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## Current and emerging pharmacotherapies for treating tobacco dependence

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Tobacco dependence remains the leading cause of death and disease in the US and a major cause of mortality around the world, yet 1 out of 5 American adults smoke and 1.3 billion adults smoke worldwide. Nicotine replacement therapies (NRTs), bupropion and varenicline, are approved by the US FDA as first-line treatments for nicotine dependence. Clonidine and nortriptyline are recommended as second-line treatments by the Agency for Healthcare Research and Quality. Although recent data suggest that varenicline is superior to bupropion for treating nicotine dependence, a majority of smokers fail to maintain long-term abstinence from smoking using FDA-approved pharmacotherapies. Thus, continued investigation of novel medications for nicotine dependence remains a critical priority. Guided by research on multiple neurobiological mechanisms of nicotine dependence, several novel medications that mimic and/or attenuate nicotine's rewarding effects, or reduce nicotine withdrawal, are under investigation. Although existing data are limited or conflicting, there is some evidence for the efficacy of selegiline, fluoxetine, naltrexone and mecamylamine in certain subgroups of smokers. New research directions, such as fast-acting NRTs, the tailored use of NRTs for subtypes of smokers, and pharmacogenetics, hold promise for new treatment approaches and, ultimately, for reducing rates of tobacco use in the US and worldwide.

**Keywords:** addiction, nicotine, pharmacogenetics, pharmacotherapy, smoking, tobacco

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### 1. Background

Despite several decades of intense research to identify new approaches to treat nicotine dependence, ~ 21% of adults in the US are regular smokers [1]. In addition, given the focus of tobacco industry marketing on the Far East and Eastern Europe, the prevalence of adult smoking in some developing countries in these regions is as high as 40 – 50% [2]. At present, an estimated 1.3 billion adults smoke worldwide, but if current trends continue, this figure will increase to 1.6 billion by 2025 [201]. Barring a dramatic turn of events in the next few years, the Healthy People 2010 objective of reducing US adult smoking to 12% will not be attained and the smoking rates in developing countries will increase by 6 – 16% by 2008 [2]. The health and economic costs of tobacco use are enormous. Each year, cigarette smoking causes > 400,000 premature deaths in the US and 4.2 million premature deaths around the world from cancer, cardiovascular and respiratory diseases, perinatal conditions and fires [2,3]. If current trends continue, tobacco use will be responsible for 7 million deaths annually by 2025 [2]. In addition, despite tobacco industry claims that tobacco control initiatives harm economies through tax revenue loss or unemployment, the current economic costs of smoking are far greater for the world's economies. For instance, the US spends \$76 billion annually in healthcare costs due

Table 1. FDA-approved and AHRQ-recommended medications for tobacco dependence.

Medication	Recommended duration*	Recommended dose*	Estimated quit rate† (95% CI)	Number of trials [Ref.]	Advantages	Disadvantages	Cost
<b>FDA-approved medications</b>							
Nicotine gum	Up to 12 weeks	2 mg for those who smoke < 25 cigarettes/day; 4 mg for those who smoke > 25 cigarettes/day	17.4% (17 – 18%)	52 [14]	Treat oral behavioural ritual and cue-elicited craving; prevent weight gain	Adverse side effects and poor compliance	\$4.00 – 5.00/day
Nicotine patch	Up to 10 weeks	Dose duration varies by cigarettes/day	13.7% (13 – 15%)	37 [14]	Better compliance and nicotine replacement; few side effects	Does not treat cue-elicited craving	\$2.50/day
Nicotine spray	Up to 6 months	8 – 40 sprays/day	24% (20 – 28%)	4 [14]	Nicotine is rapidly absorbed; treat cue-elicited craving	Unpleasant side effects and poor compliance	\$5.00 – 15.00/day
Nicotine inhaler	Up to 6 months	6 – 16 cartridges/day	17% (14 – 21%)	4 [14]	Treat oral behavioural ritual and cue-elicited craving	Unpleasant side effects and poor compliance	\$7.00 – 18.50/day
Nicotine lozenge	Up to 12 weeks	2 mg for those who smoke their first cigarette more than 30 min after waking and 4 mg for those who smoke their first cigarette within 30 min of waking	17% (15 – 20%)	4 [14]	Good nicotine replacement; treats oral behavioural ritual and treats cue-elicited craving; few side effects	Compliance is unknown	\$3.00 – 4.00/day
Bupropion	Up to 12 weeks	300 mg/day; 150 mg/day for 3 days then 300 mg/day from day 4 to end of treatment	30.5% (23 – 38%)	2 [8] 24 [13]	Good side-effect profile; low abuse liability; prevent weight gain	Relatively more costly	\$4.00 – 5.00 (300 mg)
Varenicline	Up to 12 weeks	2 mg/day; 0.5 mg for days 1 – 3, 0.5 mg b.i.d. for 4 days and 1 mg b.i.d. from day 8 to end of treatment	30%	2 [12,61]	Well tolerated; reduces withdrawal and reinforcing effects of nicotine	Limited data	Unknown
<b>AHRQ-recommended medications</b>							
Clonidine	Up to 10 weeks	0.10 mg/day for week 1, increasing by 0.10 mg/day each week as needed up to 0.75 mg/day	25.6% (18 – 34%)	5 [8]	Possibly useful for subgroup of smokers (e.g., anxious, women)	Poor side-effect profile	\$0.24 (0.2 mg)
Nortriptyline	Up to 12 weeks	25 mg/day for week 1, increasing to 75 mg/day	30.1% (18 – 42%)	4 [15] 3 [8]	Well tolerated; affordable	Overdose can be fatal	\$0.42 (75 mg)

\*Recommendations are taken from the manufacturer of the agent and/or from [8]; †6-month or greater point-prevalence quit rates, biochemically verified. AHRQ: Agency for Healthcare Research and Quality; CI: Confidence interval.

to tobacco-related diseases, and indirect costs attributable to tobacco use (i.e., lost productivity, absenteeism, recruitment and retention of replacement workers) cost the US economy \$82 billion/year [4].

