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Novel Pharmacological Approaches for Treating Tobacco Dependence and Withdrawal

Current Status

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Abstract

Increasing the diversity and availability of medications for the treatment of tobacco dependence and/or withdrawal, to aid in the achievement of smoking cessation, is crucial to meet the diverse needs of tobacco users. Despite a general awareness that smoking is harmful and widespread interest in smoking cessation, nearly 50 million adults in the US and 1.3 billion worldwide continue to smoke. Nicotine replacement therapies are effective in the treatment of tobacco dependence and withdrawal, but do not meet the needs of all tobacco users. Improvement of tobacco dependence and/or withdrawal treatments is likely to rely on novel

pharmacological approaches that include new chemical entities and new formulations of current drugs. In addition, new indications for treating tobacco dependence and withdrawal show promise for reducing tobacco use and associated disease.

This article focuses on a range of novel pharmacological approaches for the treatment of tobacco dependence and/or withdrawal, including oral and pulmonary nicotine delivery and the following non-nicotinic medications: antidepressants, an α4β2 nicotine partial agonist, an α_2-noradrenergic agonist, cytochrome P450 (CYP) 2A6 inhibitors, opioid antagonists and GABAergic medications. In addition to existing medications, this article addresses novel medications in the clinical development stage and those that have been evaluated previously. Novel medications in the clinical development stage include at least three nicotine vaccines and the cannabinoid receptor acting drug rimonabant. Medications evaluated previously include lobeline, mecamylamine and an anticholinergic drug regimen comprising atropine, scopolamine and chlorpromazine. Having not been approved by major drug regulatory authorities for the treatment of tobacco dependence and/or withdrawal, these medications have been evaluated in an experimental capacity.

Cigarette smoking remains the leading preventable cause of mortality in the US and a leading cause worldwide.[1,2] Globally, more than 1.2 billion people smoke cigarettes, and this is projected to lead to half a billion premature deaths if cessation support and efforts are not accelerated greatly.[3,4] Smoking prevalence and associated premature mortality varies widely across countries, with prevalence generally declining in developed countries and increasing in economically developing nations.[5] There is clearly a need for pharmacotherapies to aid smokers who wish to quit smoking.

The global market for approved tobacco dependence treatment medications was at least $US1.5 billion in 2007 (based on analyses of publically available sales information on leading manufacturers' websites), of which approximately $US1 billion was accounted for in the US. This market has grown slowly but, generally, steadily over the past decade because of factors such as access without prescription, new medications, increasing interest in smoking cessation and restrictions on public smoking. Importantly, while tobacco users make considerable sacrifices to spend their own money on tobacco products,[6] most appear unwilling to make such expenditures for medicines to quit smoking. Thus, precipitous growth in the medication market may require some combination of third-party coverage of costs, and more attractive and effective medicines, as discussed in this article.

The first medication proven safe and effective for treating withdrawal and aiding smoking cessation was nicotine gum, a nicotine replacement therapy (NRT) that was approved by medicine regulatory agencies in many countries in the early to mid-1980s. Since the 1990s, several additional forms of NRT have been approved and marketed, including lozenge, nasal spray, inhaler and sublingual tablet (which is not yet available in the US). Initially, approvals required a doctor's prescription, but since the 1990s, many countries have allowed access to some or all of these products without prescription (i.e. over the counter, general sales or from the pharmacy).

Meta-analyses and direct comparative studies have concluded that the gum, patch, nasal spray and inhaler treatments appear to be equally efficacious.[7-10] All of these NRT products, plus the nicotine lozenge, are endorsed by the US Public Health Service Clinical Practice Guideline[11] as first-line pharmacotherapies for the treatment of tobacco dependence. The WHO has also concluded that these

medications can and should be available to tobacco users throughout the world to help curb the epidemic of tobacco attributable morbidity and mortality.[12] Evidence for effectiveness and cost effectiveness are based heavily on nearly 2 decades of experience with NRT formulations; however, it is clear that current formulations of NRT and modalities of use do not address the needs of all tobacco users (e.g. use to reduce smoking by long-term maintenance).[13] Taken together, these data and observations illustrate both the promise and limitations of medications for treating tobacco dependence and withdrawal.

Improvement of tobacco dependence and/or withdrawal treatments is likely to rely on novel pharmacological approaches that include new chemical entities and new formulations of current drugs, the focus of this article. With the exception of oral and pulmonary nicotine delivery, this article does not address other nicotine-based medications, such as approved NRT products, which have been reviewed elsewhere.[14,15]

The aims of this review are 3-fold. First and foremost, to address non-nicotine-based medications for the treatment of tobacco dependence and/or withdrawal that include antidepressants, an $\alpha 4\beta 2$ nicotine partial agonist, an α_2-noradrenergic agonist, cytochrome P450 (CYP) 2A6 inhibitors, opioid antagonists and GABAergic medications. Second, to address novel medications in the clinical development stage for the treatment of tobacco dependence and/or withdrawal. Last, to address medications that, while not approved by major drug regulatory authorities for the treatment of tobacco dependence and/or withdrawal, have been used previously in an experimental capacity. The former includes at least three nicotine vaccines (i.e. CYT002-NicQb, NicVAX® [1] and TA-NIC) and the cannabinoid receptor acting drug rimonabant. The latter includes lobeline, mecamylamine and an anticholinergic drug regimen comprising atropine, scopolamine and chlorpromazine. While not a focus of this review, pharmacotherapy for tobacco dependence and withdrawal in adolescents is also addressed briefly.

1. Novel Medications and Novel Indications

Novel medications and novel indications of previously existing medications are necessary to assist smokers who want to quit but find current medications unacceptable, ineffective when used as directed, or prefer a treatment that does not use nicotine.[16,17] Furthermore, new medications and indications, whether nicotine containing or not, may benefit public health and have strong commercial potential because they represent more attractive medicines or modalities of using medicines. Thus, increasing the diversity and availability of tobacco dependence and/or withdrawal medications can increase the range of smokers who can be treated, thereby enabling more people to abstain, partially or completely, from continued tobacco use.[16]

Additionally, in the context of a non-specific pharmacotherapy approach to the treatment of tobacco dependence and/or withdrawal, novel medications and novel indications may be well suited to address the varying needs of smokers.[18] In this approach, treatment is delivered in accordance with the smoker's specific symptoms (e.g. nicotine withdrawal, anxiety, depression).[18] For instance, in some smokers, use of antidepressants may alleviate emergent affective symptoms, which, in turn, could facilitate continued abstinence.[18] This is particularly relevant in light of the high prevalence of psychiatric co-morbidity associated with cigarette smoking. Nicotine-dependent individuals with a comorbid psychiatric disorder comprise 7% of the population yet smoke 34% of all cigarettes smoked in the US.[19]

This approach capitalizes on medications that otherwise may have only limited overall efficacy. For instance, while a given medication may be efficacious for only 10–20% of the smoking population at large, it may be efficacious for 20–30% of a specific subpopulation of smokers. A recent estimate indicates that there are 44.5 million adult smokers in the US.[20] Based on this estimate, one can readily imagine that a medication with only

1 The use of trade names is for product identification purposes only and does not imply endorsement.

marginal relative efficacy could have a considerable impact on public health.

