had successfully quit on varenicline.[62,63] One study continued treatment for an additional 12 weeks,[63] the other for an additional 40 weeks.[62] There was a modest benefit in favour of extended treatment compared to the placebo groups.[62,63] The benefit appears to be maintained only for the period of use of varenicline.

The evidence review conducted by JBI on this question examined the two trials[62,63] which, combined, involved 1297 participants that met entry criteria (including that smoking cessation of study participants was biochemically confirmed). The relative effect was 1.23 (95% CI: 1.08, 1.41). The EAG rated the certainty of the evidence as low.

Recommendation 11 – For people who have abstained from smoking after a standard course of varenicline in combination with behavioural support, clinicians may consider a further course of varenicline to reduce relapse.
Conditional recommendation for the intervention, low certainty

Combination varenicline and other pharmacotherapy for smoking cessation

Varenicline in combination with NRT patch results in significantly higher abstinence rates than varenicline alone.[64,65] A systematic review aggregated the reported number of adverse events from these studies, and generated a pooled odds ratio (OR) with a fixed-effect model.[66] Compared with varenicline monotherapy, participants receiving combination varenicline and NRT reported increased incidence of:

- nausea (28.4% versus 25.7%; OR: 1.15; 95% CI: 0.85, 1.56)
- insomnia (18.7% versus 15.4%; OR: 1.27; 95% CI: 0.89, 1.80)
- abnormal dreams (13.6% versus 10.7%; OR: 1.20; 95% CI: 0.78, 1.84).

Frequency of headaches was similar between groups (7.1% versus 7.8%; OR: 1.01; 95% CI: 0.60, 1.72). Koegelenberg and colleagues reported that skin reactions (of any type) were more prevalent in the combination therapy group (14.4% versus 7.8%; p = 0.03).[59]

The evidence review conducted by JBI on this question found two trials involving 787 participants that met entry criteria (including biochemically confirmed cessation). The relative effect was 1.62 (95% CI: 1.18, 2.23). The EAG rated the certainty of the evidence as moderate, and concluded that, on current evidence, there is a small but not trivial improvement in smoking cessation for people taking varenicline in addition to NRT, compared to NRT alone.

Recommendation 12 – For people who are attempting to quit smoking using varenicline accompanied by behavioural support, clinicians might recommend the use of varenicline in combination with nicotine replacement therapy, compared with varenicline alone.
Conditional recommendation for the intervention, moderate certainty

There is no clinical study of varenicline combined with oral NRT. However, in clinical practice, this combination is sometimes used together. Varenicline helps to relieve background cravings and reduce the stimulatory effects of smoking, and oral NRT products alleviate cue-induced triggers.

There is a lack of evidence of the effectiveness of combination varenicline plus bupropion. One study found a benefit at 26 weeks, but not at 52 weeks; a more recent study found no benefit at either of these follow-up points.[67,68]

There is increasing evidence of the efficacy of varenicline in sub-populations of patients who smoke.

Sub-populations of patients who smoke

People with mental illness

Psychiatric comorbidity is common in those who smoke, and varenicline has been found to be safe and effective in those with stable mental illness or a past history of mental illness.[69] There is also evidence that varenicline is safe and effective to assist cessation in people with schizophrenia.[70,71]

Women

Varenicline is more effective than other cessation monotherapies, but the difference is relatively greater for women. Women have lower quit rates with NRT and bupropion compared with men, but the same response to varenicline.[72]

People who smoke and drink heavily

Varenicline reduces alcohol cravings and overall alcohol consumption in those who drink heavily, and may have a role in the concurrent treatment of alcohol and nicotine dependence, especially in men.[73–75]

Varenicline and mental illness

After initial marketing of varenicline, there were concerns about an association between varenicline and mood changes, depression, behaviour disturbance and suicidal ideation. Subsequent meta-analyses of randomised controlled trials[76,77] and observational studies[72,78,79] have not supported a causal link. The large randomised controlled trial, EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study), has given further reassurance.[64] In those with or without stable mental illness, the study did not find a significant increase in the rates of moderate-to-severe neuropsychiatric adverse events in those taking varenicline, compared with those using placebo, bupropion or nicotine patch. As expected, those with mental illness in all treatment groups had higher rates of neuropsychiatric adverse events than those without mental illness.

Patients quitting smoking with any method are at some risk of increased psychological stress, especially those with a history of mental illness. Clinicians should monitor all patients with follow-up for neuropsychiatric changes associated with withdrawals, whether taking varenicline or not, and should promptly report any adverse events.