The pursuit of effective treatments for nicotine dependence requires an understanding of the nature of the behaviour. Continued, regular tobacco use typically leads to nicotine dependence as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV [5]). A DSM-IV diagnosis of nicotine dependence requires that a smoker meet at least three of the following criteria:

- tolerance (e.g., the absence of nausea or dizziness despite substantial tobacco use)
- withdrawal (i.e., daily use for at least several weeks and, following abrupt cessation, reports of four or more of the following symptoms: dysphoria or depressed mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate and increased appetite and weight gain)
- repeated unsuccessful attempts to quit smoking
- giving up recreational or occupational activities for smoking
- continued use despite health risks
- smoking more frequently than intended

Although exact rates vary from study to study, from country to country, and depend on the measure used to assess nicotine dependence, upwards of 50% of regular smokers can be classified as nicotine dependent [6,7]. In the sections that follow, medications approved for the treatment of nicotine dependence by the US FDA are reviewed, along with nicotine dependence medications recommended by the Agency for Healthcare Research and Quality (AHRQ) [8].

## 2. Medical need

At present, the US FDA has approved three pharmacotherapies for treating nicotine dependence: nicotine replacement therapies (NRTs), bupropion and varenicline [9-11]. Two other medications, clonidine and nortriptyline, are recommended as second-line treatments for tobacco dependence by the AHRQ [8]. Although varenicline treatment produces the highest efficacy rates of all medications tested in Phase III trials so far [12], only about one out of three smokers who use FDA-approved or AHRQ-recommended medications will maintain long-term abstinence [8,12-16]. Thus, there is an urgent need for continued research to identify novel pharmacotherapies, and new approaches to the delivery of existing pharmacotherapies, for treating nicotine dependence.

## 3. Existing treatments for nicotine dependence

### 3.1 FDA-approved treatments

#### 3.1.1 Nicotine replacement therapies

As shown in Table 1, five NRTs are approved by the US FDA for the treatment of nicotine dependence: the transdermal

patch, the gum, the nasal spray, the inhaler and the lozenge. A sixth NRT, the sublingual tablet, is not available in the US, but it is used in European countries and it has shown efficacy as a treatment for nicotine dependence [17]. These agents treat nicotine dependence by: i) ameliorating withdrawal symptoms that characterise initial physical and psychological reactions to cessation, such as irritability, restlessness, depressed mood and poor concentration; ii) reducing the experience of nicotine craving on cessation and limiting possible weight gain (for gum and the patch); and iii) providing a safer way to experience the neurobiological and psychophysiological effects of nicotine. On the one hand, NRTs are, by and large, safe for smokers to use and generally double quit rates versus placebo (pooled odds ratio [OR] = 1.77, 95% confidence interval [CI]: 1.66 – 1.88 [14]). Indirect comparisons [14] and head-to-head comparisons [18] indicate comparable efficacy between the different NRTs. On the other hand, NRTs do not provide nicotine as effectively as cigarettes [19] or adequately mimic the behavioural ritual of smoking. Furthermore, at best, only a quarter to a third of smokers who use NRTs to quit smoking will remain successfully abstinent 6 months following treatment completion, even with the newly developed nicotine lozenge [14,20-25].

One reason why NRTs have limited efficacy for some smokers is that they do not deliver the nicotine into the CNS nearly as fast and efficiently as cigarettes. This shortcoming can lead to relapse when smokers experience intense cravings, as it can take up to 20 min for NRTs to work, whereas cravings can lead to relapse within 10 min [26]. A recent study examined the efficacy of rapid-release nicotine gum, compared with standard nicotine gum, for relief of cue-provoked nicotine craving [27]. A total of 319 smokers were exposed to a smoking cue (i.e., lighting a cigarette, but not smoking it), were selected randomly to chew the standard or the rapid-release nicotine gum, and repeatedly reported their craving for nicotine. The results showed that the rapid-release nicotine gum significantly reduced reported cravings compared with standard nicotine gum, thus suggesting the need for large-scale clinical cessation trials of this new rapid-release formulation of the nicotine gum. Future trials with rapid-release gum are also needed to assess the safety and the abuse liability of this new formulation of nicotine replacement [27].

Additional investigations have tested the use of NRTs for a greater duration, the use of higher dose NRTs, the use of combined NRTs and the use of NRT prior to a designated quit date. So far, studies that compared varying durations of patch use have shown no advantage in terms of quit rates for longer duration [28]; however, large-scale placebo-controlled trials of patch duration are needed to resolve this issue. Although it has been suggested that the modest efficacy of the patch is attributable to inadequate nicotine replacement with the standard clinical dose of 21 mg [29], abstinence rates with a 44-mg dose were not maintained by 12-month follow up [29], and other studies have not found significant dose response effects, even in the short term [30,31]. Relatively fewer studies

have examined the use of combined NRTs and few consistent or clinically meaningful findings have been yielded [14]. Two studies, for instance, showed that patch plus gum outperforms gum alone [32,33] and another study showed that patch plus spray outperformed patch alone [34]. In contrast, Tonnesen and Mikkelsen [35] reported that quit rates were equivalent among smokers treated with patch plus inhaler versus either NRT alone, and Croghan *et al.* [36] showed no differences in quit rates among smokers treated with the patch plus the nasal spray compared with either NRT alone. Of note, meta-analytical reviews of studies that evaluated combination NRT therapy versus a single NRT therapy have concluded that combination therapy is more effective (OR = 1.42, 95% CI: 1.14 – 1.76 [14] versus OR = 1.9, 95% CI: 1.3 – 2.6 [8]). Lastly, a recent study that randomly assigned smokers to use NRT as prescribed (i.e., starting on a designated quit day) or for 2 weeks prior to a quit day reported that use of the NRT prior to the target quit day doubled the likelihood for 4-week continuous abstinence, compared with standard NRT use [37].

