

Developments in pharmacotherapy for tobacco dependence: past, present and future

JONATHAN FOULDS^{1,2}, MICHAEL B. STEINBERG^{1,2}, JILL M. WILLIAMS^{1,2}, & DOUGLAS M. ZIEDONIS^{1,2}

¹University of Medicine and Dentistry of New Jersey, School of Public Health, Tobacco Dependence Program, and ²UMDNJ, Robert Wood Johnson Medical School, New Brunswick, NJ, USA

Abstract

*In the mid-1970s there were no effective pharmacological treatments for tobacco dependence. The invention of nicotine gum was a major treatment advance and also greatly helped our understanding of the nature of tobacco dependence. There are now eight effective pharmacotherapies (nicotine gum, patch, nasal spray, inhaler, lozenge/tablet, bupropion, nortriptyline and clonidine) available to aid smoking cessation. Other non-nicotine agents that show promise are under investigation, including glucose, rimonabant, selegiline and varenicline. Greater knowledge of the mechanisms of action of the effective non-nicotine agents should lead to better understanding of the nature of tobacco dependence. Future research into optimal treatments should examine long-term combination pharmacotherapy combined with improved psychosocial support that is partly designed to enhance medication compliance. In addition, there is a need for studies designed to evaluate the efficacy of pharmacotherapies in populations such as youth, pregnant smokers and smokers with co-occurring mental health problems. [Foulds J, Steinberg MB, Williams JM, Ziedonis DM. Developments in pharmacotherapy for tobacco dependence: past, present and future. *Drug Alcohol Rev* 2006;25:59–71]*

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Introduction

In the mid-1970s there were no effective pharmacological treatments for tobacco dependence and very few behavioural scientists or pharmaceutical companies were putting significant efforts into this area. Indeed, outside the tobacco industry [1] very few researchers considered tobacco use as a drug dependence that might require treatment with pharmacotherapy. Thirty years later the landscape of nicotine dependence treatments has been transformed, with numerous forms of effective nicotine replacement therapy and non-nicotine pharmacotherapies used widely throughout the

world and pharmaceutical companies on the verge of launching additional new non-nicotine pharmacotherapies [2].

This paper reviews some of the key research developments that have led to this transformation, and some of the research challenges that need to be addressed in order to continue to advance this field.

Early missed opportunities

With the benefit of hindsight, one can look back and see important scientific works that did not lead to the therapeutic breakthroughs they could have. An early

Jonathan Foulds PhD, Associate Professor and Director, University of Medicine and Dentistry of New Jersey, School of Public Health, Tobacco Dependence Program and UMDNJ, Robert Wood Johnson Medical School, USA, Michael B. Steinberg MD, MPH, Assistant Professor, Department of Medicine, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Tobacco Dependence Program at UMDNJ, School of Public Health, New Brunswick, NJ, USA, Jill M. Williams MD², Associate Professor, Department of Psychiatry, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Tobacco Dependence Program at UMDNJ, School of Public Health, New Brunswick, NJ, USA, Douglas M. Ziedonis MD, MPH Professor and Chair of Addiction Psychiatry, Department of Psychiatry, University of Medicine and Dentistry of New Jersey, Robert Wood Johnson Medical School, Tobacco Dependence Program at UMDNJ, School of Public Health, New Brunswick, NJ, USA. Correspondence to Jonathan Foulds PhD, Associate Professor and Director, Tobacco Dependence Program and UMDNJ, School of Public Health, Suite 210, 317 George Street, New Brunswick, New Jersey 08852, USA. E-mail: jonathan.foulds@umdnj.edu

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example here is the 1942 publication by Lennox Johnston in the *Lancet* [3], reporting on the effects of nicotine injections on tobacco craving and satisfaction. He reported that: ‘smokers almost invariably thought the sensation pleasant and, given an adequate dose, were disinclined to smoke for some time thereafter’. Johnston was clearly ahead of his time in recognising nicotine tolerance, craving and withdrawal and the potential for pure nicotine administration to substitute for tobacco. Coming at the end of World War II and prior to Doll and Wynder’s discoveries on the links between smoking and lung cancer [4,5], these insights into the nature of nicotine dependence went largely unnoticed. Perhaps more surprising is the lack of attention to another paper published in the *Lancet* in 1967 by Herxheimer and colleagues [6]. They demonstrated that a pure nicotine aerosol inhaler produced the same physiological effects as a cigarette in human volunteers and suggested that a similar product could be used as a substitute for smoking.