Development of novel medications for the treatment of tobacco dependence and/or withdrawal poses multiple challenges for the pharmaceutical industry. One challenge is to develop medications that will address the clinical needs of smokers. A second challenge, while achieving the first, is to avoid the threat of regulation under the highly restrictive provisions of the *Controlled Substance Act* (CSA).[16,21] The threat of regulation is based on the abuse potential of the given medication.[16] Because abuse potential can be influenced by increases in drug dosage and the speed of delivery, drug manufacturers are required to design their formulations or drug delivery systems to maximize desired clinical effects while minimizing undesired effects such as addictiveness.[22] A third challenge, related closely to the second, is to make the product available broadly enough to readily address the needs of large numbers of cigarette smokers, thereby contributing to public health while also ensuring sufficient commercial benefit to justify the effort. Restricting access to a treatment through the provisions of the CSA in the US and/or other regulatory systems internationally[23,24] could pose a serious barrier to consumer use and healthcare acceptance.

1.1 Novel Nicotine Delivery Systems

This section discusses two novel nicotine delivery systems, orally and pulmonary delivered nicotine. The orally delivered nicotine products comprise the nicotine 'Straw' and nicotine drops. The pulmonary delivered product comprises a true pulmonary inhaler.

1.1.1 Oral Nicotine

Orally delivered nicotine products may provide a convenient route of administration by allowing the user to consume nicotine in a beverage. The consumed nicotine would be absorbed from the intestine rather than buccally, as is the case with currently available NRT products. Two products have been proposed for the oral delivery of nicotine: the Straw and nicotine drops.

The Straw is a single-use plastic straw containing small beads of nicotine. When the smoker drinks a beverage through the Straw, the nicotine beads are swallowed. The nicotine is then absorbed from the intestine. The product is designed to be used 10–12 times a day. In a small safety and pharmacokinetic study,[25] 24 smokers who received single doses of 0, 4, 8 or 12 mg nicotine following overnight tobacco abstinence achieved maximum plasma nicotine concentrations of 6.4, 20.1 and 20.3 ng/mL, respectively. The time to maximum concentration ranged from 1.3 h (4-mg dose) to 1.9 h (12-mg dose), which probably makes this administration route too slow for use as a rescue medication, which through timing of self-administration, enables smokers to counter episodes of acute craving. No serious adverse events were reported and adverse events of only mild severity (gastrointestinal disturbance, light-headedness) were reported. Change from baseline craving scores did not differ significantly across treatment conditions. To date, no efficacy data have been published. Evaluating the kinetics and safety of the product is complicated by the potential for interactions with different beverages.

Nicotine drops would allow the smoker to place drops of a nicotine solution into a beverage. In an open-label treatment trial in 25 smokers, nicotine drops appear to have facilitated smoking cessation.[26] The treatment was tolerable and plasma nicotine concentrations were in the range of currently available NRT products. As with the nicotine Straw, difficulties in the assessment of the product would be complicated by potential interactions with different beverages.

1.1.2 Pulmonary Delivered Nicotine

A true pulmonary inhaler, unlike the currently available nicotine inhaler (which actually delivers nicotine into the mouth for buccal absorption), would deliver nicotine to the lung in a manner more comparable to cigarette smoking.

The pulmonary mode of delivery would be expected to reduce background cravings and withdrawal symptoms, and allow for rapid relief of acute cravings. In theory, because the delivery of nicotine directly to the lung would more effectively mimic

the effects of cigarette smoking on a physiological level, the smoker could more readily eliminate the need for tobacco, and subsequently taper the nicotine level over time to alleviate dependence upon nicotine altogether.

There are a number of challenges involved in the development of a pulmonary inhaler.[27] Technical challenges are not small, as the nicotine molecules would need to be condensed appropriately onto particles of approximately 1 micron median diameter to enable inhalation into the pulmonary alveoli, and the nicotine particles would need to be designed appropriately to prevent the production of unacceptably harsh sensory effects. A significant barrier to the development of a pulmonary inhaler is its potential for abuse and the regulatory implications that would follow from a system that delivers pulmonary nicotine at levels comparable to that delivered by a cigarette, especially if it delivers a form of nicotine that could more readily substitute for cigarettes with respect to satisfaction and pleasure – a goal espoused by some public health experts.[28,29] Of all potential forms of NRT, this one seems most likely to raise the real possibility of a form that might be considered sufficiently abusable to merit regulation under the auspices of the CSA.

If a true nicotine pulmonary inhaler meets criteria for a controlled substance, its marketing could be severely restricted along the lines of morphine-like analgesics. Such marketing restrictions could be expected to limit the commercial development of such a product because of the uncertain market for a tobacco dependence and/or withdrawal treatment that is regulated as a controlled substance. This issue may require resolution by WHO if the organization deems it important to encourage development of NRT products that deliver nicotine to the lung or by other means that increase its abuse liability.

1.2 Non-Nicotinic Medications

This section discusses a range of non-nicotinic medications, including antidepressants, an $\alpha4\beta2$ nicotinic partial agonist, an α_2-noradrenergic agonist, CYP2A6 inhibitors, opioid antagonists and GABAergic medications.

1.2.1 Antidepressants

The antidepressants addressed in this section include bupropion, nortriptyline, moclobomide, venlaflaxine, fluoxetine and paroxetine. These drugs have varying mechanisms of action and efficacy, as can be seen in table I and as described in the text. In general, review of table I reveals a fascinating observation: the efficacy of an antidepressant as a tobacco dependence treatment is not limited to a single pharmacological classification or mechanism of action. For instance, bupropion and nortriptyline, two antidepressants with differing pharmacology and mechanisms of action, show clear efficacy; venlaflaxine and fluoxetine, two additional antidepressants with further differing pharmacology and apparent mechanisms of action, show potential efficacy. The commonality is their primary clinical indication as antidepressants. Further investigation of antidepressants as a potential treatment of tobacco dependence, as well as research to better understanding the aetiology of tobacco dependence and the role of depression in tobacco dependence, seems clearly warranted.

Table I. Potencies (inhibition constant [K_i] in nmol/L) of select antidepressants studied for tobacco dependence treatment[30]

Antidepressant	Classification	NE-T	5-HT-T	DA-T	Efficacious
Bupropion	Atypical	52 600	9 100	526	+
Nortriptyline	TCA	4.35	18.5	1 140	+
Moclobomide	MAOI	NR	NR	NR	–
Venlaflaxine	SSRI/atypical	1 060	9.10	9 100	?
Fluoxetine	SSRI	244	0.810	3 600	?
Paroxetine	SSRI	40	0.125	500	–

5-HT-T = serotonin transporter; **DA-T** = dopamine transporter; **MAOI** = monoamine oxidase inhibitor; **NR** = not reported; **NE-T** = norepinephrine transporter; **SSRI** = selective serotonin reuptake inhibitor; **TCA** = tricyclic antidepressant; + indicates demonstrably efficacious as a tobacco dependence treatment; – indicates not demonstrably efficacious as a tobacco dependence treatment; ? indicates potentially efficacious as a tobacco dependence treatment.

The following brief summaries of the current state of the science in this area may make some of the directions for research more apparent.