A range of smoker characteristics can affect response to NRTs, suggesting the possibility for the tailored use of NRT for subgroups of smokers to improve NRT efficacy [38]. For instance, the level of nicotine dependence affects response to the gum and lozenge; smokers with a high level of nicotine dependence show higher quit rates when they receive higher doses of these NRTs [24,39]. Lerman *et al.* [18], in an open-label trial of patch and nasal spray, reported that low-to-moderate nicotine-dependent smokers, nonobese smokers and white smokers showed higher quit rates with the patch, whereas highly nicotine dependent smokers, obese smokers, and smokers from racial/ethnic minority groups showed higher quit rates using the nasal spray. Likewise, highly dependent smokers exhibited higher quit rates using the nicotine inhaler versus other NRTs [40], although replication of this finding is needed. Additional research is needed to elucidate the tailored use of NRTs for subgroups of smokers, including research to understand whether or not women are less responsive to NRT than men; some studies have shown that NRT is less effective for women compared with men [41,42], but other studies have found no effect of gender on quit rates following NRT treatment [43-45]. As is discussed below, pharmacogenetic trials are exploring the potential genetic basis of individual differences in therapeutic response [46]. In parallel, other researchers are identifying methods for increasing the use of NRTs and motivating quit attempts through innovative marketing approaches and the use of financial incentives [47].

### 3.1.2 Bupropion SR

In 1997, the US FDA approved bupropion, an antidepressant, for the treatment of tobacco dependence. A meta-analysis [13], which included 19 placebo-controlled trials with > 4000 subjects, found that bupropion more than doubled the likelihood for cessation versus placebo, up to 12 months from a quit date (OR = 2.06, 95% CI: 1.77 – 2.40). Bupropion efficacy has been demonstrated with subgroups of smokers who show high

relapse rates, including African-Americans [48], women [49,50] and highly dependent smokers [51].

The exact mechanism through which bupropion treats nicotine dependence is not fully known, but bupropion efficacy is likely mediated, in part, by the blockade of dopamine and noradrenaline uptake [52] and/or nicotinic receptor antagonist effects [53]. A second mechanism may involve the drug's ability to prevent or diminish postcessation negative mood symptoms and weight gain, which are frequently cited as causes of relapse among smokers [54,55]. Nevertheless, the vast majority of smokers who use bupropion to quit smoking do not achieve long-term abstinence. Because the benefits of bupropion in terms of addressing depressive symptoms and weight gain are mainly restricted to the treatment phase, some have speculated that research is needed to examine the benefits of extended treatments with bupropion [20]. One recent study showed that use of bupropion for up to 1 year increased long-term quit rates compared with placebo [56]; however, the results of a second study of extended bupropion treatment were negative [57]. Bupropion may be most effective for smokers who use nicotine to alleviate negative mood symptoms or to control weight, a research question currently being addressed in an ongoing trial [58].

### 3.1.3 Varenicline

Varenicline was granted US FDA approval for treating nicotine addiction in May 2006. The concept for this medication arises, in part, from research conducted in the former Soviet Union on cytisine, which is derived from a variety of plant species. Cytisine is a partial nicotine agonist, stimulating nicotinic receptors to release mesolimbic dopamine [59]. This herbal byproduct was studied in tablet form for smoking cessation, but had limited efficacy due to poor absorption and limited brain penetration [60]. Varenicline is a selective  $\alpha_4\beta_2$ -neuronal nicotinic acetylcholine receptor (nAChR) partial agonist. By activating  $\alpha_4\beta_2$ -nAChRs, which are expressed widely on dopamine and GABA neurons in the ventral tegmental area, varenicline attenuates nicotine's effect on dopamine release, while maintaining dopaminergic tone [60]. Varenicline's agonist function is thought to minimise craving and withdrawal, while its antagonist properties attenuate the reinforcing effects of nicotine, thereby reducing satisfaction from a 'slip' cigarette and the likelihood of relapse [10].

The recent FDA approval for varenicline was based on the promising results from three clinical trials. The first two trials randomised 2052 smokers to placebo, bupropion 300 mg, or varenicline 2 mg for 12 weeks and assessed quit rates up to 1 year following the start of treatment [12,61]. Assessment of continuous quit rates for the last 4 weeks of treatment (weeks 9 – 12) across the two trials at the end of treatment showed an advantage for varenicline (44%), versus bupropion (30%) and placebo (18%). The continuous quit rate for varenicline at the 1-year follow up diminished (22%), but it remained significantly better than for bupropion (16%) or placebo (10%). In a third study [62], smokers received open-label varenicline

1 mg b.i.d. for 12 weeks; subjects who remained abstinent at the end of 12 weeks were randomised to 12 additional weeks of varenicline 1 mg b.i.d. or placebo. Quit rates were assessed 28 weeks from the end of the second 12-week treatment phase. The quit rate at the end of the first 12-week treatment phase was 63%. The continuous abstinence rate at the end of the 28-week follow-up period was significantly greater for the varenicline participants versus placebo (71 versus 50%). Across all three trials, adverse events and rates of discontinuation were similar across the placebo and varenicline arms, indicating the agent was well tolerated, as well as efficacious.

### 3.2 AHRQ-recommended treatments

#### 3.2.1 Clonidine

Clonidine acts as an agonist for  $\alpha_2$ -adrenoreceptors [63] and was originally used to treat hypertension and, subsequently, withdrawal from opiate and alcohol abuse [64]. In a recent meta-analysis [65], six placebo-controlled trials showed higher quit rates for smokers taking clonidine, compared with placebo, but only one of these studies was statistically significant. Nevertheless, the OR reported for clonidine in this meta-analysis (1.89, 95% CI: 1.30 – 2.74) compares to the OR for the use of any NRT. Clonidine is unlikely to shift to a first-line medication for nicotine dependence given the adverse side effects yielded by this medication, such as sedation, constipation and hypotension. At best, given clonidine's sedative effects and ability to mitigate withdrawal from other drugs of abuse, this agent may only be useful for smokers who exhibit postcessation anxiety or are receiving treatment for other substance abuse problems, although no empirical evidence exists to support this recommendation at this time. In contrast, the results from clinical trials with clonidine suggest that women tend to respond more favourably to this agent than men, although no trial has stratified randomisation by gender to formally test this hypothesis [65].

