# Non-Nicotinic Therapies for Smoking Cessation

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## Key Words

bupropion, varenicline, vaccines, rimonabant, CYP2A6, nicotine metabolism

## Abstract

Cigarette smoking is the primary cause of numerous preventable diseases; as such, the goals of smoking cessation are both to reduce health risks and to improve the quality of life. Currently, the first-line smoking cessation therapies include nicotine replacement products and bupropion. The nicotinic receptor partial agonist varenicline has recently been approved by the FDA for smoking cessation. A newer product currently under development and seeking approval by the FDA are nicotine vaccines. Clonidine and nortriptyline have demonstrated some efficacy but side effects may limit their use to second-line therapeutic products. Other therapeutic drugs that are under development include rimonabant, mecamylamine, monoamine oxidase inhibitors, and dopamine receptor D3 antagonists. Inhibitors of nicotine metabolism are also promising candidates for smoking reduction and cessation. In conclusion, promising new therapeutic products are emerging and they will provide smokers additional options to assist in achieving smoking cessation.

## INTRODUCTION

It was more than four decades ago when the first Surgeon General's Report on Smoking and Health provided irrefutable evidence that smoking is a cause of many cancers and other diseases (**http://www.cdc.gov/Tobacco/sgr/sgr_1964/sgr64.htm**). Forty years later, tobacco smoking remains the single most preventable cause of death in the world, responsible for the death of one in ten adults annually (**http://www.who.int/tobacco/en/**). Despite successes in the public health and legislative forefronts [WHO Framework Convention on Tobacco Control (**http://www.fctc.org**)], hundreds of millions of smokers suffer from the consequences of cigarette smoking. Studies have suggested that the cumulative risks of death owing to cardiovascular and lung diseases can be drastically reduced if smokers stop smoking, even late in life (1, 2). Therefore, smoking cessation and harm reduction are means to reduce health risks associated with smoking and to improve the quality of life.

Smoking is a complex and regulated behavior that is influenced by both genetic and environmental factors (3, 4). Nicotine is the primary component of tobacco that is responsible for reward and reinforcement, as well as the withdrawal effects of cigarettes (3, 5, 6). Nicotine activates nicotinic acetylcholine receptors (nAChRs) in the CNS, and one physiological effect of nAChR activation is dopamine release in the nucleus accumbens, a region important for the rewarding properties of the drug (7). Tobacco dependence is due, in part, to both acute and chronic tolerance to nicotine effects; acute tolerance to nicotine is associated with activation and desensitization (8–10) of nAChRs, whereas chronic tolerance is related to receptor upregulation (11–16). Due to the central role of nicotine on reward pathway activation, the degree to which a smoker achieves "satisfaction" from smoking is to a large extent related to the amount of nicotine obtained from the cigarette (6). Smokers titrate their smoking behaviors to maintain an optimal amount of nicotine in the plasma and brain (5, 17, 18); therefore, the number of cigarettes smoked (nicotine acquired) is influenced by the systemic availability of nicotine (19). These findings provided the rationale for the use of nicotine as a means to reduce smoking.

Nicotine replacement products are the first line treatments for nicotine dependence approved by the U.S. Federal Drug Administration (FDA). Currently, there are many nicotine delivery devices available on the market—these include gum, transdermal patch, vapor inhaler, nasal spray, lozenge, and sublingual tablet. These treatments enhance cessation by delivering nicotine without the exposure to carcinogenic compounds found in cigarette smoke. The use of these nicotine replacement products has led to varying degrees of success in long-term smoking cessation (20, 21) which has been reviewed extensively elsewhere (22–24). The only non-nicotine medications approved by the FDA for smoking cessation are the antidepressant bupropion (Zyban, Wellbutrin) and the nicotinic receptor partial antagonist varenicline (Chantix). In addition to these therapies, other pharmacological compounds are also being developed as adjuncts to smoking cessation. Newer treatments in development include nicotine vaccines and rimonabant. At the time of preparation of this review, one of the nicotine vaccines (Nabi Biopharmaceuticals) had received fast-track review status by the FDA.