Cardiovascular safety of varenicline

Safety data from more than a dozen recent randomised controlled trials, including one conducted in the highest-risk patient population studied to date, examined the use of varenicline and cardiovascular events. These randomised controlled trials found that cardiovascular events are rare and not likely to be increased with the use of varenicline.[80] The findings are consistent with the results of several large cohort studies, which found no increased risk of cardiovascular adverse events between varenicline and bupropion for smoking cessation.[81,82] There appears to be no substantive evidence to suggest that varenicline increases the risk of cardiovascular adverse events.[39,75]

It is important to note that smoking is a major risk factor for cardiovascular disease, and the health benefits of quitting smoking are immediate and substantial.[83]

Pregnancy and varenicline

Due to the limited efficacy and pregnancy safety data, varenicline is not recommended as a smoking cessation aid for pregnant or breastfeeding women.[84]

Side effects

Nausea is the most common adverse effect of varenicline, and was reported in studies of almost 30% of those who are attempting to quit, although less than 3% discontinued treatment due to nausea.[57,58] There is some evidence that nausea can be minimised by taking tablets with food, titration and self-regulation of varenicline (0.5–2 mg/day).[85,86] Lower doses of varenicline are also effective if the full dose cannot be tolerated.[1]

Sleep disturbance and abnormal dreams were more common in the varenicline group (13.1%) than the bupropion (5.9%) or placebo groups (3.5%).[57,58]

Other less common side effects include drowsiness, headache, constipation, dizziness and flatulence.

No clinically meaningful drug interactions have been identified.

Varenicline is excreted almost entirely by the kidneys. For people with creatinine clearance below 30 mL/min, the recommended daily dosage is 1 mg/day (0.5 mg/day for three days then increasing to 1 mg/day). Avoid varenicline in those with end-stage renal failure in favour of other approaches to smoking cessation. Dose adjustment is not routinely required in older people or in people with hepatic impairment.[87]

Bupropion

Key points

- Bupropion is a non-nicotine oral therapy, originally developed and approved for use as an antidepressant.
- Bupropion significantly increases cessation rates compared with placebo.
- Bupropion has been shown to be less effective than varenicline for smoking cessation.
- Bupropion is contraindicated in patients with a history of seizures, eating disorders and those taking monoamine oxidase inhibitors.
- Bupropion is not recommended for women who are pregnant or breastfeeding.
- Bupropion should be used with caution in people taking medications that can lower seizure threshold (eg antidepressants, antipsychotics, antimalarials, oral hypoglycaemic agents).

Bupropion reduces the urge to smoke and reduces symptoms from nicotine withdrawal.

Efficacy

Bupropion significantly increases the long-term cessation rate by about 60%, compared with placebo over 12 months.[2]

Bupropion has been shown to be effective in a range of patient populations, including those with depression, cardiac disease and respiratory diseases (eg chronic obstructive pulmonary disease [COPD]).[88] It has also been shown to improve short-term abstinence rates for people with schizophrenia.[89,90] In comparison with NRT, varenicline and placebo, bupropion has not been shown to cause an increase in neuropsychiatric adverse events, including in people with a history of mental health disorders.[64]

Clinical trials have shown that bupropion is not as effective as varenicline for smoking cessation.[1,91] However, bupropion is a useful option in cases where varenicline is not appropriate (eg patient choice, side effects).

Combination bupropion and other pharmacotherapy for smoking cessation

The combination of NRT and sustained-release bupropion has not shown an additive benefit.[2] As previously stated, there is a lack of evidence of effectiveness of the combination of bupropion plus varenicline.[62,63]

Safety

Bupropion is contraindicated in patients with a history of seizures, eating disorders and those currently or recently (within the last 14 days) taking monoamine oxidase inhibitors.[92] The current recommendation is that it should be used with caution in people taking medications that can lower seizure threshold (eg antidepressants, antipsychotics, anti-malarials, oral hypoglycaemic agents).[2,92] Alcohol consumption should be minimised or avoided completely when taking bupropion, as alcohol can alter the threshold at which bupropion induces seizures. A sudden decrease in alcohol consumption can also alter the seizure threshold, and alternative medication should be considered in these situations.[92]