Early pioneers and randomised clinical trials

While these early clues to the potential of nicotine replacement went largely unnoticed, it took the ingenuity and research skills of pioneers such as Ove Ferno, Michael Russell and Murray Jarvik to demonstrate the crucial role of nicotine in tobacco smoking and to develop the first effective therapies for tobacco dependence. Their personal accounts of those pioneering days have been captured in a series of interviews published in the journal *Addiction* [7–9], and these make for fascinating reading for those interested in the early development of this field. The pharmaceutical development of 2 mg nicotine gum by AB Leo in Sweden [10,11] (and the availability of the gum and its placebo formulation for research) was a critical breakthrough, not just as a therapy but also as a tool for research on nicotine dependence [11–13]. Another important advance at that time was the development of accurate methods of measuring nicotine, cotinine and carbon monoxide in body fluids or expired air [14–16]. These methods made it possible to validate biochemically claims of abstinence in research studies [17] as well as to estimate the degree of nicotine substitution provided by replacement therapies [18]. This critical clinical research, combined with developing evidence from basic research, enabled the 1988 US Surgeon General’s Report to come to very clear conclusions about the nature of nicotine as the key addictive substance in tobacco [19]. Throughout this period, randomised placebo-controlled trials of single nicotine replacement therapies became the standard type of research and there are many [11,20–23]. Meta-analyses and reviews based on these trials have concluded consistently that nicotine replacement

therapies work, and roughly double the smokers’ chances of successfully quitting compared with placebo or no medication [24–26].

Each of the nicotine replacement therapies work by reducing the severity of nicotine withdrawal symptoms (bad mood, poor concentration, hunger, etc.) and craving [11–13]. This stabilisation of mood and cravings helps the recent quitter to focus more effectively on overcoming the strong behavioural associations and drug use triggers that develop from taking over 70 000 puffs of tobacco smoke per year (typical for a pack-a-day smoker).

The transdermal patch offers reliable moderate blood nicotine levels (about half of those achieved by smoking) and good compliance, whereas the other products offer the potential for greater dose control and the ability to prevent relapse by taking more nicotine as required. The greater effort required to achieve therapeutic nicotine levels by using the short-acting nicotine replacement therapy (NRT) products (gum, nasal spray, lozenge/tablet and inhaler) is reflected in poorer compliance. Table 1 summarises the main characteristics of the nicotine replacement therapies.

Concerns about ‘real world’ effectiveness of NRT

Amid these positive developments, concern has been raised about whether similar effectiveness is achieved by these medications in the ‘real world’ with patients who have complex comorbidities and social problems or when purchased over the counter. Many of the initial pivotal trials for new medications for the treatment of tobacco dependence took place at specialist tobacco treatment clinics with relatively intensive psychosocial support, and frequently required participants to be medically and psychiatrically healthy in order to enter the studies. The clinical trials generally offer free treatment and sometimes even payment, so there is a concern that compliance with pharmacotherapy may be better than in non-research situations. Over time, trials moved into more typical treatment settings (e.g. general hospitals [27], hospital outpatient smoking cessation clinics [28], primary care [29] and even over-the-counter settings [30,31]) and some of these studies obtained less impressive results. For example, the British Thoracic Society study randomised over 1500 patients to nicotine or placebo gum with or without an informational booklet and found that less than 10% quit overall; those receiving nicotine gum did not have better cessation outcomes than those receiving placebo [32].

However, most studies that have been designed with adequate statistical power (i.e. large sample size) to detect relatively small effect sizes and absolute quit rates have demonstrated a significant improvement over placebo at long-term follow-up, even in more typical clinical settings (such as primary care) in which

Table 1. Characteristics of each type of nicotine replacement therapy

Product	Use	Advantages	Disadvantages	Precautions	Side effects
Nicotine patch	16- and 24-hour preparations available; apply each day to clean, dry, hairless skin; start high-dose (21 mg/24 h) patch if > 10 cigarettes per day; taper to mid-dose (14 mg) in 4–6 weeks, then low-dose (7 mg) for 2 weeks	Place and forget; no prescription needed in most countries; can decrease morning cravings if worn at night	Passive—no action to take when craving occurs	Not recommended to use while smoking; caution in unstable cardiac disease (recent heart attack)*	Skin reaction (50% of patients mild, 10% causing discontinuation); rotate site each day; rash improved with hydrocortisone cream; vivid dreams or sleep disturbance can occur if worn overnight
Nicotine gum	Chew every 1–2 hours as needed; chew and park; 2 and 4 mg strength (4 mg if around 1 pack per day)	Able to use as needed; can self-dose; no prescription needed in most countries	Not pleasant to chew, poor compliance	Avoid food and acidic drinks 15 minutes before and while using (decreases absorption)	Jaw ache; nausea; hiccups
Nicotine inhaler	Puff as needed; use up to 16 cartridges/day; less needed if using combination therapy; orally absorbed—no need to inhale deeply	Can use as needed; mimics hand–mouth behaviour	Costly, visible; requires very frequent puffing to achieve therapeutic levels; poor compliance; prescription in some countries	Avoid food and acidic drinks 15 minutes before and while using	Cough, throat irritation (40%), usually mild
Nicotine nasal spray	1–2 sprays per hour; do not sniff/inhale—tilt head back and spray; aim away from nasal septum	Use as needed; rapid relief of symptoms	Cost; requires prescription in some countries; very poor compliance	Asthma, rhinitis, sinusitis, nasal polyps	Nasal irritation (80–90%); possible dependence (10–20%)
Nicotine lozenge	2 and 4 mg (4 mg if smoke within 30 min of waking); dissolve in mouth; do not chew; use 9–15 per day for 6 weeks then taper	Ease of use, No prescription needed in most countries	Poor compliance	Avoid food and acidic drinks 15 minutes before and while using	Hiccups, nausea, heartburn

