Current insights and new opportunities for smoking cessation

HAYDEN MCROBBIE

Abstract

Assisting smokers to stop smoking is often seen as a difficult task but is crucial for health improvement, especially for those with established cardiovascular disease. Healthcare professionals are now, more than ever, in a position to help smokers who want to stop. For the greatest chance of success smokers should be referred to stop smoking services that provide multi-session treatment combining intensive behavioural support with nicotine replacement therapy or bupropion. Promising new medications are being developed that will add to the current treatment strategies and may give smokers a greater chance of stopping for good.

Key words: smoking cessation, cardiovascular disease, nicotine replacement therapy, bupropion.

Introduction

Over the past two decades the incidence of heart disease has shown a steady decline in many countries. It was recently reported that in England and Wales almost 50% of this decline was attributable to the reduction in smoking prevalence. Yet approximately a quarter of the UK adult population continue to smoke and cardiovascular disease (CVD) remains a major cause of death and disability amongst this group. For those smokers with CVD, stopping smoking is the most important thing that they can do to improve their current and future health. A recent review showed that smoking cessation results in a 36% reduction in relative risk of mortality. However, for many, stopping smoking is not an easy task and only 2–3% of those who try by themselves will still be abstinent one year later. Fortunately, treatments are now available that will increase the chance of long-term abstinence. This review summarises the most effective way to help smokers to stop, and looks at the future of smoking cessation treatments.

Table 1. Tobacco withdrawal symptoms

<table>
<thead>
<tr>
<th>Withdrawal symptom</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressed mood</td>
<td>&lt; 4 weeks</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>&lt; 2 weeks</td>
</tr>
<tr>
<td>Irritability</td>
<td>&lt; 4 weeks</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>&lt; 2 weeks</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt; 4 weeks</td>
</tr>
<tr>
<td>Increased appetite and increased weight</td>
<td>&gt; 10 weeks</td>
</tr>
<tr>
<td>Decreased heart rate</td>
<td>&gt; 10 weeks</td>
</tr>
<tr>
<td>Constipation</td>
<td>&gt; 4 weeks</td>
</tr>
<tr>
<td>Mouth ulcers</td>
<td>&gt; 4 weeks</td>
</tr>
</tbody>
</table>

Nicotine dependence and withdrawal

The primary reason why many smokers find it difficult to stop is nicotine dependence. Nicotine deprivation precipitates a withdrawal syndrome producing both physical symptoms and mood disturbances such as mouth ulcers, constipation, irritability, increased appetite, poor concentration and urges to smoke (table 1). The occurrence of these symptoms, especially urges to smoke and depressed mood, can lead to relapse early in a quit attempt. Most symptoms last no longer than two to four weeks and assisting smokers through the first four weeks is therefore pivotal.
Helping smokers to stop
In 1998 the UK government produced a policy paper Smoking kills that detailed a plan to reduce smoking prevalence. It provided a tobacco control strategy and also set out plans for development of smoking cessation services. At the same time, National Smoking Cessation Guidelines were published that gave details of how services should be structured and also outlined treatment strategies. Four years on, the UK has a comprehensive and successful national smoking cessation service treating large numbers of smokers, and achieving good short-term abstinence rates (for the year 2002-2003, a total of 235,000 smokers set a quit date and 53% were abstinent at four weeks).10

Advice to quit and treatment
Brief, opportunistic, unsolicited smoking cessation advice delivered by physicians can prompt quit attempts in up to 40% of patients receiving such advice11 and can increase one-year abstinence rates by 2.5%. This simple but important intervention is outlined in key documents such as the European guidelines on cardiovascular disease prevention in clinical practice. Providing such advice is one of the quality outcome measures in the new UK General Medical Services contract.14

Physicians and all other healthcare professionals can further increase their patients’ chance of success by referring them to local stop smoking services (table 2). This is especially important for smokers with any kind of established CVD. Most are aware of the substantial risk smoking has on their health and yet are unable to stop on their own. These smokers are typically highly dependent and to become long-term abstainers they will require intensive treatment such as that provided by the NHS smoking cessation services.

