



THERAPEUTICS

Drugs for smoking cessation

Jamie Hartmann-Boyce *research associate and DPhil student*, Paul Aveyard *professor of behavioural medicine*

Nuffield Department of Primary Care Health Sciences, Radcliffe Observatory Quarter, University of Oxford, Oxford OX2 6GG, UK

A 49 year old woman who smokes attends the general practitioner for help with troubling menopausal symptoms. During the course of the consultation, the doctor offers her help to stop smoking. She has tried stopping smoking previously without help and found it intolerable. She asks if she can use drug therapy this time.

What are drugs for smoking cessation?

Of the drugs available for smoking cessation, three are widely licensed and have proved efficacy:

- Nicotine replacement therapy (NRT)—available as patches or as shorter acting oral forms (lozenges, chewing gum) or nasal sprays; reduces urges and withdrawal symptoms by substituting for nicotine inhaled via tobacco smoke¹
- Oral varenicline—a nicotinic receptor partial agonist that binds less effectively than nicotine²
- Oral bupropion—seems to be a nicotinic receptor antagonist with dopaminergic and adrenergic actions; it may work by blocking effects of nicotine, relieving withdrawal, or reducing depressed mood.³

How well do they work?

Cochrane reviews give strong evidence that all three drugs are effective. Compared with placebo, the relative risks of abstinence are 1.60 (95% confidence interval 1.53 to 1.68) for NRT, 1.62 (1.49 to 1.76) for bupropion, and 2.27 (2.02 to 2.55) for varenicline.¹⁻³ These relative risks seem to be constant over time from early in the quitting process to the long term and do not depend on whether behavioural support is provided.^{4 5} However, the absolute benefits do depend on these factors. Figure 1↓ shows absolute quit rates at the end of a typical 12 week course of treatment assuming all participants used behavioural support.

How safe are they?

NRT

NRT delivers nicotine at a lower concentration and more slowly than do cigarettes, so logically any risks from nicotine alone must be lower than those from smoking. A Cochrane review showed a statistically significant increase in chest pain and palpitations with NRT compared with placebo (2.5% v 1.4%).¹ However, there is no evidence that NRT increases the incidence of cardiac ischaemia.^{1 7}

Varenicline

There are concerns that varenicline causes adverse neuropsychiatric or cardiac events. A Cochrane review found no significant differences in neuropsychiatric events (0.15% v 0.21%) or cardiac events (0.6% v 0.5%) in trials comparing varenicline with placebo.⁶ A separate systematic review reported an excess of serious adverse cardiovascular events, but another using more appropriate methods did not^{8 9}; nor did most large comparative observational studies.²

Bupropion

Seizures are the primary safety concern with bupropion, as early trials testing the drug for depression (using a different dosage and formulation than are used for smoking cessation) suggested an increased risk. Evidence from observational studies, controlled trials, and systematic reviews consistently report seizures occurring in 1 in 1000 users.³ Concerns based on post-marketing surveillance have also been raised about possible psychiatric adverse events including changes in behaviour, depressed mood, hostility, and suicidal events. Two of the three subsequent observational analyses did not detect evidence of an increase in such events in people treated with bupropion, and

Correspondence to: J Hartmann-Boyce Jamie.hartmann-boyce@phc.ox.ac.uk

This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series adviser is Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital. To suggest a topic, please email us at practice@bmj.com

What you need to know

- Consider prescribing nicotine replacement therapy, varenicline, or bupropion to most patients starting an attempt to quit smoking
- When prescribing stop smoking drugs, stress the importance of commitment to total abstinence from the quit day onwards; adding behavioural support increases the chances of success
- Nicotine replacement therapy is safe and is more effective if a patch is combined with a short acting form
- Do not prescribe varenicline or bupropion in pregnancy, and avoid bupropion in patients at higher risk of seizures
- Monitor people taking varenicline or bupropion for adverse psychological reactions

an increase has not been detected in randomised controlled trials.³

How cost effective are they?

The costs of smoking related morbidity and mortality mean that effective smoking cessation aids are highly cost effective, which is reflected in national guidelines.^{10 11} Exact estimates of cost per quality adjusted life year (QALY) vary depending on the country, comparator, and other assumptions.¹² The cost per QALY has been estimated to range between £494 (€654; \$716) and £3554 for NRT, between £316 and £2212 for bupropion, and between £950 and £1140 for varenicline.¹²⁻¹⁴

How are they taken and monitored?**Which patients?**

Drugs are usually prescribed only to people who are about to quit. However, systematic reviews of trials of NRT and a recent trial of varenicline suggest that these drugs can induce cessation in people who want to reduce smoking, without an immediate goal to quit completely.^{15 16}

Guidelines in the United States (but not the United Kingdom) advise not treating people who smoke fewer than 10 cigarettes a day (as most trials enrol people who smoke more than 10 a day).^{10 11} It seems reasonable to offer a prescription to anyone who feels impelled to smoke when trying to quit.