Caution is needed if there is concomitant use of bupropion with certain drugs (eg tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs]). These drugs should be initiated at the lower end of the dosage range while the individual is taking bupropion. In the more common situation where bupropion is initiated for a person already taking these drugs, these may need to be decreased. Bupropion should not be used in patients taking monoamine oxidase inhibitors, including moclobemide. A 14-day washout is recommended between completing monoamine oxidase inhibitors and starting bupropion. Consultation with a psychiatrist may be considered for advice on co-prescribing bupropion with other antidepressants.[93,94]

There is no evidence that the use of bupropion for smoking cessation increases the risk of serious cardiovascular adverse events during or after treatment.[39] Due to the limited efficacy and pregnancy safety data, bupropion is not recommended as a smoking cessation aid for women who are pregnant or breastfeeding.[79]

Side effects

Seizures are the most clinically important adverse effect (0.1% risk) with the use of bupropion for smoking cessation, and fatalities have been previously been reported.[92] Therefore, bupropion should not be prescribed to patients with a current seizure disorder or a previous history of seizures. Common adverse effects are insomnia, headache, dry mouth, nausea, dizziness and anxiety. If bupropion is used in combination with NRT, blood pressure should be monitored.[83]

Recommendation 13 – Bupropion sustained release should be recommended to people who have been assessed as clinically suitable for this medication; it should be provided in combination with behavioural support. Bupropion is less effective than either varenicline or combination nicotine replacement therapy. *Strong recommendation, high certainty*

Availability of smoking cessation medicines on the Pharmaceutical Benefits Scheme

Health professionals should check for updated Pharmaceutical Benefits Scheme (PBS) listings at www.pbs.gov.au

Nicotine patches (eg 25 mg/16 hours, 15 mg/16 hours, 5 mg/16 hours, 21 mg/24 hours, 14 mg/24 hours, 7 mg/24 hours) are listed on the PBS (www.pbs.gov.au/medicine/item/10076H-11612E-11617K-11618L-11619M-3414Q-4571N-4572P-4573Q-5465P-5571F-5572G-5573H) for use as an aid to quitting for people who participate in a support and counselling program. The subsidised patches are not available at the same time as other PBS-subsidised smoking cessation therapies (ie varenicline, bupropion), but those who are unsuccessful at quitting using the nicotine patches are able to access PBS-subsidised medicines during that same 12-month period.

Oral forms of NRT subsidised on the PBS are gum and lozenges for use as the sole PBS-subsidised therapy. This means combination NRT is not currently PBS subsidised.

Under PBS rules, a maximum 12 weeks of PBS-subsidised NRT is available per 12-month period.

All forms of NRT are available over the counter in pharmacies and supermarkets in Australia.

Aboriginal and Torres Strait Islander peoples

Aboriginal and Torres Strait Islander peoples qualify for a PBS-restricted benefit listing, which provides up to two courses of nicotine patches per year, each a maximum of 12 weeks. Under this listing, participation in a support and counselling program is recommended but not mandatory. Nicotine gum (2 mg and 4 mg doses) and lozenge (2 mg and 4 mg doses) are also available on the PBS for Aboriginal and Torres Strait Islander peoples. The PBS listing does not cover two forms of NRT at once (ie no combination therapy). Access to NRT for Aboriginal and Torres Strait Islander peoples can be facilitated through the Closing the Gap PBS co-payment measure (refer to Chapter 4, ‘Smoking cessation for high prevalence groups: Closing the Gap PBS co-payment measure’).

Availability of varenicline on the PBS

Varenicline is available on the PBS as a short-term adjunctive therapy for nicotine dependence. It can be prescribed as a streamlined authority prescription for up to 24 weeks of continuous therapy for smoking cessation. Eligibility requirements include enrolling in a support and counselling program, and abstinence at 12 weeks. Making use of the Closing the Gap PBS co-payment can further reduce the cost for Aboriginal and Torres Strait Islander peoples.

The first script is a starter pack that lasts for four weeks (including dose titration), followed by a continuation batch for eight weeks of treatment. A third prescription is required for the final 12 weeks of treatment, but only for those who respond to the first 12 weeks. Under PBS rules, a maximum of 24 weeks of PBS-subsidised treatment with this drug is permitted per 12-month period.

Availability of sustained-release bupropion on the PBS

Sustained-release bupropion is available on the PBS as a streamlined authority prescription for a short-term course of treatment (nine weeks) for nicotine dependence, with a comprehensive support and counselling program. Making use of the Closing the Gap PBS co-payment can further reduce the cost for Aboriginal and Torres Strait Islander peoples.