Withdrawal-oriented therapy is the predominant form of treatment used within the UK’s smoking cessation clinics. Treatment is provided over six or seven sessions, at weekly intervals. This focuses on preventing early relapse in smokers and assists them through the most difficult time of the withdrawal syndrome. This model emphasises the importance of complete abstinence, motivational support and close supervision of medication use. Treatment can be delivered in a group or on an individual basis as both are shown to increase long-term success compared to minimal interventions.16-18 There are no direct comparisons of group and individual treatments but a recent evaluation of English smoking cessation services showed that group treatment was one of the factors positively associated with outcome.19 One reason for this may be because groups provide additional social and peer support. Some clinics increase this support further by asking pairs of smokers quitting together to call each other on a daily basis. In a general practice setting this was shown to increase short-term success compared to smokers who were not paired with a fellow quitter (27% vs. 12%, p<0.01).20

Medications such as nicotine replacement therapy (NRT) and bupropion should be recommended as first-line treatments to all smokers who want to stop, and used in combination with behavioural support.5,9,21,22

Nicotine replacement therapy
NRT is the most commonly used pharmacological treatment for smoking cessation and there is a wealth of data confirming its efficacy and safety. There are currently six different NRT products available in the UK – all are available on prescription and can be purchased in pharmacies (table 3). These products are also becoming increasingly available on general sale. Products differ in their strength, route of delivery, speed of absorption, ease of use, degree of behavioural replacement provided, and ability of dose titration. Overall, in comparison to placebo, all NRT preparations approximately double the chance of long-term abstinence (OR=1.74 [95% CI 1.64–1.86]).23 Absolute success depends on the type of support provided and the type of smoker being treated. Low levels of support and higher dependence are both associated with lower abstinence rates.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
</tr>
</thead>
</table>

**Table 2. Helping smokers to quit - Ask Motivate and Refer (AMORE)**

**Ask** all patients if they smoke.

**Motivate** current smokers to make a quit attempt. For example, you could say:

- “We need to address the issue of your smoking. You probably already know the risks involved with smoking but I cannot stress enough how important it is to stop. It is the best thing that you can do to improve your health.”

- You can add something specific to your patient, for example, for someone who has suffered a myocardial infarction:

  - “After the heart attack, quitting smoking will substantially decrease the risk of you having another heart attack. You may also like to think of all the money you could save. A 20 a day smoker will save at least £1,500 per year.”

- “I would like you to seriously consider giving up smoking.”

- “Fortunately, we have smoking cessation specialists who can help people like you quit - it’s free, and effective.”

- “The specialist would help you to set a firm quit day and provide ongoing support together with medications such as nicotine replacement therapy (there are six different products to choose from) and Zyban®. If you have a partner or other family members who smoke, my colleagues can help them also if they wish, so you can quit together at the same time.”

**Refer** smokers to the stop smoking services. For example you could say:

- “Here is a referral card. Just give our smoking cessation team a call. They’re good and can really make a difference.”
Nicotine replacement therapies act primarily by providing a 'clean' alternative source of nicotine that the smoker would have otherwise received from tobacco. Nicotine from NRT cannot compete with the speed or dose delivered by smoking but it is sufficient to reduce the severity of withdrawal symptoms and so can increase abstinence rates.

The transdermal patch is simple to use and has good treatment compliance. Drawbacks include that it takes several hours to reach peak plasma concentration, provides no behavioural replacement and does not allow for dose titration. There are two preparations: a 15 mg/16-hour daytime patch and a 21 mg/24-hour patch that is used overnight. Both release approximately 1 mg of nicotine per hour. Use full dose for 8 weeks, aiming for a dose reduction over the last 4 weeks.