Bupropion

Bupropion is an atypical antidepressant drug that is only one of two non-nicotine-based prescription medicines approved by the US FDA for the treatment of tobacco dependence. Its mechanism of action is presumed to be mediated by its capacity to block neuronal re-uptake of dopamine and/or norepinephrine.[11] Relative to other antidepressants, bupropion has a relatively high affinity for the dopamine transporter.[30] There is also evidence that it acts as a nicotinic receptor antagonist, as does at least one of its metabolites (i.e. hydroxybupropion), suggesting another potential mechanism by which bupropion could reduce smoking rates.[31,32]

Animal studies demonstrate that bupropion alters the reinforcing and withdrawal effects of nicotine. One study indicates that low doses of bupropion reduce the rewarding effects of nicotine, and the affective and somatic symptoms of withdrawal.[33] Another study examined the effects of bupropion (5–40 mg/kg) on the reinforcing properties of nicotine and food in rats under two different schedules of reinforcement.[34] The authors report that pre-treatment with the highest dose of bupropion (40 mg/kg) resulted in a 50% reduction of nicotine intake in rats self-administering 0.03 mg/kg/infusion of nicotine under a fixed ratio schedule. However, pre-treatment with bupropion does not affect the self-administration of nicotine under a progressive ratio schedule.

These findings, while challenging to interpret, may indicate that a high dose of bupropion decreases the reinforcing properties of nicotine under conditions where doses can be obtained at regular and relatively short intervals, while leaving intact the motivation to work for nicotine when doses are more widely spaced. Additionally, short-[35] and long-term[36] administration of bupropion has been shown to increase extracellular levels of dopamine in the nucleus accumbens, a pathway that has been hypothesized to play a key role in nicotine addiction.

Expanding on these findings, repeated bupropion pre-treatment has been shown to enhance the ability of this agent to decrease nicotine self-administration, perhaps contributing to the efficacy of bupropion as a tobacco dependence treatment. For instance, one study demonstrates that, while bupropion (70 mg/kg) pre-treatment acutely decreases nicotine self-administration by approximately 60–70%, repeated pre-treatment decreases nicotine self-administration completely.[37] Taken together, these results suggest that bupropion has several actions demonstrated in animals that could explain its ability to increase rates of smoking cessation in humans.

Bupropion, like NRT products, has been endorsed by the US Clinical Practice Guideline[11] as a first-line pharmacotherapy for the treatment of tobacco abstinence, thereby providing smokers who wish to give up nicotine altogether and all at once an alternative treatment option to NRT products. Bupropion has been shown to approximately double rates of smoking cessation compared with placebo, and the medication is equally effective for men and women.[38] Clinically, bupropion may act, in part, by alleviating some nicotine withdrawal symptoms that include depression. For instance, one clinical trial has shown that highly nicotine-dependent smokers who receive bupropion are more likely to experience a decrease in depressive symptoms during active treatment.[39] Additionally, in a 2-week study, bupropion 300 mg significantly reduced abstinence-associated increases in rated depression, difficulty concentrating and irritability, and attenuated a decrease in positive affect, relative to placebo.[40] Lending further to the clinical appeal of bupropion is the demonstrable efficacy of the drug in a real-life setting and its cost effectiveness.

Nortriptyline

Nortriptyline is a tricyclic antidepressant (TCA) that inhibits neuronal uptake of norepinephrine, the impetus for its evaluation as a tobacco dependence treatment.[9] It has a relatively high affinity for both the serotonin and serotonin transporters, and some affinity for the dopamine transporter.[30] There is also evidence that nortriptyline acts as a weak nico-

tinic receptor antagonist, suggesting another potential mechanism by which it could reduce smoking rates.[41]

Nortriptyline has been endorsed by the US Clinical Practice Guideline[11] as a second-line (i.e. after first-line treatments have been used or considered) pharmacotherapy for the treatment of tobacco abstinence. Several clinical trials have demonstrated the potential efficacy of nortriptyline as a treatment of tobacco dependence in smokers with[42] and without[43] a history of major depression. Nortriptyline in combination with transdermal nicotine has also been shown to enhance smoking cessation rates above levels seen with transdermal nicotine alone.[44]

A systematic meta-analysis of five randomized clinical trials has suggested that the medication, because of the low cost, should be offered by physicians as a first-line therapy[45] (also see Hughes et al.[41]). The most commonly encountered adverse effects of nortriptyline include fast heart rate, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and low blood pressure on standing.

Moclobemide

Moclobemide is a selective, reversible monoamine oxidase inhibitor (MAOI) that is not available in the US.[46,47] By inhibiting monoamine oxidase, it increases synaptic concentrations of dopamine, serotonin and noradrenaline.[46] Because moclobemide (unlike older, irreversible MAOIs) only weakly potentiates the pressor response induced by tyramine or other indirectly acting sympathomimetics, restrictions on dietary tyramine and concurrent use of over-the-counter decongestants is unnecessary.[47]

Based on its sole evaluation, moclobemide has not shown demonstrable efficacy as a tobacco dependence treatment.[48] The rationale for the evaluation was because smoking inhibits brain monoamine oxidase A and B.[49,50] Thus, substituting moclobemide for smoking might facilitate cessation.[17] In a randomized, double-blind, parallel-group, placebo-controlled, single centre study, heavy (≥20 cigarettes per day) smokers were treated with moclobemide 400 mg/day beginning 1 week prior to their quit date and thereafter for 2 months, reducing to 200 mg/day for another month. In contrast to self-reported abstinence, verified abstinence did not differ significantly between treatment conditions at 6 months or 1 year follow-up. Similarly, no between-group differences were observed on withdrawal, depression and anxiety ratings, or cardiovascular measures. There were no serious adverse effects.[48]

Venlafaxine

Because of its dual pharmacological actions, venlafaxine has been classified both as a selective serotonin reuptake inhibitor (SSRI)[51] and an atypical depressant.[17,30] Venlafaxine, like TCAs, inhibits reuptake of both serotonin and norepinephrine, but, unlike TCAs, lacks anticholinergic and cardiovascular effects.[17,30,51,52] Consistent with its pharmacological action, venlafaxine has a high affinity for the serotonin transporter, but a very low affinity for the dopamine transporter.[30] While an antidepressant, it also has an FDA-approved indication for generalized anxiety disorder,[52] and has been examined as a tobacco dependence treatment, as described here.[51,53]

Venlafaxine has been shown to have only limited efficacy among light smokers as a tobacco dependence treatment.[51] Overall, neither of two double-blind, placebo-controlled clinical trials have shown venlafaxine, in conjunction with behavioural counselling and transdermal NRT, to have a significant treatment effect on short- and long-term abstinence rates at doses of up to 225 mg/day.[51,53] However, in one trial, *post hoc* analysis indicated that light (mean = 12 cigarettes per day) smokers treated with venlaflaxine have significantly higher abstinence rates at end of treatment (18 weeks post-cessation) and 1 year follow-up than those given placebo.[51] Although intriguing and suggestive of possible efficacy, these results will need to be extended and replicated before a recommendation of venlaflaxine as a tobacco dependence treatment can be made.

