

CLINICAL REVIEW

Supporting smoking cessation

Nicholas A Zwar *professor of general practice*¹, Colin P Mendelsohn *tobacco treatment specialist*², Robyn L Richmond *professor of public health*¹

¹School of Public Health and Community Medicine, University of New South Wales, Sydney 2052, Australia; ²Brain and Mind Research Institute, University of Sydney, Level 2, Camperdown, NSW 2050, Australia

Despite the decrease in prevalence of tobacco use in developed countries, smoking remains the most common preventable cause of disease and death in the world today.

Advice on smoking cessation from doctors and other health professionals has been shown to improve quit rates and is highly cost effective.¹ Given the importance to health of tobacco use and the benefits of cessation, every doctor should encourage attempts to stop, be able to provide brief smoking cessation intervention, and be aware of referral options (see box 1).

Over the past decade there have been advances in the science and practice of smoking cessation support. These include new medicines to treat nicotine dependence, new ways of using existing medicines, and increasing use of technology to support behavioural change. This review provides an update on evidence based approaches to maximise the effectiveness of the treatment of tobacco dependence.

Who smokes?

The prevalence of tobacco use varies around the world. Of the more than one billion smokers worldwide, 80% live in low and middle income countries, where the burden of tobacco related illness is heaviest.³

As smoking rates fall in developed countries, tobacco use is increasingly concentrated in certain groups who have greater difficulty in quitting than other smokers. These include people with mental illnesses, especially schizophrenia, those with substance use problems, people from lower socioeconomic groups, and some indigenous people. There is also some evidence that those who present for treatment have higher levels of nicotine dependence than those presenting 10 or more years ago.⁴

As with other addictions, there is a strong genetic component to smoking behaviour. The estimated mean heritability for starting smoking has been calculated at 50% and for developing nicotine dependence at 56%.⁵ Genetic factors also have a substantial role in nicotine withdrawal symptoms, cigarette consumption, difficulty in quitting, and response to smoking cessation therapies.⁶ Most smokers are nicotine dependent and for these people smoking can be thought of as a chronic medical illness that requires ongoing care.⁷

Why is stopping tobacco use so important?

There is considerable urgency about providing effective smoking cessation treatment; after the age of about 35, on average three months of life are lost for each year of continued smoking.⁸ Fortunately the health benefits of cessation are substantial and rapid. The excess risk of death from smoking begins to decrease shortly after cessation and continues to decline for at least 10 to 15 years.⁹ The British doctors' study found that male doctors who stopped smoking before the age of 35 survived about as well as those who had never smoked.⁸⁻⁹ More recent data have shown that this benefit also occurs for women.¹⁰

How can health professionals help patients to quit?

Most smokers want to stop smoking, and about 40% try to stop at least once each year.¹¹ Only 3-5% of unaided attempts, however, are successful 6-12 months later.¹² Brief advice from doctors (defined as advice provided in a consultation lasting up to 20 minutes plus up to one follow-up visit) increases cessation rates by about two thirds (relative risk 1.66, 95% confidence interval 1.42 to 1.94) compared with no advice or usual care (an absolute increase of 1-3%) at 12 months, and more intensive treatment nearly doubles the chances of quitting.¹ The 5As approach originally proposed by the US Clinical Practice Guidelines¹³ provides health professionals with an evidence based framework for structuring smoking cessation support. The elements of the 5As are:

- **Ask:** Regularly ask all patients if they smoke and record the information in the medical record
- **Advise:** Advise all smokers to quit in a clear, unambiguous way such as "the best thing you can do for your health is to stop smoking"
- **Assess:** Assessment of interest in quitting helps to tailor advice to each smoker's needs and stage of change.¹⁴ Nicotine dependence should also be assessed and helps to guide treatment. Assessment of other relevant problems

Summary points

- Throughout the world tobacco smoking is the leading cause of preventable death and illness
- As smoking rates in the general population fall in developed countries, a greater proportion of smokers have coexisting problems such as mental illness
- Cessation support from doctors and other health professionals increases quit rates
- Tobacco dependence is most effectively treated with a comprehensive approach involving behavioural support and pharmacotherapy
- Effective medicines include nicotine replacement therapy, varenicline, bupropion, nortriptyline, and cytosine. The availability and registration of these medicines varies between countries