Recommend higher dose products for higher dependence smokers (those who smoke their first cigarette within 30 minutes of waking). The odds ratio for one-year abstinence was 2.14 for the low-dependence smokers and 2.69 for the higher dependence smokers. Similar data exist for the different strengths of gum.23

Although it is recommended that smokers use NRT products for up to 12 weeks, some smokers go on to use them long-term.24 For example, of those who quit using gum purchased over the counter, 5.2% use it for more than three months and 1% for 12 months or more.25 Potential long-term use of a product is related to its speed of nicotine delivery. The abuse liability of NRT is low, however, and smokers can be reassured that most will not require NRT for more than the recommended treatment period.26

Bupropion
Bupropion is an atypical antidepressant that was subsequently discovered to help smokers quit. Its precise mechanism of action in assisting smoking cessation is unknown but it is thought to act via dopaminergic and noradrenergic pathways that play an important role in nicotine dependence and withdrawal.27 In addition, it may help through its action as a non-competitive antagonist at the nicotinic acetylcholine receptor.28 Clinically, bupropion reduces the severity of nicotine withdrawal. Meta-analyses show it to roughly double the chance of long-term abstinence compared with placebo when combined with behavioural support.29 Only one published randomised controlled trial has compared the efficacy of bupropion with NRT.30 This showed significantly higher one-year continuous abstinence rates amongst those treated with bupropion compared to those treated with 21 mg/24-hour patches (18% vs. 10%, p<0.001).

Although the results suggest that bupropion is superior to
the nicotine patch, more data comparing these products are needed. Currently there is no method for deciding which smoker should receive bupropion or NRT. Bupropion may be well suited for those who do not want to use NRT, or who have tried NRT before. There are a number of contraindications and cautions to be considered before prescribing that may exclude some people from using this medication (table 4).

Bupropion received positive publicity when it was first released in the UK in June 2000 but by early 2001 press reports of serious adverse events, including some deaths, resulted in a decline in use. These safety concerns were largely unfounded and post-marketing pharmacovigilance shows no association between bupropion and the reported deaths. Bupropion has been used as an antidepressant in the US since 1989 and its adverse-event profile is well documented. Like other antidepressants it has a number of common side effects, including headache, dry mouth and insomnia that should be communicated to potential users. There is also a rare risk of seizure (less than 1 in 1,000) that is similar to other antidepressants in common use such as fluoxetine.

The efficacy of other antidepressants for smoking cessation has also been assessed. Nortriptyline has been found to increase the chance of quitting nearly three-fold. However, clinical guidelines do not recommend it as first-line treatment and it is not routinely used by smoking cessation specialists. Monoamine oxidase inhibitors, such as moclobemide, lazabemide and selegiline, look promising but further research is needed. Others, such as selective serotonin reuptake inhibitors, have not been shown to be helpful.

Combining medications
It seems logical to combine smoking cessation products to provide better management of withdrawal discomfort. A patch to provide a steady delivery of nicotine can be combined with nicotine gum to supply a burst of nicotine when needed, for example, although NRT product labelling still advises against this. These warnings are not justified and evidence suggests that a combination of two different NRT products may be advantageous over one product alone. Even if the effect is not substantial, there is no good reason for disallowing combinations. The advantage of combining NRT and bupropion is less clear.

Using smoking cessation medications in smokers with CVD
There have been some concerns regarding the use of NRT in smokers with CVD. These primarily stem from the known

<table>
<thead>
<tr>
<th>Table 4. Bupropion (Zyban®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Formulation</strong></td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td><strong>Treatment period</strong></td>
</tr>
</tbody>
</table>
| **Contraindications** | - Hypersensitivity to bupropion  
- A current or previous seizure disorder  
- CNS tumour  
- A current or previous diagnosis of bulimia or anorexia nervosa  
- Severe hepatic cirrhosis  
- Concomitant use of bupropion and monoamine oxidase inhibitors  
- A history of bipolar disorder  
- Withdrawal from alcohol or benzodiazepines  
- Pregnancy  
- Those under the age of 18 |
| **Risk factors** | A risk/benefit assessment should be undertaken before prescribing bupropion to patients with other risk factors for seizures. Factors that increase the risk of seizures include:  
- Medications that lower seizure threshold (e.g. antidepressants, antipsychotics, antimalarials, quinolones, sedating antihistamines, systemic corticosteroids, theophylline, tramadol)  
- Alcohol abuse  
- History of head trauma  
- Diabetes (see note below)  
- Use of stimulants and anorectics |
| **Special groups** | Elderly: Increased sensitivity may be an issue if more likely to have decreased renal function; 150 mg once daily is recommended.  
Diabetes: If diet controlled, prescribe full dose. If well controlled with insulin or oral hypoglycaemics, prescribe 150 mg once daily. If poorly controlled, recommend NRT |