*Patients who have had recent unstable cardiac disease or are pregnant, and those aged under 18 years are advised to seek advice from their medical practitioner before using any of the nicotine replacement therapies.

treatment was provided without concurrent intensive counselling support [33,34].

The main remaining concern about real-world effectiveness has stemmed from the results of retrospective population surveys on unselected groups of

patients who either did or did not use medication as part of their quit attempt. One influential report claimed that as nicotine replacement therapies became available ‘over-the-counter’ (OTC) in the United States, they had not been effective at increasing rates

of long-term abstinence among users compared with those trying to quit without NRT [35]. While some have taken exception to the interpretation of the data in that study [36] and other studies support the efficacy of NRT in OTC settings [30,31], it is a truism that long-term abstinence rates among individuals using a single NRT as a temporary aid to cessation are disappointingly low. This underlines the need for new pharmacological approaches to treating tobacco dependence. It should also be noted that our knowledge of the use of pharmacotherapy for cessation of non-cigarette tobacco products is relatively limited, and virtually all the studies discussed here focus on cessation of cigarette smoking. There is some evidence of increasing use of alternate tobacco products to substitute for cigarette smoking in some cultures [37,38] and use and cessation of non-cigarette tobacco products merits further study.

Non-nicotine pharmacotherapies for tobacco dependence

In 1989 Ferry [39] proposed treating nicotine addiction with the antidepressant drug bupropion, based on the observation that some smokers taking it for depression suddenly found smoking distasteful and stopped spontaneously. The pharmaceutical manufacturer originally declined to take part, unconvinced that the approach would work, so Ferry financed a small pilot study alone. Forty-four smokers were randomised to receive bupropion or placebo. None quit smoking in the placebo group but 12 (50%) who used bupropion were abstinent within 3 weeks. With that, the manufacturer funded a series of larger studies, which confirmed the efficacy of bupropion for treating tobacco and it was approved by the Food and Drug Administration (FDA) on 15 May 1997 [39].

The serendipity of this finding is a reminder to clinicians to remain vigilant to the effects of novel psychotropic agents on the smoking behaviours of their patients. Similarly, tobacco dependence in schizophrenia is impacted by the pharmacological regimen for psychosis and outcomes are enhanced with the use

of atypical antipsychotics. Clozapine treatment is associated with reduced smoking, most significantly in heavy smokers and those showing a therapeutic response to clozapine [40–42]. Treatment with atypicals is also associated with more success in quit attempts in schizophrenics motivated to stop smoking [43].

Since the discovery in the mid- to late 1990s that bupropion is an effective treatment for tobacco dependence [44,45], there has been a rapid expansion of research into potential non-nicotine treatments for tobacco dependence. To date, however, only a few of these have demonstrated efficacy and a number of potential therapies (including a number of anxiolytics, specific serotonin reuptake inhibitors, opioid antagonists and other aids such as silver acetate) appear not to be effective in helping smokers to quit. Table 2 shows the pharmacotherapies that have been shown in meta-analyses to be effective in helping smokers achieve long-term tobacco abstinence. Some of the other agents that have been considered for tobacco dependence treatment and others that are currently being evaluated are summarised in Table 3.

Potential mechanisms of non-nicotine pharmacotherapies

Antidepressants

The precise mechanisms causing some antidepressants to be helpful for tobacco dependence are not clear. It has long been observed that depressed mood is a symptom of nicotine withdrawal [12,13], and complex interactions of the same neurotransmitters involved in depression are involved in nicotine dependence. The fact that only some antidepressants help in tobacco dependence treatment, while others do not, suggests that their mode of action may be independent of their antidepressant effect [45].