#### 3.2.2 Nortriptyline

Nortriptyline is a tricyclic antidepressant that blocks the re-uptake of noradrenaline and serotonin, thereby ameliorating symptoms of nicotine withdrawal and postcessation depressive symptoms [66]. In an analysis of four placebo-controlled trials with at least a 6-month follow-up assessment of quit rates, Hughes *et al.* [15] found that nortriptyline yielded a greater than twofold increase in quit rates, versus placebo (OR = 2.79, 95% CI: 1.70 – 4.59). Likewise, in an analysis of five placebo-controlled trials with at least a 6-month follow-up assessment of quit rates, Wagena *et al.* [16] found that nortriptyline more than doubled quit rates, versus placebo (OR = 2.4, 95% CI: 1.7 – 3.6). Importantly, assessments of participant-reported adverse effects showed that only dry mouth and constipation and gastrointestinal distress were reported significantly more often among those in the nortriptyline arms versus placebo [16]. Although one study found no significant difference in quit rates between smokers randomised to bupropion versus nortriptyline [67], a more

recent study found that bupropion plus behavioural counselling yielded higher 6-month quit rates, versus nortriptyline plus behavioural counselling (42 versus 31% [68]). Lastly, as nortriptyline is far less expensive than bupropion, it may represent a more viable treatment for smokers who do not respond to first-line medications.

## 4. Market size and potential

At present, the market for pharmacotherapies for nicotine dependence is substantial. In the US alone, there are at least 44 – 45 million adult smokers [2], half of who are seriously interested in quitting smoking [69]. Worldwide, there are more than a billion smokers, although, realistically, primarily smokers in industrialised countries could afford or have ready access to pharmacotherapies for nicotine dependence. Even so, several forces will likely sustain and even increase the worldwide market for pharmacotherapies for nicotine dependence.

First, as seen by the effects of the publication of the first Surgeon's General Report on the adverse consequences of tobacco use on the prevalence of smoking in the US, increased public health awareness for the adverse health effects of tobacco use can motivate smokers to quit. As this awareness continues to grow in the US and elsewhere, the number of smokers who are ready to use proven medications for smoking cessation can be expected to increase. Second, the social climate in many countries is shifting away from acceptance of tobacco use, as evidence by the growing list of US states, Canadian provinces and countries that have enacted legislation to ban smoking in indoor public places, increase taxes on tobacco, limit tobacco advertising and require graphic anti-smoking warning labels on tobacco products. This shift can increase the use of pharmacotherapies for nicotine dependence. For example, a recent evaluation of New York City data found a 50% increase in the purchasing of nicotine patches following the start of a municipal cigarette tax, a 27% increase in the purchasing of the nicotine patch following the start of a state cigarette tax, and a 31% increase in the sale of the nicotine patch following a city wide ban on indoor smoking [70]. Third, there is growing recognition for the need for the extended use of pharmacotherapies for nicotine addiction, as nicotine addiction is more broadly recognised as a chronic illness rather than an acute condition [71,72]. Thus, the market may eventually demand long-term or even lifelong use of medications for nicotine dependence. Finally, each year additional countries experience the necessary economic and social development to become a developed, industrialised nation. As this trend continues, the list of countries that have the requisite infrastructure to dispense such medications and the base of smokers who can afford these medications will grow.

Not surprisingly, therefore, use of pharmacotherapies for treating nicotine dependence has been increasing over the past decade [73]. Two additional factors are important to consider when evaluating the market potential for pharmacotherapies for nicotine dependence. First, ease of access to these agents is

critical, and the change in the status of NRTs from prescription to over-the-counter (OTC) greatly affected market use [74]. For instance, a recent study of California smokers reported that the percentage of smokers attempting to quit smoking using the patch or the gum more than doubled up to 6 months following the change of these NRTs from prescription to OTC [75]. Likewise, national data indicate the conversion of NRT from prescription to OTC resulted in a 78 – 92% increase in the consumption of nicotine patches and a 177 – 180% increase in the consumption of nicotine gum [76]. Second, financial coverage and marketing of pharmacotherapies is also critical for enhancing use of pharmacotherapies for nicotine dependence. A recent study of the impact of a change in financial reimbursement for NRTs and bupropion in the UK showed that the use of these medications for treating nicotine dependence increased, from 8 – 9% of smokers in 1999 (before the UK National Health Service provided reimbursement for treatments) to 17% of smokers in 2002, 3 years after the reimbursement programme was started [77]. Furthermore, evaluations of programmes that distributed free NRT throughout the State of New York have shown that such programmes can lead to significant increases in quit attempts and cessation [78,79]. Finally, adequate use of NRTs may also depend on methods used to promote their use through marketing incentives and advertising. For instance, Paul *et al.* [80] reported that direct marketing of NRTs to smokers could increase interest and willingness to use these treatments, and Tauras *et al.* [81] found that advertising NRTs increased NRT use. Thus, as new agents are devised, companies should consider how easily they could be dispensed, as well as their efficacy, safety and affordability.

## 5. Current research goals

A review of data on the efficacy of available pharmacotherapies for the treatment of nicotine dependence underscores the importance of continued investigation of novel medications. Guided by research pointing to multiple neurobiological mechanisms of nicotine dependence, several novel medications that mimic and/or attenuate nicotine's rewarding effects, or reduce nicotine withdrawal, are under investigation. The following sections provide a brief overview of neurobiological targets and preliminary data on pharmacotherapies that have been screened for potential efficacy in clinical Phase II or III investigations.