Key: CNS = central nervous system; NRT = nicotine replacement therapy
adverse effects of nicotine on the cardiovascular system (CVS). Nicotine per se increases myocardial oxygen demand, causes vasoconstriction of some vascular beds, and may contribute to adverse changes in endothelial cells.52-54 Nicotine is not the only constituent of tobacco smoke that affects the CVS. Carbon monoxide, for example, contributes to a hypercoagulable state and, alone, has been shown to reduce exercise performance in patients with coronary artery disease.45

The evidence to date, and expert opinion, suggest that any risks associated with NRT are small.3,5,7,46,47,48 The Lung Health Study provided safety data from a large number of smokers using nicotine gum and showed that the rate of cardiac events was lower among gum users, even if they were smoking concurrently.50 The use of a nicotine patch in smokers with a myocardial perfusion defect resulted in an improvement in perfusion compared with smoking despite some smokers having higher plasma nicotine concentrations when using the patch.51 NRT can be used safely in smokers with stable CVD.52,53 For those with unstable CVD who cannot stop smoking without medication, NRT can be considered.46 It is recommended that a risk/benefit assessment should be undertaken when prescribing NRT to these smokers.21 Such assessment invariably points to a recommendation to use NRT.

Bupropion also appears to be safe to use in smokers with stable CVD. Results from one study showed that it almost tripled the chance of one-year success (OR=2.87; 95% CI 1.83–4.57), and had no adverse outcome on either heart rate or blood pressure.52

Opportunities for the future

The future treatment options for smoking cessation are rapidly advancing. Services are becoming mainstream across the UK and are available in every Primary Care Trust. In addition, there are a number of medications in development that will add to the current arsenal.

Nicotine products

Researchers are working on faster-acting NRT products that will help relieve withdrawal more rapidly. Others are developing different modes of delivery. There is a biphasic tablet, for example, that adheres to the buccal mucosa and releases a burst of nicotine within 30 minutes followed by a sustained release over the next one to four hours.54 New data have been published on the absorption of nicotine from small beads that are swallowed with a drink.55 The researchers showed that nicotine levels peaked between one and two hours after the nicotine was swallowed, and provided concentrations of nicotine that were at least as high as conventional NRT products. It will be interesting to see how these products perform in efficacy studies.

Glucose

It is well known that nicotine suppresses appetite and that hunger is a tobacco withdrawal symptom. It has been suggested that abstaining smokers may misinterpret hunger pangs as urges to smoke.50 Glucose is effective in reducing appetite and thus this simple sugar may be effective in reducing urges to smoke. A small number of studies have demonstrated that glucose can reduce withdrawal symptoms and increase short-term abstinence rates in comparison to placebo.55-58 Although long-term outcome data are not yet available, it seems that glucose may be of some assistance to smokers at least in the early stages of withdrawal.

Nicotine vaccine

Nicotine freely passes through the blood-brain barrier to where it exerts its effect. If it could be stopped from reaching the brain, then tobacco would no longer be satisfying to a smoker. A nicotine vaccine, consisting of a nicotine derivative bound to a carrier protein, has been developed.59 In animals and, more recently, in humans this vaccine has successfully evoked an immune reaction with the production of nicotine-specific antibodies that reduce the availability of nicotine to the brain.55 As yet there are no published data concerning its effects on smoking behaviour. How this vaccine will be best placed to help smokers needs further clarification. It is unlikely that it will be used in primary prevention (i.e. giving it to children before they even start smoking) but it may have a role in helping to prevent relapse to smoking in successful quitters.