Bupropion is chemically unrelated to other antidepressants and its effect on tobacco dependence is independent of depression. In addition to effects on adrenergic and dopaminergic systems, animal and *in vitro* evidence suggests that bupropion may act as

Table 2. Pharmacotherapies demonstrating efficacy for smoking cessation in the Cochrane Database of Systematic Reviews

Drug	Cochrane Review update	Number of comparisons	N (%) abstinent, active arm	N (%) abstinent, control arm	Odds ratio (95% CI)
Nortriptyline	10/27/04 ⁴⁵	7	102/506 (20.2)	56/515 (10.9)	2.14 (1.49, 3.06)
Bupropion	10/27/04 ⁴⁵	21	835/4158 (20.1)	323/3013 (10.7)	1.99 (1.73, 2.30)
Clonidine	10/21/04 ⁴⁶	6	98/393 (24.9)	55/383 (14.4)	1.89 (1.3, 2.74)
Nicotine (gum, patch, nasal spray, inhaler, lozenge/tablet)	11/02/04 ²⁶	105	3503/20767 (16.9)	1916/18736 (10.2)	1.77 (1.66, 1.88)

Table 3. Non-nicotine agents that are being evaluated as tobacco dependence treatments

Drug	Probable mechanism of action	Comments/current status
Anxiolytics ⁴⁷	Reduce anxiety/withdrawal discomfort	Numerous trials show little sign of efficacy
Bromocriptine ⁴⁸	Dopamine agonist	No human trials published
Glucose ⁴⁹	Reduce carbohydrate craving and withdrawal discomfort	One short-term trial published and one long-term trial completed with promising results
Moclobemide ⁵⁰	Reversible MAO-A inhibitor, increases NA and 5-HT levels	One published trial with promising results
Mecamylamine ⁵¹	NACh receptor antagonist, reduces nicotine reinforcement	Insufficient data on efficacy from published trials
Naltrexone ⁵²	May reduce reinforcing effects of nicotine via opioid antagonism	No positive results in published randomized smoking cessation trials
Reboxetine ⁵³	NA-reuptake inhibitor and inhibits NACh receptor function	No human trials published for smoking cessation
Rimonabant ⁵⁴	Selective antagonism of cannabinoid-1 receptors	Preliminary data released from large trial appears promising
Selective serotonin reuptake inhibitors ⁴⁵	Reduce low mood accompanying nicotine withdrawal	Lack of efficacy in numerous trials
Selegiline ⁵⁵	Irreversible MAO-B inhibitor	Two small trials show promising results
Varenicline ⁵⁶	Partial nicotine agonist/antagonist 'nicotine receptor modulator'	Preliminary data released from clinical trials appear promising

MOA-A (monoamine oxidase A), MOA-B (monoamine oxidase B), NA (noradrenaline), 5-HT (5-hydroxy tryptamine); NACh (nicotinic acetylcholine).

a non-competitive nicotinic receptor antagonist [57,58].

Nortriptyline is generally considered a second-line treatment for tobacco dependence, partly because it tends to have more side effects (dry mouth, sedation and constipation) than bupropion and has been studied less intensively as a treatment for tobacco dependence. Nortriptyline is believed to have actions on dopaminergic and adrenergic systems similar to bupropion and it, too, is effective, independent of depression history. Recent studies using nortriptyline combined with transdermal nicotine have also yielded supportive results. One study found abstinence rates at 6 months of 23% for nortriptyline plus patch and 10% for placebo plus patch [59]. Although nortriptyline side effects were common, this combination may represent an option for smokers for whom standard therapy has failed. Another study that extended drug and psychosocial treatment for a year (after initial combination therapy with transdermal nicotine) found that those on nortriptyline and in receipt of monthly counseling sessions had an impressive 50% rate of abstinence at 1 year [60]. It is noteworthy that in this study the group receiving extended counseling combined with placebo nortriptyline (after standard treatment with nicotine patch) also had an impressive quit rate (42%) at 1 year.

Available only in Europe at present, the antidepressant and selective norepinephrine (NE) uptake inhibitor reboxetine has promise as a tobacco treatment medication. Animal studies have found that reboxetine inhibits nicotinic acetylcholine receptor function, and decreases nicotine self-administration in animals dose-

dependently [53,61]. Because there is some evidence that smoking affects noradrenergic proteins in the locus ceruleus in a similar manner to antidepressant treatment in animals [62], there is reason to suspect that norepinephrine modulators may be effective for tobacco dependence treatment. Despite the positive pharmacological profile and few side effects of reboxetine, and its preliminary FDA approval in 1999, its development in the United States has since been halted for unknown reasons [63].

Dopaminergic drugs

The monoamine oxidase B inhibitor and dopaminergic agonist selegiline is an FDA-approved treatment for Parkinson's disease and shows promise for smoking cessation. An 8-week trial of selegiline (10 mg /day) vs. placebo revealed that selegiline was well tolerated, with improved quit rates during the last 4 weeks of the trial and at the trial end-point (7-day point prevalence smoking cessation rates at week 8) [64]. A larger study of 200 smokers is currently under way. Adding selegiline to nicotine patch reduced craving for cigarettes significantly, and was associated with more than a doubling of the 52-week continuous abstinence rate (25% vs. 11%), although this difference was not statistically significant due to the small sample size (n = 109) [55].