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## BUPROPION

Smoking and depression are highly associated, with both being influenced by dopamine levels (25, 26). As a result, a number of antidepressants have been examined for their effects on cigarette consumption. The atypical antidepressant bupropion is the only non-nicotine product approved as a first-line therapy for smoking cessation. The precise mechanisms of bupropion that are responsible for smoking cessation are not well understood; however, the effect may be partly related to the bupropion's ability to reduce cravings in abstinent smokers and to alleviate certain symptoms associated with withdrawal (27–30). Bupropion, at therapeutic doses, can bind to striatal dopamine transporters (~20% occupancy) and potentially prevent dopamine reuptake (31, 32), thereby reducing negative withdrawal symptoms. The noradrenergic system is also implicated in the pharmacological effects of bupropion. At pharmacologically relevant concentrations bupropion reduces the firing rates of noradrenergic neurons in the locus coeruleus (33), which contains neuronal projections to the hippocampus, a region implicated in drug dependence (34). However, the precise mechanism of bupropion's effects on the function of the noradrenergic system is unclear. Bupropion can also act as a noncompetitive antagonist of nicotinic receptors, suggesting that bupropion may attenuate the rewarding effect of nicotine (35–37). Finally, the metabolites of bupropion, in particular hydroxybupropion, have been demonstrated to be pharmacologically active (38); the individual effects of these metabolites on nicotine dependence have not been clarified (38, 39). The vast majority of studies have demonstrated that bupropion is more effective at improving smoking cessation than placebo (27, 40–48), with some studies showing no significant improvement in cessation rates (49, 50). Over the past few years a large amount of data has been gathered with regards to the safety of bupropion use for smoking cessation in a community setting. Overall, the drug caused few serious adverse reactions—the primary reasons associated with discontinuation of treatments were insomnia, nausea/vomiting, and dizziness (51).

## VARENICLINE

Varenicline is a partial agonist of the $\alpha4\beta2$ nicotinic cholinergic receptor; the structure of varenicline is based on the alkaloid extract cytisine from the plant *Cytisus laburnum L.* (52). As with varenicline, cytisine is also a partial agonist of the $\alpha4\beta2$ receptor (53). In parts of Europe, extracts of this plant (Tabex) are used as smoking cessation treatment (54, 55). In mouse studies, the $\beta2$ receptor subunit is required for nicotine reward as measured by conditioned place preference and receptor upregulation during chronic nicotine treatment, and the $\alpha4$ receptor subunit is important for reward and development of tolerance to nicotine (56–58). Varenicline was hypothesized to reduce nicotine-mediated activation of the dopaminergic system via partial blockade of receptor stimulation by high levels of nicotine during smoking, thus lowering the rewarding effects of nicotine. In addition, by acting as a weak agonist, varenicline could also stimulate dopamine release in the mesolimbic region and reduce craving and withdrawal during abstinence (52, 53).

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In a Phase II study, it was found that the carbon monoxide–confirmed 4-week continuous quit rates between weeks 9 to 12 were significantly higher in smokers treated with varenicline at 0.5 mg b.i.d. (45.1%) and at 1 mg b.i.d. (50.6%) compared with placebo (12.4%) (59). In another Phase II study, varenicline (1 mg b.i.d.) was found to be superior to bupropion (150 mg b.i.d.) in confirmed 4-week continuous quit rates (40.8% versus 28.6%) (60). At week 7, the carbon monoxide-confirmed 7-day point prevalence abstinence was higher for varenicline (1 mg b.i.d.) compared with bupropion (150 mg b.i.d.), and both showed statistically greater response rates than placebo (~52% and ~38% versus ~23%) (60). Subsequently, in one Phase III study, patients were given either varenicline (1 mg b.i.d.), bupropion (150 mg b.i.d.), or placebo. The varenicline group had ~1.5- and ~2.4-times greater continuous abstinence between weeks 9 to 12 compared with the bupropion and placebo groups, respectively (61). When examining the total abstinence between weeks 9 to 52, the varenicline group showed ~1.5- and ~2.5-times greater abstinence compared with the bupropion and placebo groups, respectively (61). However, another Phase III study with identical design did not find a significant difference between varenicline and placebo (61). In another study, maintenance of abstinence was compared between the patients that received 12 weeks of varenicline and patients that received an additional 12 weeks (24 weeks total) of treatment. Results indicated that 70% of the patients receiving 24 weeks of treatment were abstinent between weeks 13 to 24, whereas only 50% of the 12-week-treatment patients were abstinent (61). When examining the subjective effects associated with smoking, results obtained from the Phase III studies described above showed that varenicline provided significantly greater benefit compared with placebo. Areas of benefit, using the modified cigarette evaluation questionnaire [adopted from Rose et al. (102)], included psychological reward, smoking satisfaction, enjoyment of respiratory tract sensation, and craving reduction, but not aversion (62). In contrast, bupropion only showed benefit in the psychological reward subscale compared with placebo (62).