Rimonabant

Rimonabant is a selective cannaboid receptor (CB1) antagonist that has been shown to effectively reduce weight, reduce abdominal circumference, improve blood glucose, increase high-density lipoprotein cholesterol and reduce triglycerides. In addition, rimonabant also aids smoking cessation.60 CB1 antagonists have been shown to inhibit the dopamine-releasing effects of nicotine in the shell of the nucleus accumbens and animal studies have shown they can also decrease nicotine self-administration.61 Through this action, rimonabant may block the reinforcing properties of nicotine. Although there are no reports published in the scientific literature, a recent industry release suggests that it increases smoking cessation rates two-fold compared to placebo.62 In a randomised controlled trial of 787 smokers, the intention-to-treat analysis showed the validated continuous abstinence rates, in the last four of 10 weeks of treatment, to be 28% in those receiving rimonabant (20 mg/day) compared to 16% of the placebo group.63 This medication may be an ideal treatment for smokers with other risk factors for CVD.

Varenicline

Varenicline is another non-nicotine drug that looks promising for smoking cessation. It is a partial nicotine receptor agonist whose development stemmed from 1960s research on cytisine, a naturally-derived substance that activates the nicotinic receptor but is not addictive.64 Varenicline is said to work by reducing symptoms of withdrawal, making quitting easier. Like rimonabant, no data have yet been published.

Press reports of preliminary studies show that smokers taking varenicline achieved higher short-term success rates than bupropion or placebo (48% varenicline, 33% bupropion, 16% placebo at seven weeks).65 Apart from helping smokers stop, this med-
Key messages

- Physicians have a key role in prompting quit attempts by advising smokers to stop.
- For the greatest chance of success, smokers motivated to quit should be referred to the local stop smoking service for intensive treatment that combines behavioural support and pharmacotherapy.
- Nicotine replacement therapy (NRT) and bupropion are proven to aid smoking cessation, and are safe to use in smokers with stable cardiovascular disease. Even in those with unstable disease, any risks of using NRT are small in comparison to the risks of continued smoking.

Conclusion

Treatments for smokers have come a long way over the past 25 years. The UK now has a new profession of smoking cessation specialists who provide free and effective treatment for smokers who want to stop. A combination of pharmacotherapy and multi-session behavioural support produces the best outcomes. For the best chance of success, cardiologists and other health-care professionals should refer smokers onto the NHS Stop Smoking Service. There are still no magic cures to help smokers quit but medications such as NRT and bupropion will currently double the chances of success. In the next five years we should see a number of other treatments becoming available, which will encourage more smokers to make a quit attempt and help them to become non-smokers.

Conflict of interest

Hayden McRobbie has received hospitality and contributions to become non-smokers. Hayden McRobbie has received hospitality and contributions to become non-smokers. Hayden McRobbie has received hospitality and contributions to become non-smokers. Hayden McRobbie has received hospitality and contributions to become non-smokers. Hayden McRobbie has received hospitality and contributions to become non-smokers. Hayden McRobbie has received hospitality and contributions to become non-smokers.

References


63. Wood S. Early release of data from rimonabant studies shows drug increases weight loss and smoking abstinence: theheart.org, 2004. Available at: http://www.theheart.org


The British Hypertension Society Information Service

www.bhsoc.org

The British Hypertension Society Information Service provides up to date information on Hypertension for UK Healthcare Professionals.

In December 2002, the newly completed Hypertension Referral Centres Database was added onto the British Hypertension Society website (www.bhsoc.org). This is a useful resource for GPs wanting to refer their patients to a specialist in the field of hypertension. Listings are made available by clicking on the desired region on the UK map, this then takes you to a full listing of the hospitals within that region, the hypertension specialists, their areas of expertise and their contact details. From there you can write, ring, fax or email your referral request.

2005 brings with it even more exciting developments: a new research network database, more clinical trial feedback via BHS Live, and the BHS guidelines in review.

If you have any comments or suggestions please contact:
The Development Officer, Tel: 0208 725 3412; Fax: 0208 725 2959; Email: bhsis@sghms.ac.uk