Bupropion is available as a starter pack of 30 tablets and a continuation pack of 90 tablets. The dose of bupropion is 150 mg/day for the first three days, then increased to 150 mg twice per day. The patient should stop smoking in the second week of treatment. Under PBS rules, a maximum of nine weeks of PBS-subsidised treatment with this drug is permitted per 12-month period.

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has been shown in a relatively small number of trials to significantly increase long-term cessation when used as the sole pharmacotherapy.[2,56] A systematic review found that the use of nortriptyline for smoking cessation resulted in higher prolonged abstinence rates after at least six months, compared with placebo treatment.[95] The efficacy of nortriptyline does not appear to be affected by a past history of depression, but it is limited in its application by its potential side effects, including dry mouth, constipation, nausea, sedation and headaches, and a risk of arrhythmia in patients with cardiovascular disease. Nortriptyline can be dangerous in overdose.

Nortriptyline is not registered for smoking cessation in Australia.

The dose of nortriptyline used for smoking cessation is approximately 75 mg/day for 12 weeks. Further information about nortriptyline for smoking cessation can be obtained from the *New Zealand smoking cessation guidelines*.[16]

Recommendation 14 – Nortriptyline should be considered as a second-line pharmacotherapy agent because of its adverse effects profile. *Strong recommendation, moderate certainty*

Electronic cigarettes

Electronic cigarettes (e-cigarettes) are battery-powered devices that deliver nicotine in a vapour without tobacco or smoke. The device heats a liquid into an aerosol for inhalation, simulating the behavioural and sensory aspects of smoking. The liquid is usually made up of propylene glycol and glycerol, with or without nicotine and flavours, stored in disposable cartridges or refillable tanks. The nicotine content of e-cigarettes can vary from zero to 50 mg/mL. E-cigarette users are sometimes referred to as 'vapers' and e-cigarette use as 'vaping'.[96]

The use of nicotine-containing e-cigarettes to support cessation is controversial. As they have only been on the market for a short time, and are continually changing, their long-term safety is unknown.[97–99] Concerns about e-cigarettes include:[100]

- no tested and approved e-cigarette products are available
- a lack of high-level evidence for efficacy for smoking cessation
- a lack of evidence on health effects, particularly in the long term
- continued concurrent use with smoking (ie dual use)
- acting as a gateway to tobacco use
- the potential to promote nicotine use and renormalise smoking among those who do not smoke, especially young people.

A Cochrane review identified two completed randomised controlled trials of e-cigarettes for smoking cessation that had a follow-up at six months or longer (n = 662).[90] These two studies compared e-cigarettes containing nicotine to placebo e-cigarettes. Participants using a nicotine-containing e-cigarette were more likely to have abstained from smoking for at least six months, compared with participants using placebo e-cigarette (9% versus 4%; RR: 2.29; 95% CI:1.05, 4.96; GRADE: low). The one study (n = 584) that compared e-cigarettes to nicotine patches found no significant difference in six-month abstinence rates, but the confidence intervals did not rule out a clinically important difference (RR: 1.26; 95% CI: 0.68, 2.34; GRADE: very low).

An evidence review conducted by JBI examined trials comparing nicotine-containing e-cigarettes versus NRT for biochemically validated smoking cessation. The review identified three randomised controlled trials with 1498 participants. The relative effect was 1.69 (95% CI: 1.26, 2.28). The follow-up in these studies ranged from eight weeks to 52 weeks. The EAG rated the certainty of the evidence as low, and concluded there is a moderate improvement in smoking cessation for nicotine-containing e-cigarettes compared to NRT.

The technology of e-cigarettes delivery devices is rapidly changing, and studies in progress with more recent e-cigarette models may show different results. While there are still only a small number of randomised controlled trials, the potential benefit of nicotine containing e-cigarettes for smoking cessation is supported by population studies. These studies have reported that those who use e-cigarettes are more likely to try to quit and quit successfully than those who do not use e-cigarettes.[101,102]

When used for smoking cessation, the most common side effects of e-cigarettes are dry mouth and throat irritation. No serious adverse effect was reported among the 24 studies in the Cochrane review.[97] The JBI review examined adverse effects reported from trials and population studies, and concluded that overall, nicotine-containing e-cigarette usage is associated with the occurrence of some mild adverse effects.

The most common side effects include:[97]

- coughing
- dry/irritated mouth/throat
- nausea
- insomnia.