The safety of varenicline (compared with bupropion and placebo) has also been evaluated (60). Overall, the adverse events observed, or reasons for discontinuing treatment, were relatively mild. The percentage of patients who discontinued the study owing to adverse events was similar between varenicline (1 mg b.i.d.; 11.2%) and bupropion (150 mg b.i.d.; ~15.9%) compared with placebo (~9.8%). The most common adverse event associated with varenicline treatment was nausea (52.0% versus 21.4% and 18.7% for bupropion and placebo, respectively) (60). In a long-term (52-week) study, the primary adverse events contributing to patient dropout were nausea, abnormal dreams, and insomnia (7.6%, 2.4%, and 3.2% for varenicline, bupropion, and placebo, respectively) (60). The overall discontinuation rates were significantly higher at 28.3% in the varenicline group compared with 10.3% in the placebo group (63). The results from Phase III studies indicated that varenicline can provide greater smoking cessation compared with bupropion; however, safety issues associated with long-term use of this drug remain to be determined if it is to be used for longer than 24 weeks.

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## NICOTINE VACCINES

A newer strategy currently being investigated for smoking cessation is the nicotine vaccine. The principle of this strategy is to prevent nicotine from entering the brain. In immunized individuals, nicotine obtained from smoking is bound by nicotine-specific antibodies and cannot cross the blood-brain barrier, thus preventing its central effects (64, 65). Nicotine alone is not immunogenic (i.e., it does not elicit antinicotine antibody production); therefore, it must be conjugated to larger carrier proteins that can act as immunogenic molecules. Currently, there are at least five companies developing nicotine vaccines (Cytos Biotechnology, Nabi Biopharmaceuticals, Xenova Group Ltd., Chilka Ltd., and Independent Pharmaceutica AB). Each company uses a specific antigenic molecular approach. For example, Cytos utilizes a virus-like particle as the immunogen, whereas Nabi selected recombinant exoprotein A and Xenova makes use of a recombinant cholera toxin B (66).

An advantage of nicotine vaccines, compared with other forms of pharmacotherapy, is that daily administration of the drug is not required; only occasional booster shots are needed to maintain an adequate antibody titer. However, there are also potential drawbacks to nicotine vaccines and these have been discussed extensively elsewhere (67, 68). One of the primary concerns associated with the nicotine vaccine is that the titer of antibodies after immunization may not be sufficient to sequester all of the nicotine in arterial blood, limiting its use to prevent nicotine entry into the brain during smoking (64, 65, 67). If small amounts of nicotine enter the brain with each cigarette, the vaccine may in fact increase smoking to compensate for reduced nicotine levels (67, 68).

In animal studies, immunization with nicotine vaccines prevented the reinstatement of nicotine self-administration in rats when reexposed to nicotine after extinction of the behavior (69). However, another study found that vaccination did not prevent acquisition of nicotine self-administration, but reduced self-administration once self-administration was acquired (70). One peer-reviewed study reported the effects of vaccination on smoking behaviors (NicVAX by Nabi Biopharmaceutical) (71). In this 38-week study with ad libitum smoking it was found that the nicotine vaccine, at all doses tested (50, 100, and 200 μg; 1 primary challenge shot and 3 booster shots at each dose), did not cause compensatory smoking behaviors or precipitate withdrawal, the latter being consistent with animal data (72). In addition, the 30-day continuous abstinence rates were higher in patients receiving the highest vaccine dose (~38%) compared with placebo (~10%) (71). Careful interpretation of these results is needed, as the sample size was very small and the study was designed to evaluate the safety and immunogenicity of the vaccine rather than smoking cessation efficacy.