Bromocriptine is another dopamine agonist approved for Parkinson's disease and being studied for its effects on smoking. In a laboratory study of heavy smokers, bromocriptine was linked to reduced smoking as

measured by shorter total puffing time, fewer number of puffs, fewer number of cigarettes smoked, decreased plasma nicotine and cotinine and reduced cigarette craving [48]. There are currently no published human trials of the effectiveness of bromocriptine treatment for smoking cessation. A trial of another Parkinson's treatment and dopamine agonist, carbidopa/levodopa found no difference in quit rates compared to placebo [65].

Opiate antagonists

Opioid antagonist medications have been investigated for smoking cessation as the reinforcing properties of nicotine may be mediated through release of various neurotransmitters which impact on the endogenous opiate system. Early trials of naltrexone failed to detect a significant difference in quit rates between naltrexone and placebo [52]. Naltrexone use in a placebo-controlled laboratory study was associated with reduced number of cigarettes smoked and reduced expired carbon monoxide levels, although it significantly increased side effects, especially sedation [66]. In this study of overnight abstinence, naltrexone did not affect acute withdrawal or smoking urges. In one small trial of naltrexone augmentation of nicotine patch, naltrexone reduced the likelihood of relapse among participants who smoked during the first week of treatment [67]. However, overall the research to date on the effects of naltrexone on smoking do not suggest that it is likely to be an effective treatment for tobacco dependence.

Tobacco cessation aids using other mechanisms

Mecamylamine is a nicotine antagonist with antihypertensive effects, which may help with smoking cessation by blocking the nicotine receptor without triggering withdrawal [68]. However, no large trials have provided clear support for its long-term efficacy.

Glucose tablets have had mixed results in experimental studies but have demonstrated consistently positive results in the few clinical trials that have been conducted [49,69]. Preliminary reports from a large trial in the United Kingdom suggests that glucose significantly enhances abstinence rates at 6-month follow-up when added to nicotine replacement therapy [70]. It has been proposed that glucose satiates carbohydrate cravings that ex-smokers often mislabel as cigarette craving [49]. Given that glucose is a relatively inexpensive aid with relatively few side effects, this approach merits further investigation.

Drugs in development

One of the most promising compounds is rimonabant, a selective cannabinoid-1 receptor antagonist (CB-1). It

is believed that CB1 antagonists restore balance in food intake and energy expenditure, which may be altered in chronic nicotine users. In animal studies rimonabant reduced nicotine self-administration and nicotine-induced dopamine release in the nucleus accumbens [71,72].

Human data from the STRATUS-US Trial (Smoking Cessation in Smokers Motivated to Quit) on the effects of rimonabant (trade name Accomplia) appear promising. The STRATUS-US study enrolled 787 smokers at 11 clinical trial sites in the United States. The participants were randomised to rimonabant at a dose of 5 mg ($n=262$), 20 mg ($n=261$) or to placebo. The study lasted 10 weeks, and the smokers were permitted to smoke during the first 2 weeks but were asked to abstain after that. The quit rates for subjects in the 20 mg rimonabant dose group were double that of placebo and they showed a marked reduction in weight gain over the 10-week treatment [54]. Rimonabant was well tolerated, with few side effects. The drug has completed Phase III studies and as of late 2005 is being reviewed by medicines regulatory agencies as both a weight loss [73] and a smoking cessation medication in the United States and Europe.

Varenicline (chemical name CP-526,555) is currently in Phase III clinical trials as a smoking cessation aid. Owned by Pfizer pharmaceuticals, varenicline was discovered in 1997 and is a novel selective nicotinic receptor partial agonist that binds specifically and potently at the $\alpha 4\beta 2$ receptor. As a partial agonist it results in the release of dopamine but also blocks the effect of the full agonist (nicotine). Blocking nicotine helps it to mitigate the reinforcing and rewarding effects of smoking if the subject chooses to smoke during treatment. The effects of varenicline are identical in the presence or absence of nicotine [74].

Varenicline is believed to eliminate the reward from smoking and prevent withdrawal symptoms, but it is not believed to be addicting. It is highly absorbed after oral administration and little is metabolised, making it virtually 100% bioavailable. Varenicline is not significantly protein-bound and the compound is excreted primarily unchanged in the urine. Less than 10% is metabolised in the liver and few metabolites are created. The half-life is 17–30 hours [75].

Phase II trials have shown that varenicline is efficacious for smoking cessation. In a 7-week study varenicline 1.0 mg once daily and 1.0 mg twice daily promoted smoking cessation, with significantly greater response rates than placebo. Quit rates were highest in the varenicline 1.0 mg twice-daily group. The odds ratio for quitting smoking on varenicline compared to placebo ranged from 4.3 to 7.8 in the two existing trials. Varenicline 1.0 mg twice daily was also associated with a higher smoking quit rate than bupropion across primary and secondary efficacy measures. Varenicline

demonstrated a good tolerability profile and there were no safety issues of concern. Nausea, the most common side effect, was mild to moderate, and discontinuation due to nausea was low [76].