## 6. Scientific rationale

The development and maintenance of nicotine dependence is largely mediated by neurobiological effects of nicotine and neuroadaptive changes with chronic nicotine exposure [66]. Nicotine binds to nAChRs, comprising five subunits that combine to form individual receptors with distinct neurobiological and pharmacological properties. Among the different subunits ( $\alpha_2$ - $\alpha_1$ ,  $\beta_2$ - $\beta_4$ ), the  $\alpha_4\beta_2$  is most common among

those with high binding affinity for [<sup>3</sup>H]-nicotine and are widely expressed on dopamine and GABA neurons in the ventral tegmental area. Nicotine stimulates increased burst firing of dopamine neurons via  $\alpha_4\beta_2$ -nAChRs and also stimulates dopamine release indirectly by activating excitatory glutamate neurons via  $\alpha_7$ -nAChRs [82,83]. These effects are thought to enhance the dopamine-mediated associative learning process that results in the maintenance of nicotine self-administration and dependence [84]. In addition to these effects, nicotine modulates release of 5-hydroxytryptamine in the dorsal raphe nucleus and noradrenaline in the hippocampus, effects that appear to be mediated via  $\alpha_7$ -nAChRs [85,86]. Acute nicotine also increases release of endogenous opioid peptides that bind to  $\mu$ -opioid receptors, possibly producing direct reinforcing effects of nicotine and indirect effects via dopamine release [87-90]. Effects of chronic nicotine on these neurobiological pathways contribute further to somatic, cognitive and affective symptoms of nicotine withdrawal [91]. Thus, compounds that mimic (agonists) and/or block (antagonists) the effects of nicotine, and attenuate nicotine withdrawal, are potential therapeutics for the treatment of nicotine dependence.

## 7. Competitive environment

The following sections and **Table 2** describe medications that are being actively explored as potential treatments for nicotine dependence. This review is limited to pharmacotherapies that have been evaluated in Phase II or III clinical trials and those for which recent data are available. Several pharmacotherapies previously tested clinically and found to have limited efficacy are not discussed here. These include the tricyclic anti-depressants doxepine and imipramine, the anxiolytic buspirone, the serotonergic antagonist ondansetron and the dopamine agonist bromocriptine [66,92,93].

### 7.1 Monoamine oxidase inhibitors

The monoamine oxidase (MAO)-A and -B enzymes are involved in the metabolism of dopamine (MAO-B), noradrenaline and serotonin (MAO-A), and tobacco smoke has been shown to inhibit CNS MAO-A and -B [94,95]. As such, MAO inhibition increases self-administration of nicotine in rodent models [96]. Thus, replacement of these effects of smoking with MAO inhibitor treatment may provide an efficacious treatment option [97]. Lazabemide is a selective, reversible inhibitor of MAO-B. The single randomised clinical trial of this agent compared placebo with lazabemide 100 or 200 mg for 8 weeks [98]. Only the 200-mg dose was significantly better than placebo in intent-to-treat analysis (17 versus 10%) and in analysis of completers (35 versus 19%). However, the trial was stopped early by the pharmaceutical company due to a high rate of liver toxicities among participants in other studies with this medication.

Subsequently, the MAO-B inhibitor selegiline was tested in two clinical trials. In one study with 40 smokers, those randomised to receive selegiline 10 mg for 8 weeks had

Table 2. Potential new drug therapies for treating nicotine dependence.

Drug target/type	Efficacy data	Advantages	Disadvantages
<b>Monamine oxidase inhibitors</b>			
Selegiline Moclobemide Lazabemide	Few clinical trials, but some evidence for efficacy from available trials	Studies suggest agents are generally well tolerated	Possible liver toxicity and hypertension
<b>Selective serotonin reuptake inhibitors</b>			
Fluoxetine Paroxetine Sertraline Venlafaxine	Six clinical trials (mostly with fluoxetine), with mixed results	Medications may be effective for subgroups of smokers (e.g., depressed smokers); prevents weight gain	Side effects include sleep problems, loss of sexual desire, nausea
<b><math>\mu</math>-Opioid receptor antagonists</b>			
Naltrexone	Most clinical trials have been small and results have been inconsistent	May limit weight gain and treat poly-substance abuse	Poor side-effect profile (e.g., nausea, sedation)
<b>GABAergic agents</b>			
Gabapentin	One small study	May block nicotine reward and withdrawal	Long-term safety unknown
<b>Nicotinic agents</b>			
Mecamylamine	Two small trials; some evidence for efficacy	Well tolerated	Efficacy only with nicotine agonist
Nicotine vaccines	Efficacy data based on small number of Phase I trials	Well tolerated	Long-term safety unknown
<b>Cannabinoid receptor antagonists</b>			
Rimonabant	One large trial showing efficacy	Prevents postquit weight gain	Long-term safety unknown
Topiramate	One clinical trial with alcohol-dependent smokers	May treat poly-substance abuse	May increase positive subjective effects of nicotine
<b>NRTs</b>			
Combination Higher dose Fast-acting Pre-treatment	Few trials, some inconsistent results, but some preliminary evidence for use	Addresses unique dependence characteristics	Possible nicotine overdose

NRT: Nicotine replacement therapy.

significantly higher quit rates at the end of treatment than those receiving placebo (45 versus 15%, respectively). The quit rate for the selegiline arm at 6 months was greater than for placebo (20 versus 5%), but low statistical power yielded a nonsignificant result. Furthermore, there were no significant differences between the study conditions on adverse events, suggesting that selegiline was well tolerated. In a second trial, 109 smokers were randomised to selegiline 5 mg plus a transdermal nicotine patch or placebo plus patch for 26 weeks [99]. Although the results were not statistically significant, quit rates in the selegiline arm were greater compared with the placebo at week 8 (34 versus 25%), week 12 (32 versus 17%), week 26 (25 versus 13%) and week 52 (25 versus 11%). Based on these findings, there are two additional ongoing trials evaluating selegiline for smoking cessation (see [202]), one testing the oral form of selegiline, and the other evaluating a patch version of the medication.

The efficacy of moclobemide, an MAO-A inhibitor, has been explored in one small human study. Berlin *et al.* [100] randomised 88 heavy smokers to placebo or moclobemide 400 mg for 3 months. Quit rates for moclobemide and placebo were: 57 versus 36% at 1 month, 41 versus 25% at 3 months and 32 versus 16% at 6 months. Due to sample size and low statistical power, these comparisons were not significant. Insomnia was the most frequent adverse event, which occurred significantly more often among subjects in the moclobemide arm, versus placebo. Ongoing studies may clarify whether or not MAO inhibitors are effective for the treatment of nicotine dependence.