Cytos Biotechnology recently posted findings from a Phase II study regarding the efficacy of their vaccine on smoking cessation on the company's Web site (**http://www.cytos.com**; accessed on April 19, 2006). They reported that a larger portion of high responders (high-titer production) were continuously abstinent from smoking compared with the placebo group at 6 months (57% versus 31%) and at 12 months (42% versus 21%). These studies show promise and suggest that the vaccine may be useful for smoking cessation treatment (and possibly for relapse prevention).

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Thus far, there have been no serious adverse events associated with the vaccines. The majority (>99%) of the reported side effects were mild to moderate, with injection-site reaction, flu-like symptoms, headache, and myalgia being the most common. All effects were resolved without medical treatments (71, 73).

A particular concern associated with active immunization is whether the resulting antibody titer is sufficient to prevent all nicotine from entering the brain; rats treated with the vaccine only showed 64% reduction in brain nicotine (from 2 cigarettes equivalent of nicotine) (65). One way to circumvent the problem associated with antibody titer is through passive immunization, in which nicotine-specific antibodies are administered directly. A recent study has shown that immunization of rats with high doses (240 mg/kg) of a low-affinity monoclonal, or a high-affinity polyclonal, antibody significantly reduced nicotine distribution into the brain (up to ~75% reduction with the low-affinity monoclonal antibody) (74). This effect appeared to be dose related, with no significant difference between high- and low-affinity antibodies (74). Functionally, passive immunization prevented nicotine-conditioned place preference, reduced the development of nicotine dependence, and prevented the ability of nicotine to reduce abstinence symptoms (70, 75, 76). However, its effects on nicotine self-administration in animals, and smoking in humans, are not yet known. Nicotine antibodies may provide a potential alternative to active vaccines; however, the high costs associated with antibody production may be prohibitive.

## RIMONABANT (SR141716)

The possible involvement of the endocannabinoid system in drug dependence was suggested when it was found that delta 9-tetrahydrocannabinol and related compounds could trigger dopamine efflux in the mesolimbic system (77–79). Later, the endocannabinoid system was implicated in nicotine dependence when the levels of endogenous cannabinoid-like compounds were found to be altered during chronic nicotine administration (80). Specifically, nicotine increased levels of endogenous agonists of the $CB_1$ and $CB_2$ receptors [anandamide (AEA) and 2-arachidonoly-glycerol (2-AG), respectively] in the brainstem, a region involved in drug withdrawal (80–82). AEA levels were also increased in the limbic forebrain; however, both AEA and 2-AG levels were decreased in the hippocampus and cerebral cortex. No changes in the $CB_1$ cannabinoid receptor levels were seen in these brain regions (80). More definitive experiments demonstrating the role of endocannabinoid receptors in nicotine reward were conducted in rats. The $CB_1$ receptor antagonist SR141716 (rimonabant) prevented IV nicotine self-administration, blocked the release of dopamine in the nucleus accumbens in response to nicotine (83), and prevented both conditioned stimuli-induced nicotine-seeking behaviors and nicotine-conditioned place preference (84, 85). Finally, $CB_1$ receptor knockout mice showed nicotine-conditioned place preference in one study but not another, which may have been due to differences in dose and the route of administration (86, 87). The precise mechanism of actions of $CB_1$ receptor antagonism on nicotine reward/reinforcement remains unclear.

In a Phase III study (STRATUS-US) examining the effect of rimonabant on smoking cessation, smokers were given placebo, 5 mg rimonabant, or 20 mg rimonabant



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once daily (88). Patients were treated for 10 weeks total, 2 weeks prior to the quit date and 8 weeks following the quit date. Smoking cessation was evaluated during the last four weeks of treatment. It was found that significantly more (27.6%) patients receiving 20 mg rimonbant remained abstinent compared with those who were on 5 mg (15.6%) or placebo (16.1%) (88). In contrast, another study (STRATUS-Europe) found no significant increase in cessation for either treatment dose groups (5 and 20 mg) compared with the placebo group (24%, 25%, and 20%, respectively) (89). In a third and larger study (STRATUS-Worldwide) examining smoking relapse, significantly more patients who received 20 mg rimonabant (~42%) remained smoke-free for the entire year (89) compared with patients receiving placebo treatment (~32%). Rimonabant was well tolerated with discontinuation from the study (STRATUS-US) due to adverse events occurring in 6.9%, 6.1%, and 4.2% of patients receiving 20 mg, 5 mg, and placebo, respectively. The most common side effects were nausea and upper respiratory tract infection (88). Rimonabant has not yet been approved for use as a smoking cessation product in the United States and the moderate benefits obtained from this drug may limit its widespread use.

