There's more to quitting than nicotine

As England joins the growing list of nations to ban smoking in enclosed public places, Lisa Melton explores the medicinal arsenal that could help to kick the habit

In the beginning, when the assault on smoking began in earnest, it all seemed rather simple. If nicotine is the demon driving tobacco smoking, giving smokers a nicotine fix should keep their hands off the pack. Yet it is 30 years since the first nicotine gum was developed in Sweden and the road to a cigarette-free life is still littered with broken resolves and people smoking themselves into an early grave. That could be about to change, thanks to a new wave of drugs that will help people kick their bad habit for good.

'One billion people around the world are doing something that, if they keep at it, will kill half of them,' says Sir Richard Peto, professor of medical statistics and epidemiology at the University of Oxford, UK. At a scientific meeting in 2005, Peto exhorted researchers and pharmaceutical companies to develop smoking cessation compounds to cut tobacco deaths. 'There is a desperate need for treatments that work,' he insists.

For smokers trying to stop without help, the quit rate is dismal. According to the US Centers for Disease Control and Prevention, fewer than five per cent of those who attempt to stop remain smoke-free at twelve months.

In short

- **Drugs to treat smoking addiction are emerging onto the market**
- **A new generation of anti-smoking treatments goes beyond nicotine replacement to reduce the pleasure of smoking**
- **Anti-smoking vaccines and nicotine-free cigarettes offer a novel therapeutic approach**

Right: Castro gave up years ago, but admits it wasn't easy

Today the mood has lifted. Scientists are talking about a new drug that appears to be markedly better than any smoking cessation aid before it. Varenicline tartrate, a drug manufactured by the US pharmaceutical giant, Pfizer, helps more than one in five smokers give up. It was approved by the US Food and Drug Administration (FDA) in 2006 as a twice-daily tablet and has since become the number one smoking cessation prescription in the US.

The drug helps smokers in two ways: by cutting the pleasure of smoking and reducing the withdrawal symptoms. Robert West, director of tobacco studies at the Cancer Research UK Health Behaviour Research Centre, University College London, UK, admits he was surprised when the clinical trials results landed on his desk. 'I think it's a real advance. If I had someone that was important to me and I wanted to help them stop smoking, I would probably send them to take this drug first off,' says West, who acts as consultant for Pfizer, as well as rival companies.

The new drug, marketed in the UK as Champix, is inspired in nature. The Pfizer team scoured chemical databases for compounds that might mimic nicotine's ability to activate $\alpha_4\beta_2$ nicotinic acetylcholine receptors in the brain. Their hunt led to cytisine, a bicyclic plant alkaloid from the plant *Cytisus laburnum* or golden rain tree, used in Eastern Europe since the 1960s by smokers wanting to quit. Following a chemical logic the scientists simplified the molecule to make it more workable while maintaining its binding to nicotinic receptors.[1]

Cytisine is similar to the alkaloid morphine – the two molecules' [3.3.1] bicyclic skeletons differ only by the position of a single nitrogen atom (see p46). Capitalising on decades'

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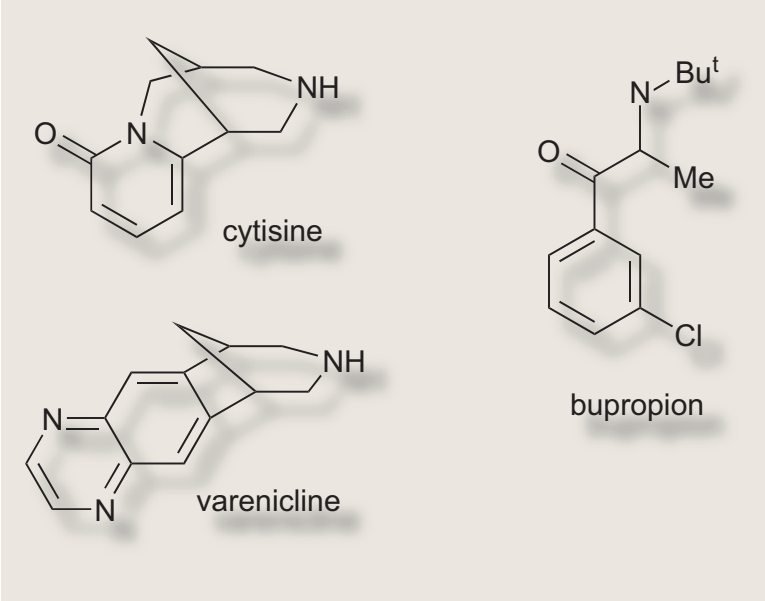

The drugs replacing nicotine

worth of morphine medicinal chemistry the Pfizer team devised a practical synthetic route to improve on cytisine. The result was a [3.2.1] bicyclic benzazapine that blocks nicotine binding to $\alpha_4\beta_2$ receptors. A further fusion of heterocycles onto the benzazapine's aromatic ring restored its ability to activate the receptors and release low levels of dopamine, a dual action similar to that of cytisine.