Fluoxetine

Fluoxetine is an SSRI that has minimal effect on norepinephrine and dopamine re-uptake.[46] Consistent with its pharmacological action, fluoxetine has

a high affinity for the serotonin transporter, but a very low affinity for the dopamine transporter.[30] While an antidepressant, it also has FDA-approved indications for bulimia nervosa and obsessive-compulsive disorder, and has been evaluated as a tobacco dependence treatment, as described here.[52]

Fluoxetine has shown modest, short-term efficacy as a tobacco dependence treatment. Results of a large, randomized, double-blind, placebo-controlled, multicentre, clinical trial reveal that among heavy smokers (mean number of cigarettes per day = 28), doses of fluoxetine 30 and 60 mg/day significantly enhance short-term abstinence rates compared with placebo[54] (also see Saules et al.[55] and Blondal et al.[56]). Moreover, three studies have shown that among abstinent smokers, there is less weight gain associated with smoking cessation while using fluoxetine relative to placebo.[55,57,58]

A potential limitation of fluoxetine as a tobacco dependence treatment is its incidence of dose-dependent, treatment-emergent adverse events.[54] The most common adverse effects of fluoxetine include nausea and somnolence.[54] Taken together, these findings suggest that fluoxetine specifically and SSRI medications in general might be useful for some smokers, particularly those concerned about post-cessation weight gain.

Paroxetine

Paroxetine is an SSRI and CYP2D6 inhibitor.[30] Relative to other antidepressants, its affinity for the serotonin transporter is highest.[30] While an antidepressant, it also has FDA-approved indications for obsessive-compulsive disorder, social phobia and panic disorder, and has been evaluated as a tobacco dependence treatment, as described here.

Based on its single evaluation, paroxetine has not shown promise as a tobacco dependence treatment. In a double-blind, placebo-controlled trial, smokers were treated with paroxetine 20 or 40 mg and nicotine transdermal patch.[59] Abstinence rates at weeks 4, 10 and 26 did not differ significantly across treatments.

Summary

It appears that some, but not all, antidepressant medications are efficacious as tobacco dependence treatments. Bupropion is currently the only antidepressant that has been approved by the FDA for this indication, but several clinical studies have demonstrated the efficacy of nortriptyline as well. Because of the weight of the evidence, the Agency for Health Care Quality and Research Clinical Practice Guidelines[60] lists nortriptyline as a second-line therapy.

The pharmacological mechanism behind the efficacy of specific antidepressants is unclear. For example, while nortriptyline has a very high affinity for the norepinephrine and serotonin transporters (inhibition constant [K_i] = 4.35 and 18.5 nmol/L, respectively),[30] bupropion has a relatively low affinity (K_i = 52 600 and 9100 nmol/L).[30] At the dopamine transporter, both drugs have some level of affinity (bupropion K_i = 526 nmol/L, nortriptyline K_i = 1140 nmol/L).[30] However, paroxetine, which has not been shown to be efficacious as a tobacco dependence treatment, has an affinity for the dopamine transporter similar to that of bupropion and higher than that of nortriptyline. Therefore, the actions of these antidepressants cannot be explained solely by their potency on the monoaminergic receptor sites. In the case of bupropion and nortriptyline, the nicotinic receptor antagonist actions of these antidepressants might be relevant in explaining their efficacy as tobacco dependence treatments.

1.2.2 α4β2 Nicotinic Partial Agonist

A medication that may aid in the treatment of tobacco users who are refractory to current treatments is varenicline, the most recently FDA-approved medication for the treatment of tobacco dependence. It received FDA approval in May 2006 and is used in the US as a prescription tobacco dependence treatment.[61,62] Varenicline is a partial agonist at the α4β2 subtype and a full agonist at the α7 subtype of nicotinic acetylcholine receptors.[63] As such, it putatively inhibits dopaminergic activation produced by smoking, while simultaneously alleviating craving and withdrawal associated with smoking cessation.[64] The development of varenicline was prompted, in part, by another α4β2 nicotinic partial agonist, cytisine,[64] which has been used for 40 years in Eastern Europe to treat tobacco dependence.[65] Moreover, as a derivative of cyti-

sine, which acts on β4-subunit-containing receptors, varenicline also may be active at these receptors.

Characteristic of a partial agonist, varenicline, even at high doses, does not produce the same response as a full agonist. Because there is a ceiling on the effects of a partial agonist, it is plausible that varenicline would have a lower risk of adverse events and a lower abuse potential than a medication containing nicotine. A variety of nicotinic acetylcholine receptor subtypes have been identified with distinct structural and functional properties. The subtype that generally has been identified as being associated with the addictive effects of nicotine is the α4β2.[66] It is plausible that a compound that binds with a high degree of specificity or with a greater affinity to this subtype, relative to nicotine, will have a higher level of safety and possibly a higher level of efficacy. However, to the extent that other subtypes might be associated with these effects, the efficacy could be muted compared with nicotine, which is less specific in its receptor affinity.

Clinical trials of varenicline suggest that the medication is efficacious as a tobacco dependence treatment and safely used. For instance, data reported from two identical randomized, double-blind, placebo-controlled trials with bupropion as a comparator revealed that treatment outcomes were markedly superior with varenicline 1 mg compared with placebo and bupropion 150 mg.[67]

The long-term safety of varenicline has been examined over a 52-week treatment period.[68] In this randomized double-blind trial, subjects either received varenicline 1 mg twice daily or placebo for 52 weeks. Results of the trial revealed that the most frequent adverse events for varenicline were nausea, abnormal dreams and insomnia. Nausea was mostly mild or moderate, and infrequently resulted in treatment discontinuation. Rates for treatment discontinuation due to adverse events were 28.3% for varenicline and 10.3% for placebo. Similar adverse events (i.e. nausea, headache, insomnia and abnormal dreams) emerged from a pooled analysis of the two varenicline and bupropion head-to-head comparison studies described in this section.[67]

1.2.3 α2-Noradrenergic Agonist

Clonidine is an α2-noradrenergic agonist that, in addition to being used in the treatment of hypertension, has been shown to diminish symptoms of both opiate and alcohol withdrawal.[69,70] Hypertension and many withdrawal states, including opioid, alcohol and, perhaps, nicotine, are associated with sympathetic overactivity.[46] The mechanism of action of clonidine for reducing blood pressure and alleviating withdrawal symptoms involves decreasing norepinephrine release, which reduces sympathetic activity.

On the basis of a five-study meta-analysis, clonidine has been endorsed by the US Clinical Practice Guideline[11] as a second-line pharmacotherapy for the treatment of tobacco dependence. Results of the meta-analysis reveal that, compared with placebo, clonidine approximately doubles abstinence rates.

Some evidence suggests clonidine is more effective for women than men.[71-73] For example, one study of heavy smokers who had failed previous attempts to quit found that those treated with clonidine had twice the rate of abstinence as those treated with placebo at the end of the 4-week treatment.[71] This effect continued through the 6-month follow-up. Further analysis of the treatment data revealed a significant clonidine effect for women only.