The JBI review further concluded that the occurrences of these adverse events are comparable to the rates experienced when participants use NRT, convention cigarettes or placebo e-cigarettes. When the EAG examined the evidence of adverse effects, it noted the lack of standardisation of e-cigarette devices and nicotine-containing e-liquids. Given this, the EAG concluded that the risk of adverse effects remained unknown.

An outbreak in the United States of lung disease associated with e-cigarette use and resulting in six fatalities has raised major concerns about safety. In the majority of cases those affected were using vaping liquid containing cannabinoids.[103] The role of other additives, in particular vitamin E acetate, in the outbreak is under investigation. In response to the outbreak, Australian health authorities issued a statement reminding the public that the long-term safety and health effects associated with use of e-cigarettes are unknown, and advising that clinicians should ask patients whether they use e-cigarettes and reiterate that no e-cigarette product has been evaluated for safety.[104]

These products are not approved for therapeutic use in Australia, and the sale of nicotine-containing e-cigarettes is illegal in all states and territories (www.tga.gov.au/community-qa/electronic-cigarettes).[105] Nicotine-containing e-liquids for e-cigarettes

is only legally available with a prescription, which can be filled by a compounding pharmacy or imported under the TGA's Personal Importation Scheme (www.tga.gov.au/personal-importation-scheme).[105] Practitioners should exercise caution in deciding whether it is in the patient's best interest to prescribe nicotine for inhalation as a smoking cessation aide.

Recommendation 15 – Nicotine-containing e-cigarettes are not first-line treatments for smoking cessation. The strongest evidence base for efficacy and safety is for currently approved pharmacological therapies combined with behavioural support. The lack of approved nicotine-containing e-cigarettes products creates an uncertain environment for patients and clinicians, as the constituents of the vapour produced have not been tested and standardised. However, for people who have tried to achieve smoking cessation with approved pharmacotherapies but failed, but who are still motivated to quit smoking and have brought up e-cigarette usage with their healthcare practitioner, nicotine containing e-cigarettes may be a reasonable intervention to recommend. This needs to be preceded by an evidence-informed shared decision-making process, whereby the patient is aware of the following:

- no tested and approved e-cigarette products are available
- the long-term health effects of vaping are unknown
- possession of nicotine-containing e-liquid without a prescription is illegal
- in order to maximise possible benefit and minimise risk of harms, only short-term use should be recommended
- dual use (ie with continued tobacco smoking) needs to be avoided.

Conditional recommendation for intervention, low certainty

There is ongoing debate about a potential role for e-cigarettes in harm reduction for people who do not want to give up tobacco or nicotine use completely (refer to Chapter 5, 'Tobacco harm reduction: Electronic cigarettes for harm reduction').

Clonidine

Based on a small number of trials, clonidine has been found to be more effective than placebo in promoting smoking cessation.[106] Prominent side effects for the use of clonidine include postural hypotension, extreme drowsiness, fatigue and dry mouth, which limit the usefulness of clonidine for smoking cessation.[107]

Clonidine is not registered for smoking cessation therapy in Australia.

A number of other tobacco cessation therapies are available or in development, as described below.[108,109]

Cytisine

Cytisine is a naturally occurring substance, chemically related to varenicline, that has been used for smoking cessation for decades in parts of Eastern Europe.[110] A Cochrane meta-analysis concludes that cytisine increases the chances of quitting, although absolute quit rates in two recent trials were modest.[1] A New Zealand study found that cytisine combined with brief behavioural support was superior to NRT in helping people who smoke to quit, but it was associated with a higher frequency of self-reported adverse events.[111]

Cytisine is not currently approved by the TGA or available in Australia.

Vaccines

Anti-nicotine vaccines have been in development for a number of years. The rationale for immunisation against nicotine is to induce antibodies that bind nicotine in the blood, thereby preventing it from crossing the blood–brain barrier.[109] It is postulated that with less nicotine reaching the brain immediately after smoking, the vicious cycle between smoking and nicotine-related gratification will be broken. The vaccines must be administered regularly to maintain long-term protection. Early pre-clinical trials evaluating different vaccines were encouraging, but to date no study has detected a statistically significant difference in long-term cessation between vaccines and placebo.[112] Nicotine vaccines are not yet licensed anywhere in the world for use as an aid to smoking cessation or relapse prevention.[11]

Given that the current available first-line medications are all efficacious, and non-drug factors make a substantial contribution to the likelihood of quitting successfully,[8] choice should be based on overall evidence of relative efficacy, clinical suitability and patient preference (Figure 2.2).

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