Nicotine vaccines

Vaccines to immunise against drugs of dependence have been studied over the past 3 decades. Over the past few years, early-stage clinical trials have examined the safety and efficacy of nicotine vaccination for treating tobacco dependence. The principle behind vaccination involves the introduction of a small amount of substance (antigen) leading to an immune response (i.e. the production of antibodies) specific to certain characteristics on the antigen's surface. The immune system keeps a memory of the antigen, and subsequent exposure can lead to large and rapid antibody response. These antibodies bind to the antigens and allow for the host's defences to eliminate them or prevent passage into the brain's circulation. While the nicotine molecule is small enough to pass freely into the brain, the combined structure of nicotine-antibody is too large to enter, reducing nicotine's rewarding effect on the brain.

Nabi Biopharmaceuticals, among other companies, has developed a nicotine vaccination (NicVAX). Phase I trials showed safety and antibody response up to 63 days post-vaccination [77]. Local reactions were mild to moderate. Single-dose vaccine produced antibodies as early as 7 days post-vaccination, and these were maintained over 4 months. Phase II trials of its vaccine were conducted at three study sites testing three dosage levels of the vaccine. A total of 63 patients, divided into three groups, were administered up to four doses of the vaccine. In September 2004, results indicated a 33% quit rate in smokers who received the NicVax at the highest dose vs. 9% in the placebo group. In July 2005, Nabi completed enrollment for its Phase II dose-ranging study. Four dose levels, 100, 200, 300 and 400 μg per injection will be given over a 6-month period, with 10 patients included per dose group. Previous trials have shown no toxicity up to the 200 μg dose, hence this study will examine whether higher antibody levels can be generated without increasing toxicity. Results from early trials of a vaccine developed by Xanova (UK) found that at 12-month follow-up, 8% of patients randomised to placebo vaccine had stopped smoking, compared to 19% and 38% of patients receiving different doses of active vaccine [78].

The clinical utility for smoking will be that in a vaccinated individual nicotine will not have as strong an effect on the brain, and thus smoking may not become as addictive. The implications for current smokers as a tool for cessation, former smokers as a tool for relapse prevention and never smokers (possibly youth) as a tool for primary prevention are varied and complex. In addition,

the vaccination has potential implications for pregnant women and the effect of nicotine on the developing fetus. More data and research are required for this novel, and potentially useful method of treatment for tobacco dependence.

Research questions on the future of pharmacotherapies in smoking cessation

1. *What can we learn about the nature of tobacco dependence from the mechanism of action of effective pharmacotherapies?*

While the scientific understanding of tobacco dependence was greatly assisted by the development of nicotine replacement therapies, so far the learning from non-nicotine pharmacotherapies has been more limited. To date we remain unclear as to the precise mechanism of action of bupropion for smoking cessation, and it appears most likely that the effective pharmacotherapies work via different mechanisms. With a widening number of therapeutic tools, there is increased potential for these drugs to help us understand more completely the nature of tobacco dependence.

2. *Might there be specific pharmacotherapies that are particularly effective for certain subgroups, and are any of them effective in special populations such as adolescents, pregnant women or people with serious mental illness?*

The few 'head-to-head' trials that have compared active pharmacotherapy treatments have yet to provide clear or consistent guidance on which type of pharmacotherapy might be better for certain patient groups (e.g. by gender, level of dependence etc). However, there are some signs that heavy smokers may do better with the nasal spray than the patch [79], women may do better with the inhaler than the gum (and men vice versa) [80] and certain genetic polymorphisms may be useful in matching patients to optimal treatments [81].

Perhaps more pressing is the need to demonstrate efficacy for smoking cessation pharmacotherapies in certain population groups among whom conventional treatments have had limited success. Notable among these groups are adolescent smokers [82], pregnant women [83] and people with serious mental illness [84]. The paper by Baker & colleagues [85] in this Special Issue on smoking cessation research explores this point further. We recommend that part of the key to demonstrating pharmacological efficacy in these groups is to combine the pharmacological therapy with effective behavioural support that is appropriate to the target population and is designed partly to maximise medication compliance. Clearly, it will also be necessary

to design studies with adequate statistical power to detect the modest effect size that may be expected. For example, to have 80% power to detect as statistically significant an expected long-term abstinence rate in the active drug condition of 20% vs. 10% in the placebo group would require at least 215 participants in each condition (i.e. total $n=430$) using a χ^2 analysis. If analyses of subgroups are planned (e.g. men vs. women or heavy vs. light smokers) then a much larger total sample would be required [86]. Designing studies with any fewer participants is usually a recipe for negative results in smoking cessation trials. Proper evaluations of efficacy in sub-populations will require relatively large multi-centre trials with these sub-group analyses planned in the design. It is unlikely that pharmaceutical companies will fund such large trials for products that have already been licensed, unless they perceive a significant potential advantage in terms of sales/profit may result from it. These companies are also cognisant of the risk of simultaneously identifying previously unknown safety concerns about the medication during such large trials. It may therefore be incumbent upon public research funders to support the large multi-centre trials necessary to identify sub-group effects.