Which drug?

Varenicline and combination NRT (a patch plus a short acting form) are the most effective treatments, but personal commitment to use is important. Take into account patient choice, precautions, and contraindications (see box 1).

When to start?

Bupropion and varenicline are usually taken for at least a week before the quit day, although longer prior use of varenicline may be more effective.²¹ Nicotine replacement is usually started on the quit day; a systematic review of trials found insufficient evidence that taking it before this is more effective.²²

Dose and duration

Drugs are effective if people make a deliberate attempt to stop smoking, and prescribers need to stress commitment to total abstinence from the quit day onwards. That said, drugs should be prescribed for as long as a person is actively trying to quit; observational evidence suggests that they help recovery from lapses and should not be stopped because of initial failure to quit.²³ The urge to smoke wanes after a period of abstinence, so drugs are needed for only a few months.

NRT—Dosing should generally follow the licence. However, systematic reviews of randomised trials show that higher doses are more effective than lower doses in more dependent smokers and that combination NRT (a patch plus a short acting form) is

more effective than one form alone.¹ Longer treatment courses do not seem to be more effective.¹

Varenicline—Dosing should generally follow the licence; meta-analysis shows that lower doses are associated with fewer adverse events but lower effectiveness. A 24 week, rather than the recommended 12 week, course may be more effective for people who struggle to become abstinent early in a quit attempt.²

Bupropion—Dosing should generally follow the licence. Higher doses do not seem to confer more benefit.³ Systematic reviews suggest that NRT plus bupropion is slightly more effective than bupropion alone but no more effective than NRT alone.^{1 3}

How to monitor and support use?

- If available, offer behavioural support alongside drug treatments, as Cochrane reviews show that this increases effectiveness. Effective support includes information on how to quit, committing to total abstinence after a quit day, and regular contact to assess progress and solve problems, offered face to face, by telephone, or electronically.²⁴
- Ask about adverse effects and help users to manage these accordingly. Monitor for adverse psychological reactions with varenicline and bupropion, and check blood pressure with bupropion.

How do they compare with other treatments?

Acupuncture and hypnotherapy—Cochrane reviews show no clear evidence that either is effective.^{25 26}

Electronic cigarettes and other electronic nicotine delivery devices—These are currently not prescribable in most countries and have a very small evidence base. A Cochrane review showed weak evidence that electronic cigarettes containing nicotine were more effective for helping people to quit smoking than those without nicotine.²⁷ Adverse effects are similar to those for NRT.

Cytisine—This is licensed for smoking cessation in only a few countries. A Cochrane review found a relative risk of 3.98 (2.01 to 7.87) for long term quitting compared with placebo.² Existing evidence suggests few safety concerns and mild adverse events (such as nausea and vomiting and sleep disorders).

Contributors: JHB and PA both contributed to the conception and design of the work; the acquisition, analysis, and interpretation of the data; the drafting and revision of the manuscript critically for important intellectual content; and final approval of the version to be published. JHB is the guarantor.

Competing interests: We have read and understood the BMJ policy on declaration of interests and declare the following interests: there was no specific funding for this article; JHB receives support from the National Institute of Health Research School for Primary Care Research; the opinions expressed in this paper are those of the authors and do not represent the position of the National Institute for Health Research; PA

Box 1: What are the precautions?**Nicotine replacement therapy (NRT)**

Ischaemic heart disease—Safe in stable cardiovascular disease. People with acute coronary syndrome or severe arrhythmias should try quitting without NRT, given the possible risk of chest pain and palpitations. NRT may be added if a quit attempt is failing, with follow-up for such symptoms

Adverse effects—Generally due to irritation at the delivery site. Patch use can lead to skin sensitivity and irritation, affecting about 20% of users but rarely causing discontinuation.¹⁷ Oral and nasal forms have been associated with coughing (8%) and mouth and throat soreness (5%); hiccups have been reported in 3% of oral users.¹⁷

Pregnancy—Can be prescribed, as systematic reviews do not show significant differences in serious adverse events between treatment and control groups in pregnancy, and NRT is safer in pregnancy than tobacco smoke, which contains many toxins.¹⁸ As nicotine may be harmful in pregnancy, avoid 24 hour patches to reduce unnecessary exposure. British guidelines suggest the risks and benefits of NRT be explained to pregnant or breastfeeding women before treatment,¹⁰ whereas US guidelines suggest not prescribing NRT in this population.¹¹ This difference is due to insufficient evidence that NRT is effective in pregnancy¹⁸