## OTHER NON-NICOTINIC PHARMACOTHERAPIES

Clonidine and nortriptyline are second-line therapies for smoking cessation that are being tested but have not yet been approved for this indication by the FDA. The noradrenergic tricyclic antidepressant nortriptyline inhibits serotonin and noradrenalin reuptake. It has demonstrated some efficacy in smoking cessation (90, 91), likely by reducing withdrawal symptoms. Odds ratios for smoking cessation using nortriptyline alone in four studies ranged from 1.2 to 5.5, with only one study lacking a statistical significant benefit (90–93). The smoking cessation rates achieved with nortriptyline appear to be comparable to those achieved with bupropion [pooled odds ratios: 2.1 (1.5–3.1) versus 2.0 (1.7–3.4)] (94). Nonetheless, the current lack of extensive testing and safety information for smoking cessation limits the use of nortriptyline as second-line therapy (94).

Clonidine is an $\alpha$-2-adrenergic receptor agonist used primarily for the treatment of hypertension, although it has also been used for treatment of opiate and alcohol withdrawal (95, 96). Clonidine may alleviate withdrawal symptoms associated with tobacco use (97, 98). A recent Cochrane analysis reviewed the efficacy of clonidine for smoking cessation from six studies and found that clonidine treatment was associated with increased smoking cessation [pooled odds ratio of 1.89 (95% CI: 1.30–2.74)]; however, when analyzed separately only one study showed significant improvement in smoking cessation (99). Furthermore, adverse effects such as dry mouth, sedation, and postural hypotension limited its general use.

Mecamylamine is a nicotinic antagonist originally used as an antihypertensive (100). At low doses, mecamylamine is effective at blocking the rewarding effects of nicotine and enhancing short-term smoking cessation, especially in conjunction with transdermal nicotine (101, 102). Moreover, although an antagonist of nicotinic receptors, low doses of oral mecamylamine did not appear to precipitate withdrawal in

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smokers (103). Additional studies are required to ascertain the long-term effectiveness of mecamylamine in smoking cessation.

Other compounds that have been assessed for smoking cessation include the monoamine oxidase inhibitors (MAOIs). Cigarette smoking has been demonstrated to inhibit MAO-A and MAO-B, potentially by reducing metabolism of dopamine (104). A preliminary study found that the reversible MAO-A inhibitor moclobemide significantly reduced self-reported smoking rates, although several individuals who reported abstinence had higher than acceptable plasma levels of the nicotine metabolite cotinine, suggesting continued smoking (105). The irreversible MAO-B inhibitor selegiline has also been demonstrated to provide some relief from smoking, but this effect was short term with no significant benefit in the treatment group compared with the placebo group in the last four weeks of an eight-week study (106). The reversible inhibitor of MAO-B lazabemide was also evaluated for smoking cessation, although the study was terminated due to concerns of hepatotoxicity (107).

Emerging evidence indicates that the dopamine receptor D3 (DRD3) is involved in the motivational aspects of drug-seeking behaviors (108–112). One study showed that the DRD3-selective antagonist SB-277011-A reduced the relapse to nicotine self-administration triggered by nicotine in rats but it did not affect nicotine self-administration (108). Another study found that the DRD3 partial agonist BP-897 blocked nicotine-conditioned place preference in rats (111). Furthermore, DRD3 appears to be involved in conditioned stimulus associated with addictive substances but not natural reinforcers (e.g., food and sex) (113). Therefore, modulators of DRD3 may be useful for relapse prevention in smoking cessation (114).