Sources and selection criteria

This review is based on evidence synthesis from relevant Cochrane systematic reviews; review and distillation of clinical practice guidelines from Australia, the United States, and New Zealand; information from UK National Centre for Smoking Cessation and Training (www.ncsct.co.uk); and other evidence from the authors' personal libraries. We have focused on developments since the review by Aveyard and West in 2007.²

such as mental health conditions, other drug dependencies, and comorbidities is necessary to develop a comprehensive treatment plan

- Assist: All smokers should be offered help to quit
- Arrange: Follow-up visits have been shown to increase the likelihood of long term abstinence¹⁵ and are especially useful in the first few weeks after quitting.

In the United Kingdom the National Centre for Smoking Cessation and Training approach of “very brief advice” is increasingly used. The steps are:

- Establish smoking status (ASK)
- ADVISE that the best way of quitting is with a combination of behavioural support and drug treatment
- Provide a referral or offer behavioural support and follow-up appointments (ASSIST).

A recent Cochrane meta-analysis found that reducing the number of cigarettes smoked before quit day and quitting abruptly produced comparable quit rates. Patients can be given the choice of quitting in either of these ways.¹⁶ There is a range of options for referring patients for cessation support (box 1).

How is nicotine dependence assessed?

Most smokers are nicotine dependent, and the level of dependence is a predictor of withdrawal symptoms and the intensity of treatment required. Smoking within 30 minutes of waking is a reliable indicator of nicotine dependence. Smoking within five minutes of waking indicates more severe dependence.¹⁸ Cravings and withdrawal symptoms experienced in previous quit attempts are also a useful guide. The number of cigarettes smoked a day is less predictive; smoking more than 10 cigarettes a day, however, is associated with a higher likelihood of dependence (see box 2).

What are evidence based approaches to counselling and behavioural therapy?

Cochrane meta-analyses have found that cognitive and behavioural therapy delivered by health professionals has a significant effect on quit rates. Individual counselling improves long term quit rates by 39% compared with minimal behavioural intervention (relative risk 1.39, 95% confidence interval 1.24 to 1.57)¹⁸ and group programmes double success rates compared with self help programmes (1.98, 1.6 to 2.46).¹⁹

Aspects of counselling and behavioural advice include:

- Building rapport and boosting motivation

- Assisting with choice of drugs and ensuring that patients have a realistic expectation of how they can aid quit attempts—for example, by reducing withdrawal symptoms
- Describing withdrawal symptoms and cravings and exploring ways of managing these such as distraction strategies (for example, doing exercise)
- Agreeing on a quit date and promoting the “not-a-puff” rule
- Dealing with barriers to quitting such as stress and weight gain. Stress management strategies include breathing and progressive muscle relaxation techniques. Drinking water and choosing low fat foods can help to minimise weight gain
- Discussing strategies for coping with smoking triggers. For example, minimal or no alcohol in the early weeks of a quit attempt is advised
- Getting support from family and friends, patient support services, and printed materials
- Promoting lifestyle changes such as exercise and avoiding high risk situations
- Relapse prevention.

Interventions can also be delivered by telephone, text message, and the internet. A meta-analysis of five trials of mobile phone based interventions found an increase in the long term quit rates compared with control programmes (relative risk 1.71, 95% confidence interval 1.47 to 1.99).¹⁹ Internet based programmes have the advantage of being low cost and can be individualised to meet the smoker's needs. There is evidence from three trials that interactive and individually tailored internet based interventions are more effective than usual care or written self help (1.48, 1.11 to 2.78).²⁰ Motivational interviewing has a role in encouraging ambivalent smokers to try to quit. A meta-analysis of motivational interviewing versus brief advice or usual care yielded a modest but significant increase in quitting (1.27, 1.14 to 1.42).²¹ The four guiding principles²² that underlie motivational interviewing are:

- Express empathy
- Develop discrepancy (the gap between goals or values and actual behaviour)
- Roll with resistance
- Support self efficacy.