The result is varenicline, which latches on to some of the same critical $\alpha_4\beta_2$ receptors. But while nicotine sets off a cascade of feel-good dopamine in the brain's pleasure centres, with varenicline the dopamine burst is smaller and long-lasting. This low-level nicotine buzz can see a smoker through the worst cravings until they are ready to quit. At the same time, the drug partially blocks nicotine's access to these receptors. So should a person lapse and smoke a cigarette while taking varenicline, the nicotine rush would prove less satisfying.

Two randomised Phase III clinical trials have shown that people on varenicline increased their odds of quitting by almost three-fold for 12 months compared with those on placebo drugs. This new drug is also superior to bupropion (Zyban), an antidepressant that roughly doubles a person's chance of stopping smoking.

Peter Hajek, professor of Clinical Psychology at the Wolfson Institute of Preventive Medicine, London considers varenicline to be an important development but is not convinced that it merits a breakthrough tag. 'We still have this ceiling of 30 per cent long-term success rate which has not been breached,' Hajek says. Having a new anti-smoking weapon, however, will attract people who have tried quitting and failed. 'It gives them new hope. They may see that there is another tablet and have another go, and a proportion of them will succeed.'

Despite costing 50 per cent more than other smoking cessation medications, Champix was granted draft approval for use on the UK's National Health Service (NHS) in May. But its price may still make some primary care trusts reluctant to prescribe it. Hajek points out that a Bulgarian pharmaceutical company, Biogenic stimulants, currently markets cytisine as Tabex, which mimics the effects of nicotine, and blocks the receptors at the same time for smoking cessation. 'Cytisine is very cheap. If it does the same thing that'll be important,' says Hajek. The problem is that there are only limited data on its efficacy. A placebo-controlled trial of cytisine is about to start, and the results will be available in two to three years time.

Nicotine gum often leaves ex-smokers dissatisfied

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What's on offer

Smoking is an astonishingly hard habit to break. Smokers who are committed to cut their dependence can resort to nicotine gum, patches, nasal sprays, and inhalers. Since nicotine is the key addictive substance in tobacco, replacing the nicotine helps lessen those awful withdrawal pangs. Nicotine replacement therapies roughly double smokers' chances of giving up compared with placebo or nothing at all.

Would-be quitters can also be prescribed GlaxoSmithKline's Zyban (bupropion) – an unusual smoking-cessation medication that was originally licensed to treat depression. As clinicians observed that smokers taking the anti-depressant found smoking distasteful, it was eventually launched in 1997 to cut smoking dependence.

Exactly why bupropion improves quitters' chances is not clear. It acts on the brain to quash the craving nicotine tobacco products produce but other antidepressants including selective serotonin reuptake inhibitors such as fluoxetine (Prozac) are not effective, suggesting that the mechanism is unrelated to its mood-enhancing properties. It was initially hailed as a 'wonder drug' though in practice it has proved only as effective as nicotine-replacement therapies.

Munchies and vice vaccines

The perfect anti-smoking drug remains elusive, but the recent emergence of rimonabant triggered excitement in the smoking cessation field. Manufactured by French pharmaceutical company, Sanofi-Aventis and marketed as Acomplia, the drug is licensed to tackle obesity but has the potential to treat addictions. It faced a troubling setback in the US this month, as an FDA advisory committee declined to recommend its approval for obesity due to concerns about psychiatric side effects (see page 18).

HAMISH KIDD / SCOTT OLLINGTON

Rimonabant was derived, in part, from observing the appetite-stimulating effects of cannabis, the 'munchies' that smokers experience. The Sanofi-Aventis team found an agent that damps down that hunger and craving for snacks by blocking a particular class of cannabinoid–1 (CB1) receptors in the brain. Targeting this endocannabinoid system, the clinical data suggest, can also help people give up smoking.

The idea of a combined weight-control and smoking-cessation pill is alluring. Weight gain is a common side-effect for smokers who give up. If safety issues don't prove insurmountable, this could give rimonabant an edge in the smoking cessation market. 'The drug could merit a licence, perhaps for overweight smokers,' says West. Unfortunately, the manufacturers are unlikely to market this drug for smoking cessation because, on its own, rimonabant seems to be no more effective than nicotine replacement therapy.

Vaccines may be the breakthrough everyone hopes for. Nabi Biopharmaceuticals, a company based in Florida, US, is developing the NicVax nicotine vaccine to treat smoking addiction. It works by introducing a small amount of antigen, in this case a nicotine derivative bound to a carrier, that will lead to an immune response that churns out antibodies. If a person smokes, the antibodies soak up the nicotine circulating in blood. As the combined structure of nicotine molecule and antibody becomes too large to penetrate the blood–brain barrier, so smoking would stop being a rewarding experience.

The company's Phase II clinical trial results found a 33 per cent quit rate in smokers who received NicVax at the highest dose. A spin-out company from the University of Colorado, Aktiv-Dry plans to reformulate Nabi's injectable vaccine using a drug powder consisting of particles one to three microns in diameter that can be inhaled – rather than injected – and easily delivered to the lungs.