Similar findings were reported in a study involving highly nicotine-dependent smokers.[73] For instance, among smokers receiving clonidine, significantly higher abstinence rates were observed for women, compared with men, at each of four follow-up visits (at 6, 12, 24 and 52 weeks). These results suggest that clonidine may be efficacious in the treatment of tobacco dependence, but the conditions under which it is most appropriately used are not well defined.

The most common adverse effects of clonidine are constipation, dizziness, drowsiness, dryness of mouth, and unusual tiredness or weakness. However, there are more severe adverse effects that clinicians and patients should be aware of, such as allergic reaction, decreased heart rate, or unusually elevated or decreased blood pressure, as well as

contraindications and drug interactions that should be evaluated prior to prescription.

1.2.4 Cytochrome P450 (CYP) 2A6 Inhibitors

In humans, approximately 70–80% of nicotine is metabolized to cotinine.[74] The majority of this metabolic conversion is catalyzed by the genetically polymorphic CYP2A6 enzyme.[75] Genetic variations in the CYP2A6 allele have been shown to strongly affect both nicotine pharmacokinetics as well as smoking behaviour.[76]

Based on this, it is theoretically possible that inhibition of the CYP2A6 enzyme could be used as a strategy for treating tobacco dependence. Specifically, inhibition of this enzyme could be used as part of a harm reduction strategy to reduce the number of cigarettes consumed. It could also be used along with NRT to enhance the levels of nicotine in the body without increasing the dose of nicotine consumed. For example, compared with placebo, the strong CYP2A6 inhibitors methoxsalen and tranylcypromine, given in combination with oral nicotine, significantly increase mean plasma nicotine concentrations, as well as significantly reduce desire to smoke.[77]

There are currently no CYP2A6-inhibitors indicated for the treatment of tobacco dependence, and the current regulatory environment may be less than favourable for the promotion of this concept. First, harm reduction is not fully recognized as an acceptable strategy, relative to complete cessation. Secondly, it is very difficult to obtain approval for a combination product (e.g. a CYP2A6 inhibitor plus an NRT product) because one would need to show a significant incremental increase in abstinence rates using the combination relative to the use of NRT alone, without any increase in adverse events. An extremely large clinical trial would be needed to demonstrate this effect. In addition, from a marketing perspective, it is likely to be difficult, without a rather large incremental benefit, to convince consumers to spend money on two medications when there are single-drug therapies available.

1.2.5 Opioid Antagonists

The opioid system may be involved in the reinforcing properties of several drugs of abuse, and may be involved in the reinforcing properties of nicotine. This may imply that opioid antagonists may attenuate the reinforcing value of cigarette smoking. Opioid receptor antagonists, such as naloxone and naltrexone, have demonstrable efficacy in decreasing cigarette consumption and self-reported smoking satisfaction and increasing smoking cessation rates,[78-81] suggesting that opioid receptors may modulate the reinforcing effects of nicotine[82] (also see Sutherland et al.[83] and Nemeth-Coslett and Griffiths[84]). Opioid antagonists addressed in this section include naltrexone and nalmefene.

Naltrexone

Naltrexone is an opioid antagonist that has been shown to be effective for the treatment of alcohol dependence and it has recently been approved for this indication by the FDA.[85] Two studies have examined the effects of naltrexone during smoking abstinence.[83,86] These studies generally demonstrated little effect of naltrexone on tobacco withdrawal, smoking behaviour or satisfaction from smoking. Currently available data provide little support for the use of naltrexone as a tobacco dependence treatment.

Nalmefene

Nalmefene is another opioid antagonist currently marketed in the US as an injectable formulation. A recent phase II study of an oral formulation of the drug suggests that it may have some efficacy as a tobacco dependence treatment.[87] In this trial of 76 smokers, patients taking nalmefene 40 mg experienced higher abstinence rates at all timepoints relative to placebo, although the duration of the trial was not reported. However, those subjects who received an 80 mg dose of the product did not achieve abstinence rates that were numerically superior to placebo. The report stated that the drug was generally well tolerated, and the most common adverse events were insomnia and nausea.

1.2.6 GABAergic Agents

In theory, medications that affect GABA neurotransmission may decrease the reinforcing properties of nicotine, and thus may be useful as a tobacco

dependence medication.[82] Dopaminergic neurons projecting from the ventral tegmental area (VTA) to the nucleus accumbens[88] receive descending GABAergic input from the ventral pallidum and the nucleus accumbens.[89,90] Dopaminergic tone in the VTA and nucleus accumbens is inhibited by these GABAergic neurons.[91,92] At the VTA, inhibition of dopaminergic activity involves GABAergic inhibitory afferents to dopaminergic ventral tegmental neurons[89,93] and interneurons within the VTA.[94] In the nucleus accumbens, inhibition of dopaminergic activity involves medium spiny GABA neurons.[94] Based on this, a medication that modulates GABA could be a useful tobacco dependence treatment. GABAergic medications addressed in this section include: vigabatrin, baclofen, gabapentin and tiagabine.

Vigabatrin

Administration of vigabatrin (γ-vinyl-GABA or GVG), an irreversible GABA transaminase inhibitor,[95] abolishes expression and acquisition of conditioned place preference, nicotine-induced increases in synaptic dopamine,[96] and dose-dependently decreases nicotine self-administration in rats.[95] Vigabatrin is not currently approved in the US, but it is currently marketed in many countries as a treatment for epilepsy. However, because of the adverse effect profile, the medication is not likely to be a candidate for treating tobacco dependence.

Baclofen

Baclofen, a selective $GABA_B$ agonist, has been shown to have some promise as a treatment for cocaine dependence.[97,98] There is also clinical and preclinical evidence that baclofen could be useful for treating tobacco dependence. Baclofen decreases nicotine self-administration in rats,[99,100] suggesting that enhancement of GABA transmission via $GABA_B$ receptors may antagonize the reinforcing effects of nicotine. However, the effects of baclofen on tobacco smoking have been examined in only one clinical study.[101] Acute administration of baclofen was not demonstrably efficacious in reducing cigarette smoking or nicotine craving ratings.

Gabapentin

Gabapentin is an antiepileptic medication, which is structurally related to the neurotransmitter GABA, but it does not modify $GABA_A$ or $GABA_B$ binding, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.[102] In a small, open-label, smoking-cessation trial,[103] only 1 of 17 subjects in the gabapentin group demonstrated continuous abstinence between weeks 3 and 6 post quit, compared with 5 of 19 subjects in a group of subjects who received bupropion. This suggests that gabapentin is unlikely to be useful as a tobacco dependence treatment.

Tiagabine

Tiagabine is also an antiepileptic medication that has received some attention as a tobacco dependence treatment. Tiagabine enhances the activity of GABA by binding to recognition sites associated with the GABA uptake carrier.[102] By this action, tiagabine blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding on the surfaces of post-synaptic cells. There has been little study of this medication in smokers. However, one study has shown a significant treatment effect for the subjective responses to nicotine, such that tiagabine, compared with placebo, attenuates the ratings of 'good effects' and 'drug liking'.[104] Tiagabine treatment also attenuates the craving for cigarettes and enhances the cognitive performance in abstinent smokers.

Taken together, these results indicate that there are neurobiological mechanisms by which medications that affect GABA neurotransmission might be useful as a tobacco dependence treatment. There has been relatively little study of these medications, particularly in clinical trials. However, because of the preclinical and laboratory data collected thus far, it appears possible that a medication that interacts with GABA could prove beneficial.