Box 1: Referral options for smoking cessation support

Telephone quitlines are available in many countries. Proactive telephone counselling is preferred as it has been shown to be more effective than reactive counselling¹⁷

In the UK, the National Health Service (NHS) provides a range of services including telephone and online support, quit kits, and a mobile phone application through <http://smokefree.nhs.uk/>

Specialised services are available in some countries either in hospitals or community settings. In the UK specialised support is available through local stop smoking services. Information is available at <http://smokefree.nhs.uk/>. In the US there are a growing number of dedicated providers. Details are available on the Association for the Treatment of Tobacco Use and Dependence website www.attud.org. In Australia the number of smoking cessation professionals is also increasing. Information is available at www.aascp.org.au

Box 2: Nicotine dependence*Assessment of nicotine dependence*

Nicotine dependence can be briefly assessed by asking about:

- Minutes after waking to first cigarette?
- Number of cigarettes a day?
- Cravings or withdrawal symptoms in previous quit attempts?

Indication of nicotine dependence

- Smoking within 30 minutes of waking
- Smoking more than 10 cigarettes a day
- History of withdrawal symptoms in previous quit attempts

During the assessment of need for drug treatment, consider also the patient's previous experience and views on pharmacotherapy for smoking cessation

What is the role of pharmacotherapy in smoking cessation?

In meta-analyses of randomised clinical trials, several drug treatments have been shown to assist smoking cessation. Pharmacotherapy is appropriate in patients who are found to be nicotine dependent (see box 2 on assessment of nicotine dependence). Medicines are most effective when given in combination with behavioural support. The most widely available preferred pharmacotherapy options are nicotine replacement therapy, varenicline, and bupropion. All these drugs have been shown to be effective in a range of patient populations including smokers with depression, schizophrenia, and cardiac and respiratory diseases. Figure 1 summarises the effect of these medicines compared with placebo.

A Cochrane network analysis concluded that combinations of nicotine replacement therapy and varenicline are the most effective quitting aids and are of similar efficacy.²² Head to head comparisons between bupropion and nicotine replacement monotherapy showed equal efficacy.²³ Clinical suitability and patient preference are important in guiding the choice of pharmacotherapy or combination of therapies (see fig 2).

Nicotine replacement therapy

Nicotine replacement therapy is available in a long acting form (nicotine patch) and in several short acting products (nicotine gum, inhalator, mouth spray, lozenge, microtablet, nasal spray). Other forms are in development. A Cochrane systematic review found that nicotine replacement therapy is an effective aid to long term cessation (relative risk 1.60, 95% confidence interval 1.53 to 1.68), and the efficacy is similar between all available forms.²⁴ Combination nicotine replacement therapy (nicotine patch combined with a rapid delivery form) should be recommended to smokers who are unable to quit or who experience cravings or withdrawal symptoms with monotherapy.²⁵ There is evidence from nine trials that this type of combination nicotine replacement therapy is more effective than a single type (1.34, 1.18 to 1.51).²⁴ Pre-cessation treatment with a nicotine patch (usually started two weeks before quit

day) can increase the rate of successful quitting compared with starting treatment on quit day (1.34, 1.08 to 1.65; six trials).²⁴ Nicotine replacement therapy is generally safe and well tolerated. Side effects, which can include nausea, headache, and dizziness, are generally mild and improve over time. Nicotine patches can cause skin irritation and disturbed sleep, and oral preparations can cause hiccups, sore mouth, and heartburn. Nicotine replacement therapy can be safely used in people with stable cardiovascular disease (fig 2).