Another nicotine vaccine developed by the UK-based Xenova found that at 12-month follow-up, eight per cent of patients randomised to placebo vaccine had stopped smoking while 38 per cent of patients receiving the high dose of the active vaccine managed to stay smoke-free.

Not everyone is convinced that vaccines will do the trick. Success relies heavily on antibody concentrations. So while vaccination may help steer wayward quitters indulging in one cigarette, the antibody concentrations may not be enough to counter a serious relapse.

Vaccines may be the smoking cessation breakthrough that everyone hopes for

'There is a horror reaction to nicotine, a feeling it is evil'

Nicotine – good, bad or ugly?

If people smoke for nicotine, why are nicotine replacement therapies not more effective?

The problem is that people dislike nicotine replacement therapy, though nobody is sure why. Perhaps the products are too slow to provide the nicotine rush they crave, or the strongly-worded labelling on the packages may be off-putting. 'There is a horror reaction to nicotine, a feeling it is evil,' says Hajek.

'We now know that for a smoker, nicotine in nicotine replacement products is absolutely safe, probably no more dangerous than drinking tea or coffee,' Hajek remarks. A more liberal use of nicotine replacement therapy, as recently licensed, is good news. It means that people can now use patches, gums and inhalers more effectively, in combination, and in advance of their set 'quit day' boosting their chances of success.

But David Balfour challenges the

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idea that nicotine alone explains why people become so highly addicted to tobacco smoke. 'Nicotine alone is not powerfully addictive,' explains Balfour, who is professor of behavioural pharmacology at Ninewells Hospital and Medical School in Dundee, UK. Nobody gets 'high' on nicotine as they do with other common drugs of abuse. 'What smokers seem to find pleasurable is the act of smoking itself, not necessarily the drug,' he says.

Under nicotine's spell, Balfour argues, everything a person does becomes more pleasurable. Within seconds of puffing on a cigarette, nicotine enters the brain. Acting through nicotinic receptors, it triggers a dopamine overflow in the nucleus accumbens region of the brain. Dopamine lingers and remains elevated for 30 to 60 minutes, enhancing the pleasure from every act a person engages in during that time. Since a pack-a-day smoker typically inhales 70 000 puffs a year, the brain learns to associate these behaviours with pleasure.

So while taking nicotine helps soften withdrawal symptoms, skin patches and sprays can't replace the pleasure conjured up by the act of smoking a cigarette. 'Somehow you have to tackle those pathways in the brain associated with behaviour to help the person quit,' says Balfour, who believes that factors such as the irritation caused by inhaling tobacco smoke becomes an important part of a smoker's enjoyment.

A smoke-free UK will be inhospitable to those who remain hooked

'What smokers find pleasurable is the act of smoking itself, not necessarily the drug'

A nicotine-free cigarette could be the answer. Research by Jed Rose at the University of Nebraska-Lincoln has found that smoking a novel cigarette – where nicotine has been replaced by black and red pepper capsaicinoids – provides a rewarding sensation close to that of a conventional cigarette. For a while, at least, smokers are content to smoke nicotine-free cigarettes. Coupling these with nicotine patches could provide the ultimate anti-smoking strategy, some scientists believe. While the patches take care of the craving for nicotine, the smoke extinguishes the need for sensory pleasure from smoke irritation. Tackling both pathways separately might be more efficient approach as it breaks the link between the pleasure obtained from nicotine and that from sensory irritation in the brain.

Another potential approach to treating nicotine addiction has emerged from smokers that lose the urge to smoke after suffering damage to a particular area of the brain. A study published in the journal *Science* was inspired by a patient who smoked two packs of cigarettes a day but, after suffering a stroke that damaged his insula, lost the urge to smoke and stopped immediately.[2] The scientists at the University of Iowa identified 19 patients with similar injuries and found that 13 had also given up the habit quickly and easily. The insula lies at the centre of the brain and is thought to translate information from other parts of the body into hunger, pain or cravings for a drug. Because it carries out many vital roles, disrupting this brain region to help people give up smoking would require extreme caution.

For those who remain hooked, future legislation looks inhospitable. Tobacco smoking is so terribly harmful that an eventual outright ban is highly likely. As West puts it: 'Once cigarettes are banned, people will look back and say "that was bizarre". Cigarette manufacturers are the only manufacturers of any product anywhere in the world that are allowed to sell something with known high levels of carcinogens. Even traces of carcinogens in a famous brand of spring water led to whole batches being recalled. As far as I am concerned, the tobacco industry is getting away with murder.'

Further reading

1 J W Coe *et al*, *J. Med. Chem.*, 2005, **48**, 3474
2 N H Naqvi *et al*, *Science*, 2007, **315**, 531
3 G Bock and J Goode, *Understanding Nicotine and Tobacco Addiction*, Chichester, UK, John Wiley & Sons, 2006