3. Can existing pharmacotherapies be used more effectively?

The research evidence may be lagging behind the clinical practice of those at the cutting edge of providing specialist tobacco dependence treatment. For example, while both the Cochrane review on the efficacy of nicotine replacement therapy [26] and the US Clinical Practice Guidelines [25] support the efficacy of combinations of medications over monotherapy, there are relatively few studies of combination pharmacotherapy and it is unlikely that these will ever be able to cover all the possible combinations.

A concrete example can be given here from the authors' own clinical service, the Tobacco Dependence Clinic at UMDNJ—School of Public Health. During 2001–2, 442 patients attending this clinic set a quit-date and completed a 4-week follow-up. Of this group, 378 (85.5%) reported using cessation medications during their quit attempt [87]. Of those who used medications, 70% used combination therapy. The most commonly used treatment regimens among the 378 who used medications included patch + inhaler (26%), patch + inhaler + bupropion (15%), patch alone (13%), inhaler + bupropion (10%) and inhaler alone (9%). In total, 25 different combinations of pharmacotherapy were used by these 378 patients.

In multivariate analysis of the initial 273 patients seen in the UMDNJ Clinic (controlling for baseline demographic variables and cigarette consumption), including all patients with data on medication use at

4 weeks and assuming that those lost to follow-up by 6 months are smoking, the odds ratio of 6-month abstinence was 2.4 ($p=0.082$) for using one medication, 2.7 ($p=0.041$) for two medications and 4.1 ($p=0.008$) for three or more medications compared with those who had used no medications 4 weeks after their target quit date [88].

Patients at the UMDNJ Tobacco Dependence Clinic are encouraged to continue on their medications at full dose until they have experienced 14 consecutive days without noticeable cravings, withdrawal symptoms or near lapses, rather than stick to the brief 6–12 week use indicated on the labelling. Of those patients who reported follow-up data at 6 months (203 of initial 273), 35% (71 of 203) were still using medications at their 6-month follow-up. Those patients continuing to use medications at this point were more likely to be abstinent at the 6-month point (49 of 71 = 69% abstinent) compared to those who were no longer taking medications at the 6-month point (43 of 132 = 33% abstinent) [87]. This raises the issue of long-term use of pharmacotherapies, which is another area of research that warrants exploration.

Our clinical impression is that patients do better on long-term and combination pharmacotherapy [84], and the initial signs from randomised trials using this type of treatment approach appears to support this [60]. The study by Hall and colleagues [60] represents one of only a few that properly treats tobacco dependence as the chronic disease that it is—a disease requiring long-term therapy just like other chronic diseases. We therefore recommend more studies of long term combination pharmacotherapy vs. 'standard care' (short-term monotherapy), and we are conducting a randomised trial on this in patients with co-occurring medical conditions.

4. Can pharmacotherapies that are effective for smoking cessation also be useful for tobacco harm reduction?

To date, research has focused on evaluating efficacy for long-term tobacco cessation, but researchers are beginning to explore the effects of alternate indications such as reduced smoking, long-term maintenance therapy or treatment of nicotine withdrawal during periods of temporary tobacco abstinence. Many in the field of tobacco control have been sceptical of such proposals, partly through concern that these may divert attention (and scarce resources) from the ultimate goal of tobacco cessation [89].

There is very good evidence that when smokers reduce the number of cigarettes smoked they increase the puff volume per cigarette (nicotine compensation), resulting in less reduction in toxin exposure than might be expected [90] and limited or no health benefit [91]. However, some of the early studies combining

pharmacotherapy with reduced smoking have produced encouraging effects, including stimulating more smokers to quit [92,93]. We therefore recommend further research examining the short-term and longer-term effects of the use of pharmacotherapy for tobacco harm reduction goals that may fall short of long-term tobacco and/or medication-free living.

5. Can improved psychosocial treatments enhance pharmacotherapy outcomes?

Although pharmacotherapies alone can be effective in reducing withdrawal symptoms and improving treatment outcomes, the integration of behavioural therapy increases the quit rate by another 50–100% [25]. There is also a wide range of psychosocial treatment options now available, including internet counselling (involving ‘chat room’ support groups) and telephone counselling services, as well as individual and group face-to-face counselling (see papers in this Special Issue by Borland & Segan [94] on the Quitline telephone counselling service and Etter [95] on stopping smoking via the internet). Studies have found that more intensive behavioural therapy doubles the quit rate compared to minimal psychosocial intervention [25,96,97] but more research is needed to compare the new wider range of options for psychosocial treatment.