Varenicline

Varenicline is a partial nicotine agonist that acts centrally to relieve cravings and withdrawal symptoms as well as reducing the rewarding effect of smoking. A Cochrane meta-analysis of 14 trials of varenicline found it more than doubled sustained abstinence rates at six months' follow-up (risk ratio 2.27, 95% confidence interval 2.20 to 2.55).²⁵ The most common adverse effect is nausea, affecting about 30% of users; but this is mild to moderate and leads to discontinuation of treatment in only about 3%.²⁵ Nausea is reduced by gradual up-titration of the dose and by taking the drug with food. There have been post-marketing reports of depression, agitation, changes in behaviour, and suicidal ideation, although a causal association with varenicline has not been established.²⁵ A recent meta-analysis of data from 17 trials found no evidence of higher rates of suicidal events, depression, or aggression/agitation in participants taking varenicline compared with placebo. This was the case in participants both with and without a history of psychiatric disorders.²⁶

Bupropion

Bupropion was originally developed as an antidepressant. It reduces both the urge to smoke and symptoms of nicotine withdrawal. A meta-analysis of 36 trials of bupropion found that it substantially increases quit rates over placebo (relative risk 1.69, 95% confidence interval 1.53 to 1.85).²⁷ There is a further modest increase in efficacy when it is combined with nicotine replacement therapy.^{14, 23} Bupropion is contraindicated in patients with a history of seizures and eating disorders and

patients taking monoamine oxidase inhibitors. It should be used with caution in people taking drugs that can lower seizure threshold, such as antidepressants and oral hypoglycaemic agents (fig 2⇓).²⁸

Second line options

The tricyclic antidepressant nortriptyline doubles cessation rates compared with placebo treatment at six months (relative risk 2.03, 95% confidence interval 1.48 to 2.78).²⁷ Side effects include dry mouth, constipation, nausea, sedation, and headaches. Nortriptyline is not licensed for smoking cessation. It is dangerous in overdose and can increase the risk of arrhythmia in patients with cardiovascular disease.

Cytisine is an inexpensive plant derived partial nicotine agonist that is available for smoking cessation in parts of eastern Europe but is not licensed in the UK. In a Cochrane meta-analysis of two recent trials comparing cytisine with placebo, the risk ratio was 3.98 (95% confidence interval 2.01 to 7.87).²⁵

Effects of smoking and smoking cessation on drug metabolism

Chemicals in tobacco smoke accelerate the metabolism of many common drugs by inducing the cytochrome P450 enzyme, CYP1A2. This can substantially lower the serum concentrations and effectiveness of these drugs in smokers (table 1⇓). Conversely, blood levels of these drugs might rise when smoking is stopped. Patients should be monitored for adverse effects, and dose reductions might be required. Immediate dose reductions should be considered for drugs with a narrow therapeutic index—such as olanzapine, clozapine, and warfarin—to avoid drug toxicity.²⁹ Patients should also be advised to reduce caffeine intake.

How do I treat special groups?

Pregnant women

Smoking in pregnancy has important adverse effects on the fetus and increases complications in pregnancy, including low birth weight, preterm birth, miscarriage, and placental abruption. A Cochrane systematic review found smoking cessation interventions in pregnancy reduce the proportion of women who continue to smoke in late pregnancy by about 6%.³⁰ There is inconclusive evidence of the effectiveness and safety of nicotine replacement therapy during pregnancy and other forms of pharmacotherapy are contraindicated.³¹ If nicotine replacement therapy is used, the benefits and risks should be discussed with the patient. Although nicotine is presumed to have some risk, clinical trials of therapeutic nicotine have not generally reported adverse fetal effects.³¹ Available data and expert opinion suggest that it is less harmful than continued smoking.^{28 32} Intermittent (oral) nicotine replacement therapy is generally recommended as this delivers a lower total nicotine dose.