## 7.2 Selective serotonin re-uptake inhibitors

Selective serotonin re-uptake inhibitors (SSRIs), which are considered safer and better-tolerated antidepressants, are potential treatments for nicotine addiction given the role of 5-hydroxytryptamine (the target of SSRIs) in mediating the

addictive potential of nicotine. The SSRIs paroxetine, fluoxetine and sertraline, and the serotonin and noradrenaline re-uptake inhibitor venlafaxine, have been examined as treatments for nicotine addiction. A pooled analysis across five trials with SSRIs found no significant treatment effects (OR = 0.91, 95% CI: 0.41 – 3.28 [13]). However, as described below, the individual studies suggest that SSRIs may be effective for subgroups of smokers.

One study examined sertraline for smoking cessation, but found no significant effects over a 6-month follow up compared with placebo [101]. Another study examined paroxetine for smoking cessation, and also found no significant effects over a 6-month follow up compared with placebo [102]. A subgroup analysis, however, with only compliant participants indicated that there was a short-term increase in cessation rate with paroxetine (74% for 40 mg and 64% for 20 mg) compared with placebo (46%).

The efficacy of fluoxetine has been evaluated in four randomised trials. Hitsman *et al.* [103] randomised 253 smokers to placebo or fluoxetine 30 – 60 mg for 10 weeks. Although there were no significant differences in quit rates across treatment arms, subgroup analysis showed that the quit rates were significantly higher for fluoxetine participants with high levels of baseline depressive symptoms, versus those with low levels of baseline depressive symptoms. In a separate trial, Blondal *et al.* [104] also showed that fluoxetine was more effective than placebo, only for participants with high levels of depressive symptoms. In contrast, a third trial with fluoxetine found no main effect for treatment or variation in responsiveness to the medication depending on past or current depressive symptoms [105]. The largest trial with fluoxetine reported no significant differences in quit rates, versus placebo [106]; however, a subgroup analysis with only study completers found that fluoxetine yielded higher quit rates (54% for 30 mg and 62% for 60 mg) versus placebo (44%). Finally, the single investigation of the serotonin and noradrenaline re-uptake inhibitor venlafaxine for smoking cessation [107] found that the medication was more effective than placebo, but only for lighter smokers.

Thus, the efficacy data for SSRIs suggest that these agents do not have sufficiently high overall efficacy to recommend as a first-line treatment, but may be effective treatments for subgroups of smokers.

### 7.3 $\mu$ -Opioid receptor antagonists

There is a growing body of empirical evidence from preclinical animal and human studies implicating the endogenous opioid system, and the  $\mu$ -opioid receptor in particular, in the reinforcing effects of nicotine administration. Nicotine exposure increases the release of endogenous opioid peptides that bind to  $\mu$ -opioid receptors, possibly producing direct reinforcing effects of nicotine, as well as indirect effects via dopamine release [87-90]. However, clinical investigations of the efficacy of the  $\mu$ -opioid receptor antagonist naltrexone for smoking cessation have yielded equivocal results [108]. Two relatively small trials suggested that naltrexone may have

greater efficacy than placebo [109,110]. A third small trial, which compared naltrexone 50 mg plus the patch and behavioural counselling with placebo plus the patch, provided additional encouraging evidence [111]. In contrast, Wong *et al.* [112] found no evidence for the efficacy of naltrexone relative to placebo for treating nicotine addiction. Most recently, O'Malley and colleagues [113] randomised 400 smokers to placebo or naltrexone 25, 50 or 100 mg (with nicotine patch) for 6 weeks. Although no significant differences were detected in 4- or 6-week continuous abstinence rates, treatment completers in the 100-mg dose condition showed significantly higher quit rates, versus treatment completers in the placebo arm (72 versus 48%). Because low-dose naltrexone may prevent postcessation weight gain [110,113], this medication may be effective for smokers who report weight-gain concerns. There is also evidence suggesting that naltrexone is more efficacious as a treatment for nicotine dependence for females, than for males [109].

### 7.4 GABAergic agents

Nicotine's effects at nAChRs and  $\mu$ -opioid receptors (via opioid peptides) on inhibitory GABAergic interneurons modulate dopamine release and nicotine reward. Thus, medications that target the GABA pathway may reduce the rewarding properties of nicotine [114,115]. Tiagabine, a selective inhibitor of the GABA transporter-1, increases GABA concentrations, reduces nicotine craving postabstinence and enhances cognitive performance versus placebo [116]. Baclofen, a GABA-B receptor agonist, decreases levels of nicotine intravenous self-administration in mice [117], and reduces the hedonic aspects of smoking among humans [118]. Gabapentin is a non-selective GABA agonist used for the treatment of epilepsy. Although the exact mechanisms of action are not completely understood, gabapentin has been shown to increase brain concentrations of GABA and reduce glutamate levels [119]. Given GABA's inhibitory effects and glutamate's excitatory effects on dopaminergic neurons, these actions may result in reductions in dopaminergic activity, suggesting a plausible mechanism for effects on smoking reward. In a smoking cessation efficacy trial, White *et al.* [120] randomised 36 smokers to bupropion or gabapentin and followed subjects for 6 weeks. Gabapentin was well tolerated and led to greater (but nonsignificant) reductions in cigarette consumption, compared with bupropion among those who failed to quit. However, overall quit rates in the final 3 weeks of treatment were only 6% in the gabapentin arm, versus 26% in the bupropion arm of the trial.

### 7.5 Nicotinic agents

#### 7.5.1 Mecamylamine

In humans, mecamylamine, a nonselective nAChR antagonist, is the only medication of this type to be tested as a possible treatment for nicotine dependence. In human laboratory studies, mecamylamine has been shown to reduce nicotine reward and cigarette consumption [121]. However, in some

studies, short-term, but significant, increases in tobacco consumption have been seen following treatment with mecamylamine, a phenomenon referred to as an 'extinction burst' [122,123]. Smokers may initially increase cigarette consumption to overcome the blockade of psychophysiological effects from the medication. However, this short-term increase in smoking may eventually give way to higher quit rates [123].