Breast feeding—Can be used, as NRT is safer than secondhand smoke for the infant

Varenicline

Psychological effects—Assess for suicidality after starting, particularly in people with current or previous depression (based on UK and US regulatory advice). However, the best current evidence does not show an increased risk¹⁹

Ischaemic heart disease—Can be used, as best current evidence does not show an increased risk²⁻⁹

Other adverse effects—Mainly nausea (causing discontinuation in 0.6-7.6% of users in randomised trials), constipation, headache, insomnia, and vivid dreams; discontinuation rate due to adverse events is about 9.5% (versus 8.0% for placebo)⁶

Pregnancy and breast feeding—Avoid use as safety is unknown

Bupropion

Seizures—Contraindicated in patients with a history of seizures or conditions that predispose to seizure (anorexia, brain tumour, or alcohol or benzodiazepine withdrawal)

Blood pressure—Measure blood pressure before and during treatment, and consider stopping if clinically important rises occur. Bupropion may rarely increase blood pressure, particularly when co-administered with NRT²⁰

Psychological effects—Monitor for possible adverse effects (such as behavioural change, hostility, depressed mood, and suicidal ideation), given conflicting evidence on this risk

Other adverse effects—Most commonly insomnia (30-40%), dry mouth (10%), and nausea; 7-12% discontinue owing to adverse events³

Drug interactions—Avoid in people taking drugs that extensively induce or inhibit the cytochrome P450 system (such as phenytoin); if concomitant use is necessary, reduce doses of drugs that inhibit CYP2D6 (such as sodium valproate) to avoid toxicity.³ Bupropion is metabolised to its active form by CYP2B6, so drugs that are substrates for CYP2B6, including clopidogrel, could reduce the effectiveness of bupropion

Pregnancy and breast feeding—Avoid use as safety is unknown¹⁸

Tips for patients

- Do not be put off trying to stop smoking if you feel you lack willpower. You can learn techniques to boost your motivation when you are feeling low and cravings strike. Getting support from a trained stop smoking counsellor can teach you these techniques and other helpful strategies and will boost your chance of success
- Medication does not make you want to stop smoking, but it reduces the strength of craving for cigarettes and helps with mood control. You are more likely to stop smoking with medication than without it
- Varenicline and combination NRT (a patch plus a short acting form) are the most effective stop smoking medications
- Do not be deterred by your own or other people's failed quit attempts. Learn what you can from them and maximise your chances next time by using medication and getting support
- Commit yourself to the "not a puff rule," which means no smoking after quit day. People who think of themselves as non-smokers now are more likely to succeed than those who think of themselves as trying to stop smoking
- Reducing your medication early is not a sign of recovery—stopping medication early means that you are more likely to relapse. Cravings come and go, and it is better to trust the science than what feels right to you at that moment. As with other forms of medication, it is more effective if you complete the course
- Try not to worry about becoming addicted to stop smoking medication or nicotine replacement in particular. Cigarette addiction is what may kill you. Most people can stop these medications without problems; if you go on using NRT long term, remember that the harm from cigarettes comes from the tar and not the nicotine

How patients were involved in the creation of this article

We thank two members of the UK Centre for Tobacco and Alcohol Studies smokers' panel with whom we held discussions before drafting the article; these discussions informed what was included in the sections on dosage, treatment duration, and tips for patients. Panel members also commented on the full article, resulting in revisions to the tips for patients.

is funded by the UK Centre for Tobacco and Alcohol Studies; PA has done one day of consultancy for Pfizer on smoking cessation, leading to payments to him and the University of Oxford.

Patient consent: Not required (patient case hypothetical).

Provenance and peer review: Commissioned; externally peer reviewed.

- 1 Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012;11:CD000146.23152200.
- 2 Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012;4:CD006103.22513936.

- 3 Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014;1:CD000031.24402784.
- 4 Stapleton J. Cigarette smoking prevalence, cessation and relapse. *Stat Methods Med Res* 1998;7:187-203. doi:10.1191/096228098671391775. 9654641.
- 5 Etter JF, Stapleton JA. Nicotine replacement therapy for long-term smoking cessation: a meta-analysis. *Tob Control* 2006;15:280-5. doi:10.1136/tc.2005.015487. 16885576.
- 6 Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;5:CD009329.23728690.
- 7 Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792-8. doi: 10.1056/NEJM199612123352402. 8943160.