## INHIBITORS OF NICOTINE METABOLISM

### Nicotine Metabolism

Because nicotine elimination is a key factor in determining the number of cigarettes smoked, a novel strategy that may be useful for smoking cessation is to reduce the elimination of nicotine, and one way to achieve this is to inhibit its metabolism. In humans, approximately 80% of nicotine is metabolized to cotinine (115). Approximately 90% of the conversion of nicotine to cotinine is mediated by the hepatic enzyme CYP2A6 (116). This conversion is a two-step process that involves the initial formation of nicotine-$\Delta$-$^{1'(5')}$iminium ion by CYP2A6 (117, 118). The iminium ion is then converted into cotinine by the cytosolic enzyme aldehyde oxidase (116, 119). Nicotine is also excreted unchanged and metabolized to other minor metabolites, but these pathways account for only a small portion of the metabolic fate of nicotine (120–124). Cotinine is further metabolized to *trans*-3-hydroxycotinine, mediated solely by CYP2A6 (125, 126). As CYP2A6 is the primary enzyme that metabolizes nicotine, alterations (e.g., inhibition) in the amount or function of this enzyme will significantly affect plasma nicotine levels during smoking and during NRT treatment and thus may alter smoking behaviors and the efficacy of NRTs (127, 128).



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## Genetic Variation in *CYP2A6* and the Impact on Nicotine Metabolism and Smoking Behaviors

*CYP2A6* is a highly polymorphic gene; currently, there are 23 numbered *CYP2A6* allelic variants and many additional single nucleotide polymorphisms (**http://www.imm.ki.se/CYPalleles/cyp2a6.htm**). Many of the genetic variants have been shown to alter the expression, stability, and function of the CYP2A6 enzyme. For instance, *CYP2A6*4* is a gene deletion variant where no enzyme is produced; individuals with two alleles of this variant have impaired nicotine metabolism forming very low levels of cotinine (129–131). In terms of smoking behaviors, slower metabolizers (individuals with $\leq$50% in nicotine metabolism activity) have reduced smoking behaviors, such as consuming fewer cigarettes per day (as indicated by self-report and lower carbon monoxide levels), and are at lower risk for being dependent smokers (128, 132, 133). Slower metabolizers also smoke for shorter durations and were more likely to quit smoking compared with normal metabolizers (133, 134).

## Inhibition of CYP2A6 Activity

Based on the effect of *CYP2A6* genotypes on the nicotine metabolism and smoking behaviors, it was hypothesized that one could reduce smoking by mimicking defects in the CYP2A6 enzyme (phenocopying). Furthermore, if inhibition of nicotine metabolism can mimic a gene defect, the long-term behavioral effects of these inhibitors may be predicted based on available pharmacogenetic and behavioral studies. CYP2A6 inhibitors studied in experimental settings (for inhibition of nicotine metabolism and reduction of smoking behaviors) include methoxsalen (8-methoxypsoralen, 8-MOP) and tranylcypromine (TCP). Methoxsalen is both a competitive and a mechanism-based inhibitor of CYP2A6, whereas TCP is a competitive inhibitor (135–138). Both drugs are potent and selective inhibitors, although at higher concentrations they can inhibit other CYPs (135, 138–141).

## Improving Smoking Cessation Through CYP2A6 Inhibition

By mimicking defects in nicotine metabolism, one can effectively increase the systemic availability of coadministered nicotine. In practical terms, concurrent use of inhibitors of CYP2A6 with NRT products should enhance smoking cessation. For example, users of nicotine gum may benefit from the concomitant use of a CYP2A6 inhibitor. Much of the nicotine released during the chewing of nicotine gum is absorbed by the buccal (oral) cavity, while a significant portion is swallowed (142). Of the nicotine swallowed (as in nicotine gum or in a pill form), approximately 80% is metabolized before entering systemic circulation via first-pass metabolism (143). Thus, inhibition of this first-pass metabolism with a CYP2A6 inhibitor would increase the nicotine acquired from the gum. In a human study examining the effect of the CYP2A6 inhibitor methoxsalen on nicotine levels obtained from nicotine gum, it was found that following three days of methoxsalen (10 mg t.i.d.) plus nicotine

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gum (4 mg), the mean plasma nicotine levels were significantly higher compared to a placebo inhibitor plus nicotine gum (15.3 versus 10.1 ng/ml; $p < 0.01$) (144).