So far, two clinical trials have examined this agent for treating nicotine addiction, both in combination with nicotine patch. In the first study, Rose *et al.* [124] randomised 48 smokers to patch plus placebo or patch plus mecamylamine 2.5 – 5 mg for 5 weeks. The rate of continuous abstinence for mecamylamine participants was significantly higher than for placebo participants at the end of treatment (50 versus 17%) and at 12 months (38 versus 4%). The second study [123] randomised 80 smokers to mecamylamine 2.5 – 5 mg plus patch, patch only, mecamylamine 2.5 – 5 mg only or no medication for 4 weeks. The rate of continuous cessation among mecamylamine-treated subjects (mecamylamine only and mecamylamine plus NRT) was significantly greater than the rate for nonmecamylamine-treated participants (NRT only plus no drug; 48 versus 28%). At a 6-month follow-up assessment, the mecamylamine plus patch group showed a significantly higher quit rate (40%) versus the pooled data from the mecamylamine-only group (15%), the patch-only group (20%) and the no drug group (15%). Further research is needed to assess if the positive results for nicotine antagonists can be replicated and if mecamylamine's efficacy is dependent on the coadministration of a nicotine agonist [125].

### 7.5.2 Nicotine vaccine

At least three pharmaceutical companies have been exploring the use of immunotherapy or 'vaccines' for the treatment of nicotine addiction. This approach is designed to use nicotine-specific antibodies to prevent nicotine from crossing the blood–brain barrier and to decrease the rate of nicotine metabolism [126,127]. The properties of nicotine vaccines can prevent the reinforcing effects from smoking by blocking access to the brain as well as delaying nicotine withdrawal by slowing nicotine metabolism. Animal studies have shown that nicotine vaccines can reduce the amount of nicotine reaching cortical nicotinic receptors by as much as 65% [127] and attenuate the amount of dopamine stimulated by nicotine [128].

Clinical trials with nicotine vaccines are ongoing, so there are limited data on which to draw conclusions regarding efficacy at this point. Preliminary results have been released for the vaccine Nicotine- $\beta$  (Cytos). Cornuz *et al.* [129] reported that the efficacy of the vaccine depended on the immunogenic response of the smoker; quit rates between placebo and vaccine arms were no different among participants with low immunogenic responses, but quit rates among vaccine participants with a high immunogenic response were significantly greater than for placebo (57 versus 31%). A second nicotine vaccine, NicVax (Nabi), has also been

evaluated in a small study. Hatsukami *et al.* [130] randomised 68 smokers to 50, 100 or 200  $\mu$ g of the nicotine vaccine. Participants received injections on 4 days over a 6-month period and were monitored for an additional 38 weeks. Even though participants were not instructed to quit smoking, 30-day abstinence rates varied significantly across treatment arms, with ~ 40% of participants who received the 200  $\mu$ g dose reporting abstinence, compared with < 10% for the remaining conditions. In addition, the vaccine doses were well tolerated and did not result in compensatory smoking, a potential adverse side effect of nicotinic receptor antagonists. Finally, TA-NIC (Xenova) is currently under investigation in a Phase I trial with 60 smokers. Preliminary results from this trial indicate that the vaccine is well tolerated, immunogenic and yields higher quit rates after 12 weeks versus placebo (43 versus 9% [203]). Collectively, the current data on nicotine vaccines are limited and conclusions regarding their safety and efficacy are premature.

### 7.6 Cannabinoid receptor-1 antagonist

The cannabinoid-1 receptor (CB<sub>1</sub>) modulates dopamine release, thereby influencing motivational processes underlying nicotine dependence [131]. Based on such data, Sanofi-Synthelabo began testing the CB<sub>1</sub> receptor antagonist rimonabant for smoking cessation. In rodent models, this agent reduced nicotine self-administration, while increasing cortical and nucleus accumbens concentrations of serotonin, noradrenaline and dopamine [132].

Three large Phase III trials are assessing the efficacy of rimonabant for smoking cessation. Preliminary results from one study, the Studies with Rimonabant and Tobacco Users (STRATUS-US), have been reported [133]. In this trial, 787 smokers were randomised to placebo or rimonabant 5 or 20 mg for 10 weeks; participants received behavioural counselling and were followed for 42 weeks off-treatment. Using an intention-to-treat analysis, rimonabant 20 mg doubled the odds of quitting versus placebo (OR = 2.0, 95% CI: 1.3 – 3.1); 27.6% of patients on rimonabant 20 mg quit smoking versus 15.6% with rimonabant 5 mg and 16.1% with placebo. In addition, the preliminary data suggest that this agent can prevent postcessation weight gain and indicate that this agent is well tolerated. Although rimonabant has been FDA approved as a pharmacotherapy for weight loss, it has not received FDA approval as a treatment for nicotine addiction. The long-term safety and efficacy record for this medication will remain unknown until the ongoing clinical trials (e.g., STRATUS-Europe) are complete and the results from these trials are published. Nevertheless, rimonabant's potential as a weight loss and smoking cessation drug represents an exciting potential for the identification of an effective method to treat the two leading causes of premature death in the US [134]. The current data on rimonabant also support the continued study of other potential cannabinoid receptor antagonists for treating nicotine addiction.

### 7.7 Topiramate

Recent data suggest that topiramate may deserve additional examination as a treatment for nicotine dependence. This agent has multiple neurobiological effects, including increased dopamine and serotonin release, blockade of AMPA/kainate subtypes of glutamate receptors and activation of GABA neurons [135]. Preliminary studies indicate that topiramate can effectively treat withdrawal from benzodiazepines [136] and opioids [137], as well as alcohol and cocaine dependence [138,139]. So far, only one study has evaluated topiramate for treating nicotine dependence. Johnson *et al.* [140] examined the effects of topiramate on smoking behaviour among individuals enrolled in a treatment programme for alcohol dependence. The overall sample included 150 alcohol-dependent individuals, but a subgroup analysis was conducted with 94 alcohol-dependent smokers. Subjects were randomised to topiramate 300 mg/day or placebo for 12 weeks. Biochemically confirmed cessation at the end of 12 weeks of treatment was significantly greater for topiramate subjects (17%) versus placebo participants (7%). This effect is particularly noteworthy given that abstinence from alcohol use, not smoking cessation, was the objective of the treatment programme, and smoking cessation counselling or instructions were not provided to participants in this trial.