1.3 Novel Medications in the Clinical Development Stage

This section addresses medications in the clinical development stage, namely, nicotine vaccines and

rimonabant. Nicotine vaccines discussed include CYT002-NicQb, NicVAX® and TA-NIC.

1.3.1 Nicotine Vaccines

A vaccine against nicotine induces antibodies that can bind nicotine molecules in plasma before the drug reaches the neural receptors that produce effects normally associated with smoking. For example, in one study, rats received either active or placebo vaccine, and 30 minutes later received nicotine at 0.03 mg/kg intravenously, equivalent on a mg/kg basis to the nicotine intake from two cigarettes by a smoker.[105] Compared with control, the active vaccine reduced the brain nicotine concentration in a dose-related manner (65% reduction at the highest dose of vaccine). Pre-treatment with active vaccine also reduced the distribution of nicotine to the brain when five repeated doses of nicotine (equivalent to the nicotine intake from ten cigarettes) were administered over 80 minutes. Because vaccines reduce the amount of nicotine that reaches the brain and neural receptors, it would be predicted that the reinforcing effects of nicotine would be reduced substantially. This was supported in one study that showed that immunization with a nicotine vaccine prevented the nicotine-induced increase in dopamine release in the shell of the nucleus accumbens, a biochemical correlate to the rewarding properties of nicotine.[106] Another study revealed that exposure to nicotine after a period of extinction does not reinstate self-administration of nicotine among immunized rats, suggesting a muted reinforcing effect of nicotine.[107]

The potential mechanism and clinical utility of a nicotine vaccine is intriguing. In theory, by greatly reducing or eliminating the nicotine that reaches the brain, the reinforcing efficacy of tobacco smoking would also be reduced, eventually leading to extinction of the behaviour (smoking). However, if the amount of nicotine that reaches the brain is reduced, rather than completely eliminated, it is possible that some smokers would actually increase tobacco consumption, at least in the short-term, in order to achieve the levels of nicotine obtained normally during smoking. Results of early research suggest that a nicotine vaccine would be useful as a relapse prevention treatment. The observation that animals do not reinstate nicotine self-administration after extinction when treated with vaccine[107] suggests that, among people who quit smoking, a lapse (a single smoking bout) may not result in a full blown relapse because of the reduced reinforcing value of smoking. Finally, nicotine vaccines could theoretically be used in adolescents to prevent initiation of tobacco use. However, the risks, benefits and ethical implications of such an intervention will undoubtedly require much more thorough evaluation before such application could be recommended.[108]

There are at least three companies that have an anti-nicotine vaccine in early clinical development: Cytos (CYT002-NicQb), Nabi (NicVAX® [Nicotine Conjugate Vaccine]) and Celtic Pharma (TA-NIC).[109]

CYT002-NicQb

CYT002-NicQb is based on the virus-like particle formed by the recombination coat protein of the bacteriophage Qb. In a phase I study of 40 healthy non-smoking volunteers, participants received two intramuscular injections of CYT002-NicQb or placebo at intervals of 4 weeks.[110] Nicotine-specific IgM antibodies became apparent after day 7 and nicotine-specific IgG antibodies were observed by day 14. Antibody levels were boosted by the second injection. The vaccine was shown to be safely used and well tolerated. In a double-blind, phase II study, 340 moderate to heavy smokers were immunized five times with CYT002-NicQb or placebo at monthly intervals.[111] Continuous abstinence between month 2 and month 6 was slightly, but not significantly, higher in those in the active arm of the study. However, a robust effect was observed in a subgroup of subjects with the highest anti-nicotine antibody titres. Furthermore, there was no indication that smokers who resumed smoking attempted to compensate for the neutralizing effects of nicotine by smoking more.

NicVAX®

NicVAX® is a nicotine-recombinant *Pseudomonas aeruginosa* exprotein A conjugate vaccine. In a phase II study, smokers (n = 68) who were not interested in quitting were assigned to one of three

doses of the nicotine vaccine or placebo.[112] Subjects were injected on days 0, 28, 56 and 182, and monitored for a period of 38 weeks. Results show that the nicotine vaccine was safely used and well tolerated. Vaccine immunogenicity was dose related, with the highest dose eliciting antibody concentrations within the anticipated range of efficacy. In addition, although not a trial of smoking cessation, the 30-day abstinence rate was significantly different across the four doses, with the highest rate of abstinence occurring with the highest dose of NicVAX®. There was no evidence of compensatory smoking or precipitation of nicotine withdrawal with the nicotine vaccine.

TA-NIC

TA-NIC is an immunotherapeutic vaccine.[113] It has been evaluated in the UK in two phase I–II studies involving 120 smokers.[114] Results of these studies revealed no unexpected adverse events and indications of efficacy in the TA-NIC group compared with placebo.[114] Enrolment for a large phase IIb study (>520 participants) in the US was completed in October 2007.[115] This placebo-controlled, double-blind, multicentre, dose-ranging (two vaccine doses) study is evaluating the safety and efficacy of TA-NIC in managing smoking cessation when given in combination with current standard support treatments (e.g. counseling and behavioural modification).[114,115] The primary endpoint of the study is the 6-month smoking abstinence rate.[114,115] Initial results are expected in Q2 2008.[115]

In summary, it appears that nicotine vaccines may be efficacious as a tobacco dependence treatment. However, it is likely that approval and marketing of these products will not occur for at least 2–3 years.

1.3.2 Rimonabant

A new medication that may aid in the treatment of tobacco users who are refractory to current treatments is rimonabant, a cannabinoid antagonist that acts by selectively blocking cannabinoid-1 (CB1) receptors. Published data indicate the potential of rimonabant for treating tobacco dependence and withdrawal as well as for weight loss. In 2006, rimonabant was approved for marketing in Europe for weight control, but not smoking cessation, and was judged to be potentially approvable in the US for weight control. The ruling on an eventual smoking cessation indication is unclear. The European approval for rimonabant is as an adjunct to diet and exercise for the treatment of obese patients or overweight patients with associated risk factors, such as type 2 diabetes mellitus or dyslipidaemia.[116] For public articles discussing the US and European actions on rimonabant please see drugdevelopment-technology.com[117] and Sargent.[118]

The CB1 receptor plays a role in the regulation of appetitive behaviour (e.g. food and water consumption, drug self-administration). For example, one study has shown that exogenously administered cannabinoid receptor agonists stimulate food consumption in animals and humans.[119] Furthermore, the endocannabinoid system appears to at least partially mediate the effects of nicotine in rodents. For instance, in an extensive evaluation of its motivational effects, rimonabant has been shown to decrease nicotine self-administration even though it was not functioning as a 'substitute' with respect to physiological and other behavioural effects.[120] This is evidenced by the following findings: administration of rimonabant (0.3 and 1 mg/kg) decreases nicotine self-administration (0.03 mg/kg/injection); and, rimonabant (0.3–3 mg/kg) neither substitutes for, nor antagonizes, the nicotine cue in a nicotine discrimination procedure. Secondly, using brain microdialysis, rimonabant (1–3 mg/kg) blocks nicotine-induced dopamine release in the shell of the nucleus accumbens and the bed nucleus of the stria terminalis. These results suggest that activation of the endogenous cannabinoid system may participate in the motivational and dopamine-releasing effects of nicotine.