An oral (pill) form of nicotine is not currently available despite this being a preferred route of drug administration. The large first-pass metabolism prevents pharmacologically relevant levels of nicotine from reaching the systemic system. Higher doses of oral nicotine, to overcome first-pass metabolism, are not possible as higher concentrations of nicotine can cause gastrointestinal irritation (143). Therefore, it may be possible to increase the efficacy of oral nicotine by inhibiting the first-pass metabolism. In a human experimental study, it was found that the addition of the CYP2A6 inhibitor methoxsalen (10 and 30 mg) to 4 mg of oral nicotine significantly increased the subjects' mean plasma nicotine level (>70%) and decreased the subjects' desire to smoke compared with oral nicotine alone ($p < 0.05$) (145). In another study, oral nicotine (4 mg) and methoxsalen (30 mg) significantly reduced the number of cigarettes smoked, level of breath carbon monoxide, number of puffs, as well as inhalation intensity compared with placebo. The subjects also had increased latency to lighting the second cigarette (146).

Administration of TCP (2.5 and 10 mg) increased the plasma concentrations of nicotine by 43% and 65%, respectively, in abstinent smokers receiving 4 mg of oral nicotine and reduced the subjects' desire to smoke (145). These studies provided the first evidence that inhibiting nicotine metabolism could reduce smoking behaviors. Nonetheless, further studies are needed to examine the long-term cessation rates in individuals treated with CYP2A6 inhibitors and oral nicotine.

Although methoxsalen is effective at reducing smoking behaviors in the presence of oral nicotine, CYP2A6 inhibition alone may also reduce smoking and increase quitting, similar to the pharmacogenetic findings in slow metabolizers (128, 132–134); however, this remains to be tested. One company (Nicogen) is currently conducting Phase II clinical trials for smoking reduction and cessation using these approaches.

## Tobacco-Specific Nitrosamines

One of the most potent procarcinogens present in tobacco smoke is 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The primary metabolic detoxification pathway of NNK is the conversion to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), which is then conjugated to NNAL-glucuronide (147, 148). Conversely, NNK can also be activated, via α-hydroxylation, to a reactive metabolite capable of forming DNA adducts (149, 150). CYP2A6 has been demonstrated to be one of the enzymes responsible for this α-hydroxylation (151). Consistent with this, a recent epidemiology study found that individuals that are *CYP2A6*-poor metabolizers have significantly lower risk for developing lung cancer, even after adjusting for the number of cigarettes smoked (152). In animal models, exposure to NNK leads to formation of lung tumors (153–155) and studies in mice have shown that administration of methoxsalen reduced the formation of NNK-induced lung tumors (156, 157). Administration of methoxsalen in human smokers rerouted excretion of NNK as increased NNAL and NNAL-glucuronide, suggesting significant inhibition of the α-hydroxylation of NNK (158). Therefore, in addition to enhancing



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smoking cessation, inhibitors of nicotine metabolism can potentially provide harm reduction in smokers attempting to quit.

### Discovery of Novel CYP2A6 Inhibitors

Both quantitative structure-activity relationship models for CYP2A6 inhibitors and the crystal structure of CYP2A6 are available (159–161). It has been predicted that favorable substrates for CYP2A6 are small, hydrophilic, and exhibit the ability to adopt a planar structure (159, 160, 162). Over the past few years a large number of compounds have been tested for their ability to inhibit CYP2A6 activity (138, 160, 163–165). The compounds that are most potent and selective inhibitors of CYP2A6 were found to be structural analogues of nicotine and coumarin (160, 165). It is conceivable that novel compounds can be developed that can act as both inhibitors of nicotine metabolism and partial agonists of nicotinic acetylcholine receptors that can attenuate the reinforcing properties of nicotine (53). The combination of CYP2A6 structural information and improvements in QSAR analysis techniques should greatly enhance the ability to discover and develop specific and potent inhibitors of CYP2A6.