Adolescents

Adolescence is the primary time when people start smoking and transition from experimentation to dependence occurs. A meta-analysis of interventions shows some benefit from interventions based on motivational enhancement or tailored to stage of change.³³ There is currently insufficient evidence to determine whether pharmacotherapy is effective for adolescent smokers. It is, however, reasonable to offer nicotine replacement therapy and behavioural support after assessment of nicotine

dependence and motivation to quit. In many countries nicotine replacement therapy is now licensed for use in this age group.²⁸

People with mental health problems

The rate of smoking in people with mental illness is about twice the rate in those without mental illness. In general, the more severe the psychiatric diagnosis, the higher the prevalence of smoking. People with mental illness also smoke more heavily than other smokers, are more nicotine dependent, and might need more intensive or prolonged support to quit. There is evidence, however, that they are just as motivated to quit as the general population.³⁴

The doses of medicines used to treat depression and psychotic disorders might also require adjustment after smoking cessation (table 1⇓). Contrary to common perceptions smoking cessation is not associated with worsening of psychiatric illnesses and in fact improvement is more common.³⁵

Table 2⇓ provides a summary of the use of smoking cessation pharmacotherapy in special populations.

What are the emerging approaches in smoking cessation?

Nicotine vaccines have been researched, but a Cochrane meta-analysis of four trials found no benefit in long term cessation compared with placebo.²³

Electronic cigarettes (e-cigarettes) are battery powered devices that deliver nicotine in a vapour without tobacco or smoke. E-cigarettes can relieve cravings and symptoms of nicotine withdrawal as well as simulating the behavioural and sensory aspects of smoking.³⁶ A small number of randomised controlled trials have suggested that e-cigarettes could have a role in cessation and harm reduction, though further research is needed before recommendations for their use can be confidently made.^{36 37} Concerns about e-cigarettes include a lack of evidence for long term safety, a lack of regulation, the possibility of use acting as a gateway to smoking, potential for dual use while a person is still smoking, and the renormalisation of smoking behaviour.³⁸

Physical activity is routinely recommended as an aid to quitting. Short bursts of moderate exercise, such as brisk walking, rapidly reduce cigarette cravings and symptoms of withdrawal.³⁹ Regular exercise also attenuates post-cessation weight gain for up to two years, improves mental wellbeing, and has general health benefits. The clinical trials so far have not shown an effect of exercise on cessation rates.⁴⁰

Mindfulness is increasingly being explored to assist smoking cessation, especially in smokers with mental illness. Mindfulness involves being aware of present moment experiences such as cravings, withdrawals, and negative affect, instead of responding automatically with a cigarette. Focusing on and accepting these uncomfortable sensations can cause them to diminish.⁴¹ Several studies to date have found that a course of mindfulness training (usually eight weeks) can help reduce cravings, withdrawal symptoms, and cigarette intake and might improve rates of abstinence.⁴²⁻⁴⁴

Which strategies have not been shown to work?

Meta-analyses of trials of acupuncture and hypnotherapy have not shown either to be effective.^{45 46}

How do I help patients avoid relapse?

Relapse is a return to regular smoking. Most smokers relapse in the first eight days after a quit attempt.¹² Common triggers for relapse are alcohol, negative emotional states, and exposure to smoke. There is currently no evidence from randomised trials of effective behavioural interventions to prevent relapse.⁴⁷ In terms of pharmacological interventions, extended treatment with varenicline (defined as an additional 12 weeks) had a significant benefit in one trial, but pooled results of six studies with bupropion showed no effect. There have been mixed results with nicotine replacement therapy, with two studies of orally administered therapy showing a benefit.⁴⁸

Is there a role for harm reduction?

Smokers who are not willing or able to quit in the short term can use nicotine replacement therapy to reduce their tobacco intake. The health benefits of long term reduction in smoking are uncertain, though cutting down with nicotine replacement therapy nearly doubles the odds of quitting altogether.⁴⁸

For smokers who have quit, the long term use of nicotine replacement therapy might help to reduce the harm from smoking. Evidence from studies with up to five years' follow-up suggests that nicotine replacement products do not pose a significant health risk.⁴⁸ Most of the health effects of tobacco are caused by the toxins and carcinogens in tobacco smoke, not nicotine. The exception to this is in pregnancy, when nicotine reduces fetal growth and animal studies suggest that it is toxic to the fetal brain and lungs.⁴⁸

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Tips for non specialists

- Identify and document smoking and offer support for smoking cessation at every opportunity
- Provide support based on the 5As or refer, depending on the clinical context
- Encourage comprehensive treatment consisting of behavioural support and pharmacotherapy for smokers addicted to nicotine