STRATUS-US (STudies with Rimonabant And Tobacco USe – US) is the first of three studies of rimonabant for the treatment of tobacco dependence to be completed, and the findings of this study were presented at the 2004 American College of Cardiology annual meeting.[121] The study found that rimonabant was an efficacious tobacco dependence treatment. Also, consistent with the role of cannabinoid

receptors in the regulation of appetitive behaviour, was the finding that smokers who quit in the rimonabant group gained less weight than those that quit in the placebo group. Weight gain is a common adverse effect of smoking cessation, with the average gain being as much as 13 pounds (5.9 kg) after 1 year of continuous abstinence.[122] Furthermore, many smokers report weight gain to be one of the factors associated with relapse.[123] Thus, a medication that reduces the weight gain associated with cessation may decrease the likelihood of relapse during a quit attempt.

The most common adverse effects of rimonabant where incidence was higher with rimonabant 20 mg than placebo were nausea and upper respiratory tract infection. No cardiovascular safety concerns were identified with rimonabant. Thus, rimonabant appears to be a safely used and effective tobacco dependence treatment with a novel mechanism of action that can prevent the post-cessation weight gain viewed by many smokers as an adverse effect of quitting.

Regulatory approval of rimonabant for the treatment of tobacco dependence apparently will require additional clinical trials because the existing studies were not considered definitive by the FDA or European regulatory authorities. Whether such trials will be conducted and an application submitted for a tobacco dependence or smoking cessation indication is unknown, but undoubtedly, any decision by the manufacturer, Sanofi, will consider factors such as commercial potential and how such an indication may affect the weight control market.

1.4 Novel Medications Evaluated Previously

This section addresses novel medications that have been evaluated previously for the treatment of tobacco dependence, and includes lobeline, mecamyline and a prescribed anticholinergic drug regimen comprising atropine, scopolamine and chlorpromazine. Shortcomings common among these drugs include little or no efficacy and/or a poor adverse effect profile.

1.4.1 Lobeline

Lobeline, along with nicotine, was one of the first drugs ever used as a tobacco dependence treatment.[124] It is an alkaloid, classified as a partial nicotinic agonist, that is derived from *Lobelia inflata*, an Indian tobacco plant.[125] Lobeline has been used widely in a variety of proprietary tobacco dependence treatments.[125]

A recent review by Stead and Hughes[125] examined the effectiveness of lobeline in achieving long-term smoking cessation. The review failed to identify any adequate long-term trials that could provide evidence that lobeline can aid smoking cessation. The authors concluded that, based on the trials published in the past 60 years, there is no evidence that lobeline can help people quit smoking. The review indicated further that even short-term studies fail to provide consistent evidence that lobeline has an effect on smoking behaviour.

The adverse effects of lobeline include nausea, dizziness and vomiting. Lobeline-containing tablets and pastilles may produce throat irritation.[125]

1.4.2 Mecamylamine

Mecamylamine is a non-competitive antagonist at the nicotinic acetylcholine receptor site. In theory, a nicotinic antagonist would block the physiological and reinforcing effects of cigarette smoking, which should subsequently decrease the reinforcing value of smoking, which, in turn, would lead to extinction of the behaviour.

When mecamylamine is administered to smokers, it has increased rather than decreased *ad libitum* smoking behaviour, presumably because smokers' compensated for partial receptor blockade, but has also attenuated smoking satisfaction as well as other physiological, behavioural and reinforcing effects of nicotine.[126] These effects are consistent with a partial pharmacological blockade. There is some evidence that mecamylamine may be useful for some recalcitrant smokers as a tobacco dependence treatment.[127] However, the adverse effects of the medication (e.g. hypotension, constipation) may limit its utility.[128]

Mecamylamine in combination with nicotine transdermal medication has been investigated as a

tobacco dependence treatment, and may produce better cessation outcomes than nicotine alone. One randomized, double-blind, placebo-controlled, clinical trial has shown that a combination of the nicotine patch plus mecamylamine produces end-of-treatment abstinence rates 3-fold higher than those for nicotine patch alone, with benefits for the combined treatment group remaining apparent through 12 months.[129] Mecamylamine also significantly reduces cigarette craving, negative affect and appetite. However, adverse effects such as constipation and dizziness were common. These results suggested that mecamylamine, combined with nicotine replacement, may ultimately prove to be a useful aid in treating tobacco dependence. A more recent randomized, double-blind, controlled, multicentre trial found that a combination nicotine/mecamylamine transdermal delivery system did not yield incremental efficacy over nicotine patch alone.[130] These results suggest that effects potentially gained by adding mecamylamine to NRT are small.

1.4.3 Atropine, Scopolamine and Chlorpromazine Combination

Anticholinergic drugs act primarily at muscarinic sites in the cerebral cortex, which are involved in the mediation of nicotine withdrawal.[131] Blocking these sites may eliminate withdrawal symptoms associated with smoking abstinence.[131]

A pilot study examining the effects of a prescribed anticholinergic drug regimen comprising atropine, scopolamine and chlorpromazine for the treatment of tobacco dependence was conducted in the 1980s and reported in brief form.[131] The study has never been replicated, and its theoretical rationale is unclear in that the anticholinergics studied were muscarinic antagonists, not nicotine antagonists. Worth noting, all of the anticholinergics studied, whether taken individually or together, could yield adverse effects that could make people very uncomfortable. Consequently, it is possible that any therapy that makes people generally uncomfortable may produce some nonspecific reduction in smoking.

1.5 Pharmacotherapy for Tobacco Dependence and Withdrawal in Adolescents

Because the risks of long-term dependence and premature mortality are so high for tobacco-using youth, this population might seem to be prime candidates for pharmacotherapy use. The benefit-to-risk ratio for pharmacotherapy for dependence and withdrawal is widely considered to be highly favourable for most adult cigarette smokers, except where contraindications are present.[11] However, in contrast, there is less evidence of benefit for adolescents, no validated guidance for dose selection as well as a broader range of concerns, thus, supporting a higher degree of caution in the use of pharmacotherapy.[132-134] Concerns include the possibility that use of a nicotine medication could exacerbate the addiction in a young person who may have quit smoking by adulthood, as many do,[132,133] and the possibility that use of antidepressants may increase the risk of suicidal thoughts.