### Animal Models for Testing Novel CYP2A6 Inhibitors

With an increasing number of potential CYP2A6 inhibitors being discovered (138, 160, 163–165), a more practical model is needed to test their specificity, efficacy, toxicity profile, and impact on nicotine-mediated behaviors. Rodents are the most frequently used animal models for studying the pharmacology of nicotine. While these models are invaluable for understanding the underlying mechanisms of nicotine dependence, there are clear limitations that should be considered. For instance, rats are not a suitable model for studying inhibitors of nicotine metabolism by CYP2A because the primary enzymes that metabolize nicotine in these animals belong to the CYP2B family (166, 167). In mice, the majority of nicotine appears to be metabolized by CYP2A5 (118). The mouse CYP2A5 has 86% amino acid sequence similarity to human CYP2A6. From the point of view of drug development, extrapolation of animal data to humans requires caution because interspecies differences can translate to differing effectiveness of the inhibitors on nicotine metabolism. Mice transplanted with human hepatocytes (replacing more than 80% of mouse hepatocytes) have been generated (168–171) and this model may represent an optimal strategy for the evaluation of inhibitors of nicotine metabolism in vivo and their effects on nicotine-mediated behaviors.

## CONSIDERATION OF NONPHARMACOLOGICAL FACTORS IN SMOKING CESSATION

Although the central pharmacological effects of nicotine are crucial for tobacco dependence, nicotine is not solely responsible for human smoking behaviors. Many studies have examined the contribution of nonpharmacological aspects of cigarette smoking to tobacco dependence (reviewed extensively in Reference 172). For instance,

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neither pure nicotine nor denicotinized cigarettes alone completely abolished cravings or provided the subjective satisfaction of smoking regular cigarettes (173, 174). The nonpharmacological components of tobacco dependence have been partly attributed to the sensory aspects of cigarette smoke (e.g., taste, pharyngeal/tracheobronchial sensory cues). Administration of local anesthetic to the airway significantly reduced craving as well as satisfaction from smoking (175, 176) and blockade of olfactory/taste stimuli from smoking reduced self-administration of cigarette puffs, especially in women (177). Together, these findings indicate that nonnicotinic factors play an important role in smoking, which may reduce the success of NRTs in smoking cessation (178).

Despite the accumulating evidence suggesting the importance of nonpharmacological factors in tobacco dependence, there are currently no treatments that specifically target these components. There have been attempts to design non-nicotine inhaler/aerosol products that mimic the sensations of cigarette smoking (179, 180); but thus far no commercial products have been developed. Denicotinized cigarettes are successful at relieving some of the cigarette cravings, therefore they may be useful for dissociating the reinforcing properties of cigarette smoke (sensory cues) from that of nicotine (173, 174). However, the harmful effects (from cigarette smoke) may limit this approach. Finally, behavioral counseling can help patients stop smoking, and this should be combined with newer pharmacological treatments to determine if greater benefits exist compared to either therapy alone (181, 182).

## FUTURE PERSPECTIVES

The first Surgeon General's Report on Smoking and Health Tobacco stated that "cigarette smoking is a health hazard of sufficient importance in the United States to warrant appropriate remedial action" (**http://www.cdc.gov/Tobacco/sgr/sgr_1964/sgr64.htm**). Indeed, the health consequences of tobacco smoking are staggering and truly effective strategies to reduce smoking and to improve public health are needed. Tobacco dependence is a chronic disease of a complex nature but thus far the primary treatments are the NRTs, which deliver only one component responsible for the addictive properties of cigarettes. Although NRTs are important in reducing harm exposure and can improve the overall successful quit rates, many smokers who quit eventually relapse, even with relapse prevention interventions (183). Therefore, to achieve better smoking cessation rates, more comprehensive treatment strategies are required. Antidepressants such as bupropion can reduce cravings as well as withdrawal symptoms. The long-term benefits of the newly approved drug varenicline remain to be seen. Newly developed drugs such as nicotine vaccines are seeking approval for smoking cessation and their long-term benefits compared with existing treatments are not yet determined. Inhibition of nicotine metabolism as a means for smoking cessation shows promising results, but the long-term efficacy remains to be determined. Finally, nonpharmacological factors associated with tobacco dependence need to be addressed as they appear to be crucial for the addictive properties of cigarettes.

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## DISCLOSURE STATEMENT

R.F.T. is a shareholder in Nicogen, a company focused on novel treatment approaches involving inhibition of hepatic CYP2A6.

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**Errata**

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