However, a recent study that examined the effects of topiramate on subjective evaluations of nicotine suggests that further investigations of this agent as a treatment for nicotine addiction should be done cautiously. Sofuoglu *et al.* [141] conducted a double-blind crossover study in which participants received either placebo or topiramate 25 or 50 mg followed by either intravenous saline or nicotine. The results showed that administration of topiramate enhanced the subjective pleasurable effects of nicotine. Additional research is warranted to examine the potential for topiramate as a treatment for nicotine addiction, including the evaluation of this agent with non-alcohol-dependent smokers and the examination of the possible mechanism of effect for topiramate.

## 8. Potential developmental issues: pharmacogenetics

The emerging field of pharmacogenetics has the potential to advance the science of nicotine dependence treatment by generating new knowledge about genetic factors that influence clinical treatment outcome. The basic premise of this approach is that inherited differences in drug metabolism (pharmacokinetics) and drug targets (pharmacodynamics) have important effects on treatment outcome [142,143]. Thus, rather than concluding that a medication is ineffective based on overall trial data, one can determine whether a particular treatment is very effective for some smokers, but not at all effective for others [46].

The first publication on pharmacogenetics and bupropion treatment [144] focused on the role of the C1459T variant in

the cytochrome P450 (CYP)2B6 gene, which has been implicated in bupropion kinetics as well as in brain metabolism of nicotine [145]. Smokers with the decreased activity T variant of CYP2B6 (slower metabolisers) reported greater increases in cravings for cigarettes following the target quit date and had significantly higher relapse rates. Among females, greater bupropion efficacy was observed for those with the decreased activity variant. Additional investigations have examined the role of genetic variation in the dopamine pathway, including common polymorphisms in the dopamine transporter gene (SLC6A3 VNTR) and the DRD2 gene (Taq1A, -141C Ins/Del, C957T). There is preliminary support for enhanced efficacy of bupropion among smokers who carry increased activity alleles for DRD2 [146-148]. This effect appears to be modified by CYP2B6 genotype [147]. Finally, there is recent evidence for an association between bupropion treatment outcome and genetic variation in the catechol-*O*-methyl transferase (COMT) enzyme that inactivates dopamine [149].

With regard to NRTs, the role of variation in the nicotine-metabolising enzyme CYP2A6 was examined in the open-label trial of nicotine patch versus nicotine nasal spray. An initial report [150] indicated that CYP2A6 slow metabolisers had significantly higher levels of plasma nicotine after 1 week of nicotine patch treatment, compared with those homozygous for the wild-type alleles. An additional analysis from this trial [151] found that 3-hydroxy-cotinine/cotinine ratio, a phenotypic marker of CYP2A6 activity, predicted both plasma nicotine levels after 1 week of patch therapy, as well as abstinence in this treatment group. The role of dopaminergic genes in response to NRT has been examined in placebo-controlled trial of transdermal nicotine patch conducted in a large general practice group in the UK [152,153]. In contrast to findings for bupropion described above, the patch was found to be significantly more effective than placebo for carriers of the A1 allele of DRD2, which has been associated with decreased receptor density. Consistent with these findings, carriers of the DRD2-141 T allele, associated with decreased transcriptional efficiency, were more likely to achieve abstinence with either form of NRT than those homozygous for the C allele [148]. Furthermore, this effect was moderated by genotype for the dopamine receptor interacting protein neuronal calcium sensor 1 [154]. Functional genetic variation in the COMT gene (val/Met polymorphism) has also been associated with abstinence in the open-label NRT trial [155]. Additional pharmacogenetic analyses of NRT outcome have reported a significant association of the OPRM1 A118G variant with NRT response [156] and no association with the serotonin transporter promoter polymorphism [46]. Although these findings are preliminary and must be validated prior to translation to practice, this field shows promise for refining the delivery of tobacco dependence treatment by tailoring the type, dose and duration of therapy based on the genetic profiles of individuals.

## 9. Expert opinion and conclusion

The potential growth in the worldwide prevalence of smoking, along with the relatively suboptimal response to currently approved medications for nicotine dependence, indicates the need for research to discover new agents for this condition, as well as new methods for using existing agents that can boost treatment response. There is reason for some optimism, with the recent FDA approval of varenicline for treating nicotine addiction. Guided by research pointing to multiple neurobiological mechanisms of nicotine dependence, several additional novel medications that mimic and/or attenuate nicotine's rewarding effects, or reduce nicotine withdrawal, are under investigation. Although existing data are limited or conflicting, there is some evidence for the efficacy of selegiline, fluoxetine, naltrexone and mecamylamine in certain subgroups of smokers. Furthermore, research concerning smoker characteristics related to responsiveness to NRTs and the potential development of fast-acting NRTs may help clinicians to tailor the use of NRT type, dose and duration to the smoker's characteristics, thereby enhancing NRT effectiveness. Likewise, methods to offset the costs of NRT and innovative marketing approaches to increase the appeal of, and access to, NRTs may significantly increase use of NRT products, in turn, broadening the impact of OTC therapies on the population smoking rate. Finally, although the results from pharmacogenetic studies of treatments for nicotine addiction offer limited potential for individualising patient care at this point, future research in this

pioneering area may eventually lead to substantial breakthroughs for individualised treatments for nicotine addiction [157] and additional significant reductions in the worldwide prevalence of smoking. Nevertheless, given the projections for substantial increases in the rate of tobacco use in developing countries, and the lack of resources in these countries to sustain the needed infrastructure for effective treatment for nicotine dependence, efforts must be directed toward the development of low-cost treatments that can be broadly disseminated. Low-cost treatments for nicotine dependence, coupled with innovative marketing of these treatments, should also be seen as a priority in developed countries to further the important advances made thus far in reducing the rate of tobacco use over the past several decades. Partnerships between pharmaceutical companies and government agencies to develop, test and market new treatments for nicotine dependence, as done with treatments for other medical illnesses and diseases, may be critical if additional significant reductions in the worldwide prevalence of smoking are to be realised.

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