The over-the-counter labelling of nicotine replacement products in the US reflects the current uncertainties in benefit-to-risk ratio by including adolescents among the three special populations that warrant consultation with a health professional before using the medications (along with pregnant women and individuals with a history of heart disease). In fact, no tobacco dependence treatment pharmacotherapy is labelled as proven safe and effective for adolescents, although labelling does not categorically contraindicate such use of the medications, except for varenicline. The US Clinical Practice Guidelines[11] supports use of nicotine replacement medications and buproprion in adolescents with a 'C' level of evidence as compared with the 'A' level of evidence for adults, which is consistent with the theory and preliminary data that such medicinal use might be considered, while reflecting greater concerns and less evidence of benefit. The guidelines were last revised prior to the approval of varenicline.[11]

In consideration of nicotine replacement medications and bupropion for adolescent tobacco users, the following studies offer a useful perspective. For

example, nicotine replacement medications have generally been shown to be well tolerated in adolescents.[135-138] However, the results on efficacy are mixed, with some positive results shown for patch, and no positive results shown for gum. One randomized clinical trial found that adolescents who were given nicotine patch had abstinence rates significantly higher than those given placebo.[135] Another study did not find significantly higher rates of abstinence for active versus placebo patches, but did find a significant reduction in withdrawal and craving in the active group.[136] A third study of nicotine patch found no effect on abstinence relative to placebo.[138] A study that compared nicotine patch with nicotine patch plus bupropion found no difference between the treatment groups, but did find high rates of sustained abstinence in both groups.[139] In a placebo-controlled study of nicotine gum in adolescents, there was no significant treatment effect.[135]

We are not aware of any randomized, placebo-controlled trials of bupropion for smoking cessation in adolescents. As mentioned in the previous paragraph, one study found that bupropion plus nicotine patch produced high rates of cessation; however, there was no incremental efficacy relative to nicotine patch alone.[139] An open-label trial of bupropion in adolescents found high rates of efficacy.[140] In both of these studies, the drug was well tolerated. However, product labelling cautions that bupropion may increase the risk of suicidality in adolescents; thus, this risk must be considered in prescribing this medication to adolescents as an aid for smoking cessation. There are no published studies addressing the risks and benefits of varenicline in adolescent cigarette smokers.

Taken together, present evidence suggests that for adolescents, behavioural therapies should be attempted before medications are used and that medications should be used with oversight by a health professional and consideration of additional labelled guidance and cautions.[132] Judicious use of the medications for youth who are refractory to behavioural treatments should not be ruled out because youth clearly do become addicted to tobacco, showing evidence of both dependence and withdrawal,[141] and it is pharmacologically plausible that the medications could be of benefit. Clearly, additional research is needed to provide a strong foundation for guidance for the use of existing medications in adolescence, and possibly the development of new pharmacotherapies. For example, further research on the trajectory from initial tobacco use to dependence and the measurement of dependence severity are among key questions to be explored to develop a strong foundation for adapting treatment to adolescents.[142-144]

2. Conclusion

It is now clear that treatment of tobacco dependence can be a cost-effective path to disease control and prevention of premature mortality by aiding smoking cessation. Moreover, there is clearly a need for pharmacotherapies to aid smokers who wish to quit smoking, but who are unable to quit without such assistance. However, it is equally clear that many people find currently available treatments ineffective or unacceptable. Thus, the benefits and limitations of presently available treatments provide a powerful impetus for further treatment development.

This article has focused on a range of novel pharmacological approaches for the treatment of tobacco dependence, including oral and pulmonary nicotine delivery and the following non-nicotinic medications: antidepressants, an $\alpha 4\beta 2$ nicotine partial agonist, an α_2-noradrenergic agonist, CYP2A6 inhibitors, opioid antagonists and GABAergic agents. Among existing medications, the most efficacious ones include the anitdepressants bupropion and nortriptyline, the partial nicotinic agonist varenicline and the α-noradrenergic agonist clonidine. Consistent with their demonstrable efficacy, bupropion has been endorsed by the US Clinical Practice Guideline[11] as a first-line pharmacotherapy for the treatment of tobacco dependence, while nortriptyline and clonidine have been endorsed by the US Clinical Practice Guideline[11] as second-line pharmacotherapies for the treatment of tobacco dependence.

The population of tobacco users within the US and globally is enormously diverse and so are the aetiological factors contributing to their dependence. Therefore, it seems extremely unlikely that any single therapy will prove to be effective and acceptable for all tobacco users. As indicated here, there are fewer than ten different medications approved by the FDA or at least recognized by the US Public Health Service Clinical Practice Guideline[11] as effective aids to smoking cessation through the treatment of tobacco dependence and/or withdrawal. It is plausible that differences in route of administration, behavioural effort, adverse effects and pharmacology would result in differences that would lead to some individuals finding only a specific product acceptable and effective, although some cigarette smokers might be equally likely to achieve cessation with any of several medications. This conclusion, in turn, suggests that with each new type of medication, it is likely that the fraction of the population of cigarette smokers that could be effectively treated is increased, but that the incremental increase may be small and not identical across products.

Essentially, new medications that, independent of their absolute efficacy, prove effective in people who are refractory to presently available treatments may serve as optimal alternatives to otherwise equally efficacious existing treatments. In such scenarios, new medications would have a considerably higher relative efficacy than currently available medications. The degree to which new medications are acceptable and efficacious in new populations will be an important determinant of their ultimate contribution to public health.

A treatment implication is that people should be encouraged to try alternate treatments, should they find initial treatments unacceptable or ineffective. This is analogous to treating other chronic disorders such as asthma, hypertension, or diabetes (as has been discussed by McLellan et al.[145,146]) or, for that matter, depression, pain, insomnia, and many other diseases and conditions for which the first medication or medications developed may have been inadequate for any number of reasons. If, in addition to medication type, we add the possibility of medication combinations (e.g. nicotine patch plus gum and/or bupropion) and novel applications (e.g. nicotine patch preloading, using medications to reduce smoking until ready to quit), it is plausible that the range of potentially treatable tobacco users could be expanded further. This approach to treatment may be best embodied by the Mayo Clinic Nicotine Dependence Tobacco Treatment Center, which appears to produce overall strong treatment results by its willingness to apply one treatment after another, and/or in combination, until benefit is achieved.[147,148]

A novel application mentioned here that warrants further discussion is nicotine patch preloading. Compared with placebo, pre-cessation use of nicotine patch has been shown to more than double (23% vs 50%) continuous abstinence rates at 4 weeks and nearly double (12% vs 22%) sustained abstinence rates at 6 months.[149,150] Importantly, nicotine pretreatment has been shown to be well tolerated and equally effective in light and heavy smokers.[150]

It is also possible that medications could be used in new ways to reduce the long-term disease risk of smoking. For example, medications might enable lasting smoking reduction in persons unable or unwilling to completely give up tobacco, thus reducing disease risk. Alternatively, by enabling short-term abstinence through the treatment of withdrawal, medications may prove to be an important gateway to eventual complete cessation.

A drug development implication is that it is likely that public health and medicine will be well served by continued exploration of new medications, modes of delivery, and protocols for use to ever expand the ability to effectively help people achieve lasting abstinence or perhaps at least lasting, clinically significant reductions in tobacco toxin exposure. This article does not make clear what direction in development would most likely have the greatest public health impact so it would seem premature at this time to either rule in or out technologically feasible new approaches. The seriousness of unremitting cigarette smoking with respect to individual health and public health begs for increased, not diminished, dedication to research, development

and regulatory flexibility in the search for more effective use of existing treatments and development of new treatments.

In closing, perhaps the most striking conclusion of the present review is drugs with widely differing mechanisms of action can be effective in the treatment of tobacco dependence and/or withdrawal, suggesting that the drug development net be broadened further in the search for medications to help turn the tide on one of the most devastating epidemics in human history.

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