Practice guidelines for nicotine dependence treatment have all recommended behavioural therapies as first-line agents and that pharmacotherapies should be integrated with behavioural and psychosocial components [25,98]. Psychosocial interventions can be helpful at all phases of tobacco dependence treatment. A key part of improving outcomes of pharmacotherapy for smoking cessation (whether as combination or monotherapy) will involve improving the generally poor compliance with existing therapies [80]. Behavioural and systems interventions that improve compliance exist [99] and should be used and evaluated more often in tobacco treatment research.

Unfortunately, although integrating psychosocial and pharmacological treatments enhances quit rates when compared to either alone, only about 3–5% of smokers who make a 24-hour quit attempt actually receive counselling as part of their treatment [100]. Smokers encounter numerous barriers to participation in behavioural therapy, including lack of recommendation by the medication prescriber, the lack of awareness of available services, the fear of added costs, waiting times, time constraints and concern about stigma if seeking counselling.

Although it is suggested frequently that smokers prefer to avoid counselling, or to obtain such assistance via the telephone [101,102], some recent evidence suggests that when face-to-face counselling by a trained provider is offered in a convenient manner, it is accepted

by a high proportion of smokers. The recent success of the English smoking cessation services [103] has been based largely on the willingness of large numbers of smokers (over 500 000 per year) to attend for face-to-face treatment. A recent US study [104] found that 68% of smokers in primary care expressed an interest in receiving treatment and 78% of eligible patients enrolled. The smokers in these US primary care practices were given the option of (a) a free course of nicotine patches; (b) the patches plus access to a telephone assessment and individualised supportive mailings; or (c) b plus face-to-face counselling at the family practice. The most popular choice was the face-to-face counselling (42%), followed by the telephone counselling session and mailed intervention (33%), followed by the patch alone (25%). This study concluded that free, readily accessible smoking cessation treatment offered in primary care settings is accepted and used by the majority of unselected smokers and that the more intensive face-to-face interventions are preferred. This mirrors our own experience in Middlesex county in central New Jersey (USA), with a population of 573 000 adults in 316 square miles. The state has a free, well-publicised and high-quality telephone counselling service for smokers (offering free call-back counseling sessions and achieving 6-month abstinence rates of approximately 30%), and in our county there is also free access to a specialist treatment clinic offering intensive face-to-face treatment. Over the past 4 years (2001–4), more than twice as many smokers from Middlesex county have attended this intensive face-to-face clinical service as have engaged in counselling on the quitline. This again suggests that where intensive face-to-face treatment is made accessible, it is valued and utilised by a significant proportion of smokers. For more on counselling on the quitline, see the paper by Borland & Segan [94] in this Special Issue.

People with a recent (past month) mental disorder consume 44% of the cigarettes smoked in the United States each year, and have double the smoking prevalence of people without mental health problems [105]. The high rates of tobacco dependence among individuals with a mental illness or substance use disorder and the worse clinical outcomes with lower intensity treatment of tobacco dependence for this population suggest that there is a need for integrated and intensive treatment options for this population [106]. Of note, several intensive therapies have been successfully adapted for smokers with depression [107], schizophrenia [42], or alcohol or other drug addictions [108]. The panel of the 2000 US Clinical Practice Guidelines [25] achieved consensus in recommending the use of the primary psychosocial treatment components for tobacco dependence described above for smokers with psychiatric comorbidity. They also, however, recommended continued

research on the efficacy of tailored interventions in this population due to the unique issues relevant to smokers with co-occurring psychiatric disorders. Addressing these unique issues as part of psychosocial therapy will be important in helping this population to quit smoking. These issues have also been explored in the papers by Baker *et al.* [85] and Wilhelm *et al.* [109] in this Special Issue.

Conclusions

Since the first licensing of 2 mg nicotine gum in Switzerland in 1978, research on pharmacotherapy for tobacco dependence has expanded dramatically. Since the identification of effective non-nicotine pharmacotherapies, there has been particular interest in evaluating both new compounds and existing medications that previously had other indications. Pharmaceutical companies may have a natural tendency to focus research spending on development and licensing of the next potential new blockbuster drug, but academic researchers and public funding agencies should continue to focus on research that has the greatest potential for furthering scientific understanding and public health benefit. Significant advances in these areas may result from better understanding of the mechanisms of action of existing and new pharmacotherapies, and from a more effective combination of existing pharmacotherapies with improved psychosocial treatments (including those delivered via telephone or new technologies).

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