Additional educational resources

UK National Centre for Smoking Cessation and Training (www.ncsct.co.uk/)—delivers training and assessment programmes, support services for local and national providers and conducts research into behavioural support for smoking cessation. This includes the "very brief advice" training module

Society for Research on Nicotine and Tobacco and the Society for the Study of Addiction (www.treatobacco.net)—provides information on treatment of tobacco dependence. The website has links to clinical practice guidelines for cessation from around the world

United States Smoking Cessation Guidelines (www.ahrq.gov/professionals/clinicians-providers/resources/tobacco/treating-tobacco-use.html#.UrJWcieRNSY)—http://literature review and meta-analysis of intervention and clinical practice guidelines based on the 5As approach

Australian Smoking Cessation Guidelines (www.racgp.org.au/your-practice/guidelines/smoking-cessation/)—clinical practice guidelines aimed at a wide range of health professionals

New Zealand Smoking Cessation Guidelines (www.health.govt.nz/publication/new-zealand-smoking-cessation-guidelines)—clinical practice guidelines based on the ABC approach: **A**sk about smoking status; give **B**rief advice to stop smoking to all smokers; and provide evidence based **C**essation support for those who want to stop smoking)

Questions for future research

- What is the role of e-cigarettes in cessation and harm reduction and how should their use be regulated?
- Does exercise increase smoking cessation rates?
- Can pharmacogenetics guide personalised choices of drug treatment and, if so, is it more effective?

Tables**Table 1 | Drugs that interact with smoking. Blood concentrations rise after cessation of smoking**

Class	Drug
Antipsychotics	Olanzapine, clozapine. Haloperidol, chlorpromazine, fluphenazine
Antidepressants	Duloxetine, fluvoxamine, tricyclic antidepressants, mirtazapine
Anti-anxiety agents	Alprazolam, oxazepam, diazepam
Cardiovascular drugs	Warfarin, propranolol, verapamil, flecainide. Clopidogrel (efficacy increased in smokers)
Diabetes	Insulin, metformin
Other	Naratriptan, oestradiol, ondansetron, theophylline, dextropropoxyphene
Others	Caffeine, alcohol

Table 2| Suitability of preferred pharmacotherapy in special populations. Quitting smoking can alter the metabolism of several drugs. Adapted and reproduced with permission from the Royal Australian College of General Practitioners²⁸

	Varenicline	Bupropion	NRT
Pregnant and lactating women	ND	ND	Yes*
Children and adolescents (age 12-18)	ND	ND	Yes
People with smoking related diseases:			
Cardiovascular disease	Yes†	Yes	Yes‡
Chronic obstructive pulmonary disease	Yes	Yes	Yes
Diabetes	Yes§	Yes§	Yes§
Severe renal impairment	Yes¶	Yes¶	Yes
Moderate to severe hepatic impairment	Yes	Yes¶	Yes
People with mental illness:			
Any	Yes**	Yes	Yes
Depression	Yes**	Yes	Yes
Schizophrenia	Yes**	Yes	Yes
People with substance misuse disorders	Yes	Yes††	Yes
Existing contraindications to use	Yes‡‡	Yes‡‡§§	Yes‡‡

NRT=nicotine replacement therapy; ND=lack of safety data.

*There is currently inconclusive evidence to determine whether or not NRT is effective or safe when used in pregnancy for smoking cessation, if it is used risks and benefits should be discussed with patient; intermittent dosing products preferable.

†Association between varenicline use and non-fatal cardiac events has been suggested, Subsequent studies and meta-analysis have not found association.

‡Caution is advised for people in hospital for acute cardiovascular events such as myocardial infarction, unstable or progressive angina, severe cardiac arrhythmias, or acute phase stroke. NRT can be used under medical supervision, where the clinician should balance risk of using nicotine replacement against risk of smoking.

§Closely monitor blood sugar concentrations as insulin or other drug requirements might change.

¶Dosing adjustment required.

**Close follow-up required. Check for any unusual or serious changes in mood or behaviour at two-three week follow-up visit and after treatment is completed.