- 8 Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events associated with varenicline: a systematic review and meta-analysis. *CMAJ* 2011;183:1359-66. doi:10.1503/cmaj.110218. 21727225.
- 9 Prochaska JJ, Hilton JF. Risk of cardiovascular serious adverse events associated with varenicline use for tobacco cessation: systematic review and meta-analysis. *BMJ* 2012;344:e2856. doi:10.1136/bmj.e2856. 22563098.
- 10 National Institute for Health and Care Excellence. *Smoking cessation services*. NICE, 2008.
- 11 Tobacco Use and Dependence Guideline Panel. *Treating tobacco use and dependence: 2008 update*. Department of Health and Human Services, 2008.
- 12 Shahab L. *Cost-effectiveness of pharmacotherapy for smoking cessation*. National Centre for Smoking Cessation and Training (NCSCT), 2012. (available at http://www.ncsct.co.uk/usr/pub/B7_Cost-effectiveness_pharmacotherapy.pdf).
- 13 Woolacott NF, Jones L, Forbes CA, et al. The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation. *Health Technol Assess* 2002;6:1-245. doi:10.3310/hta6160. 12269277.
- 14 Zimovetz EA, Wilson K, Samuel M, Beard SM. A review of cost-effectiveness of varenicline and comparison of cost-effectiveness of treatments for major smoking-related morbidities. *J Eval Clin Pract* 2011;17:288-97. doi:10.1111/j.1365-2753.2010.01439.x. 21029268.
- 15 Moore D, Aveyard P, Connock M, Wang D, Fry-Smith A, Barton P. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 2009;338:b1024. doi:10.1136/bmj.b1024. 19342408.
- 16 Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA* 2015;313:687-94. doi:10.1001/jama.2015.280. 25688780.
- 17 Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tob Induc Dis* 2010;8:8. doi:10.1186/1617-9625-8-8. 20626883.
- 18 Coleman T, Chamberlain C, Davey MA, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2012;9:CD010078.22972148.
- 19 Gibbons RD, Mann JJ. Varenicline, smoking cessation, and neuropsychiatric adverse events. *Am J Psychiatry* 2013;170:1460-7. doi:10.1176/appi.ajp.2013.12121599. 24030388.
- 20 Thase ME, Haight BR, Johnson MC, et al. A randomized, double-blind, placebo-controlled study of the effect of sustained-release bupropion on blood pressure in individuals with mild untreated hypertension. *J Clin Psychopharmacol* 2008;28:302-7. doi:10.1097/JCP.0b013e318172424e. 18480687.
- 21 Hajek P, McRobbie HJ, Myers KE, Stapleton J, Dhanji AR. Use of varenicline for 4 weeks before quitting smoking: decrease in ad lib smoking and increase in smoking cessation rates. *Arch Intern Med* 2011;171:770-7. doi:10.1001/archinternmed.2011.138. 21518946.
- 22 Lindson N, Aveyard P. An updated meta-analysis of nicotine preloading for smoking cessation: investigating mediators of the effect. *Psychopharmacology (Berl)* 2011;214:579-92. doi:10.1007/s00213-010-2069-3. 21060996.
- 23 Ferguson SG, Gitchell JG, Shiffman S. Continuing to wear nicotine patches after smoking lapses promotes recovery of abstinence. *Addiction* 2012;107:1349-53. doi:10.1111/j.1360-0443.2012.03801.x. 22276996.
- 24 Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2012;10:CD008286.23076944.
- 25 White AR, Rampes H, Liu JP, Stead LF, Campbell J. Acupuncture and related interventions for smoking cessation. *Cochrane Database Syst Rev* 2014;1:CD000009.24459016.
- 26 Barnes J, Dong CY, McRobbie H, Walker N, Mehta M, Stead LF. Hypnotherapy for smoking cessation. *Cochrane Database Syst Rev* 2010;10:CD001008.20927723.
- 27 McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst Rev* 2014;12:CD010216.25515689.

Published by the BMJ Publishing Group Limited. For permission to use (where not already granted under a licence) please go to <http://group.bmj.com/group/rights-licensing/permissions>

Figure

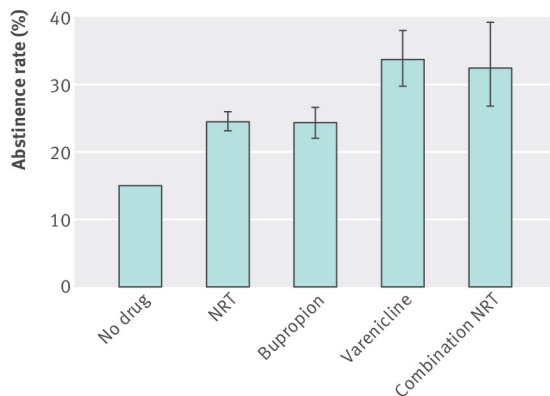


Figure 1 Absolute abstinence rates for smoking cessation drugs, based on data from network meta-analysis.⁶ In countries such as the United Kingdom, this might represent quit rates at the end of a 12 week course of drug in participants attending a low intensity behavioural support programme for first four weeks of a quit attempt. Absolute quit rates vary across countries and depend on how cessation is defined, when it is measured, and whether behavioural support is provided. Combination nicotine replacement therapy (NRT) refers to use of both a patch and a rapid acting form of NRT