Careful monitoring required for mood changes, depression, behaviour disturbance, and suicidal thoughts.

††Caution with alcohol abuse.

‡‡Hypersensitivity to active substance or any excipients.

§§Contraindications: seizures, anorexia, bulimia, central nervous system tumours, monoamine oxidase inhibitor treatment within 14 days.

Figures

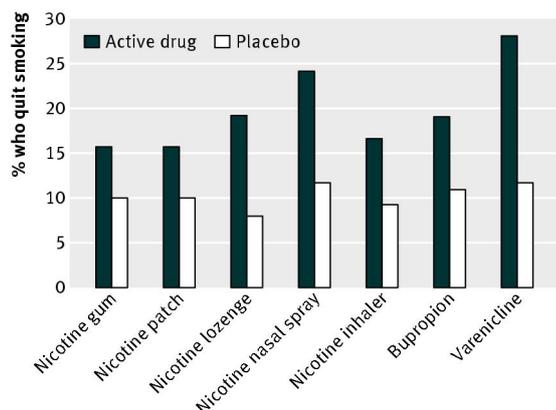


Fig 1 Long term (≥ 6 months) quit rates for widely available drugs for smoking cessation. Data adapted from Cochrane Database of Systematic Reviews^{24 25 27}

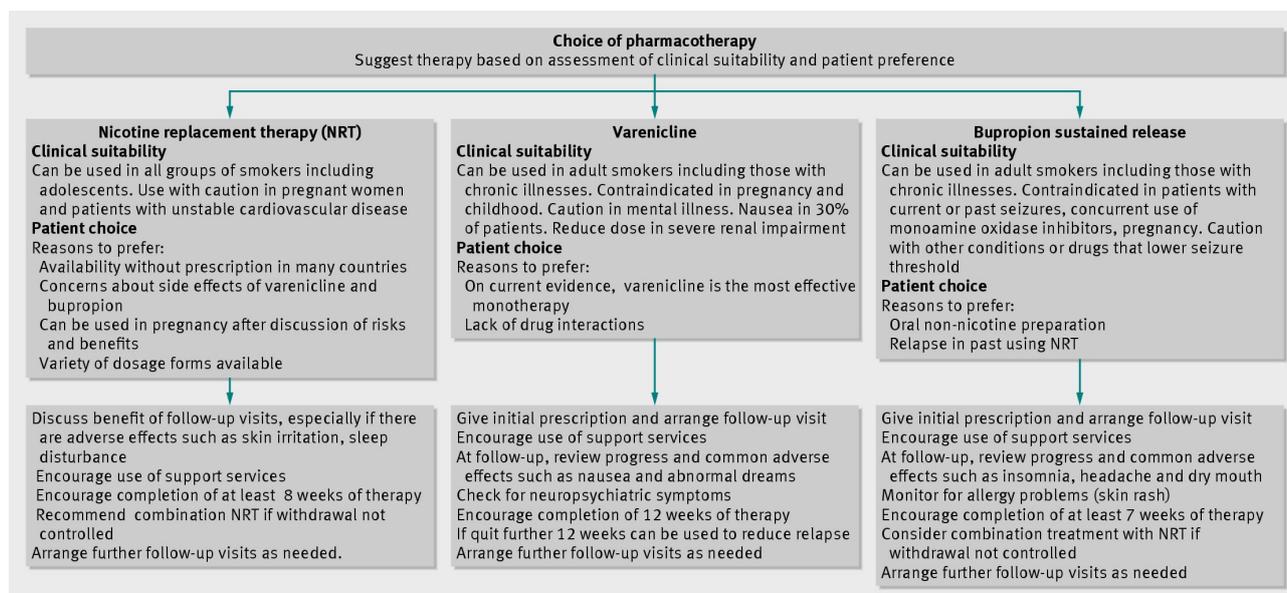


Fig 2 Pharmacotherapy treatment algorithm for nicotine dependent smokers. Adapted and reproduced with permission from the Royal Australian College of General Practitioners²⁸