# Recent advances in the treatment of tobacco dependence

Robert M. Anthenelli[a,b,*]

[a]Tri-State Tobacco & Alcohol Research Center and Addiction Sciences Division, University of Cincinnati, College of Medicine, Cincinnati, OH, USA
[b]Mental Health Care Line (116-A), Cincinnati VA Medical Center, 3200 Vine Street, Cincinnati, OH 45220, USA

## Abstract

Tobacco dependence is the leading preventable cause of adult morbidity and mortality in the world. Despite the magnitude of this global public health problem, relatively few medications (i.e. nicotine replacement therapy and sustained-release bupropion) are currently approved for the treatment of this pandemic.

Nicotine and other components in tobacco smoke are more likely to produce a dependence state in cigarette smokers than alcohol and cocaine in regular users of those drugs of abuse. As our understanding of the neurobiology of tobacco dependence increases, so, too, grows the number of potential therapeutic targets by which we can intervene in this devastating addiction. The purpose of this manuscript is to review three novel mechanisms of action that may serve as therapeutic targets for the pharmacologic treatment of tobacco dependence. For each of these therapeutic targets, we discuss medications in development that affect these pathophysiologic mechanisms.

First, we examine the role of the endocannabinoid system (ECS) in the development of nicotine dependence and highlight the development of rimonabant, the first selective antagonist of the cannabinoid type 1 (CB-1) receptor. Second, we explore how heterogeneity among various subtypes of nicotinic receptors might be exploited to develop more specific agents acting at these receptors such as varenicline—a partial agonist at the $\alpha4\beta2$ nicotinic receptor. Finally, we examine how selective inhibitors of monoamine oxidase (MAO) such as selegiline might be used as adjunctive medications for the treatment of tobacco dependence.

Published by Elsevier B.V. on behalf of Association for Research in Nervous and Mental Disease.

*Keywords:* Tobacco dependence; Nicotine; Nicotinic acetylcholine receptors (nAChRs); Mesocorticolimbic dopamine pathway; Endocannabinoid system (ECS); Rimonabant; Varenicline; selegiline

## 1. Introduction

Tobacco dependence is the leading preventable cause of death among adults in the United States [1] and elsewhere throughout the world [2]. While the percentage of adult cigarette smokers in the United States has declined from its peak of approximately 43% in the mid-1960s to its current level of approximately 22% in 2003 [3], global smoking prevalence rates in developing countries are declining at a much slower rate [4]. The World Health Organization estimates that there are approximately 1.25 billion smokers worldwide at present and that global mortality due to tobacco-related diseases should rise from approximately 5 million deaths annually in 2004, to over 10 million deaths per year in 2030 [2].

Given the enormity of this global public health problem it is intriguing that relatively so few medications have been developed, to date, to combat this pandemic. The United States Food and Drug Administration has currently approved only two types of pharmacotherapy for tobacco dependence: nicotine replacement therapy in a variety of formulations (e.g. polacrilex gum, transdermal patches, nicotine inhaler, nicotine spray, nicotine lozenges) and sustained-release bupropion [5]. Each of these agents has been found to be more effective than placebo in numerous randomized clinical trials as summarized in Table 1 below. However, despite their clear advantage over placebo at doubling or even trebling a smoker's odds at quitting smoking, current pharmacotherapies for tobacco dependence are generally underutilized and 7–8 out of 10 smokers are still likely to relapse to smoking within 1 year after using these agents [6]. Off-label use of nortriptyline and clonidine

* Corresponding author. Address: Mental Health Care Line (116-A), Cincinnati VA Medical Center, 3200 Vine Street, Cincinnati, OH 45220, USA. Tel.: +1 513 861 3100x4914; fax: +1 513 475 6568.
    *E-mail address:* robert.anthenelli@med.va.gov

Table 1
Currently approved first-line[a], and off-label second line[b] pharmacotherapies for the treatment of tobacco dependence: cumulative odds ratios and estimated abstinence rates compared with placebo[c]

| Agent | Estimated OR | Estimated abstinence rate (placebo versus agent) |
| --- | --- | --- |
| Bupropion SR[a] | 2.1 | 17.3 versus 30.5% |
| Nicotine Gum[a] | 1.5 | 17.1 versus 23.7% |
| Nicotine Patch[a] | 1.9 | 10.0 versus 17.7% |
| Nicotine Spray[a] | 2.7 | 13.9 versus 30.5% |
| Nicotine Lozenge[a] | 2.0 | – |
| Nortriptyline[b] | 3.2 | 11.7% versus 30.1% |
| Clonidine[b] | 1.9 | – |

OR, odds ratio; 95% C.I. all >1.

[a] Currently approved first-line medications have been approved by the US Food and Drug Administration (FDA) and are recommended as the first agents to use in the treatment of tobacco dependence.

[b] Although not FDA-approved for this indication, these medications are recommended for use as aids to smoking cessation in the Clinical Practice Guideline: Treating Tobacco Use and Dependence [5].

[c] Data shown are modified from the Clinical Practice Guideline: Treating Tobacco Use and Dependence [5] except estimated ORs for nicotine lozenge [42] and clonidine [67] which are adapted from Cochrane Database Systematic Reviews.

as second-line aids to smoking cessation has been recommended [5,6], but these medications suffer from high rates of unwanted side effects such as weight gain, dry mouth and sedation. Thus, there is clearly a need to develop new medications for the treatment of tobacco dependence.

The purpose of this article is to provide the non-specialist with a brief review of some of the key neurobiological elements involved in the development and maintenance of tobacco dependence. Rather than presenting a broad overview of all of the medications currently under development as aids to smoking cessation, instead we focus on three neural mechanisms on which our center has been conducting studies and about which we have first-hand familiarity working with some of the medications being developed that target these systems. For more exhaustive reviews on both currently available and novel pharmacotherapies for nicotine dependence, it is recommended that the reader see the recent excellent reviews by George and O'Malley [7] and Foulds et al. [8].

## 2. Why is tobacco smoke so addicting?

In order to rationally develop new pharmacotherapies for tobacco dependence, it is important to understand elements of the neurobiology of tobacco addiction. As discussed below, tobacco dependence is preferred over other terms such as nicotine dependence since it is likely that other components in tobacco smoke contribute to the addiction process beyond just nicotine (see Section 5 below).

In the United States and in other Western developed countries, the health risks of cigarette smoking are now widely known. These public health efforts have been partially successful as evidenced by the fact that over 70% of cigarette smokers express a desire to want to quit smoking with 30% (in Western Europe) to 50% (in the US) of smokers actually making a quit attempt each year [5]. However, most of these quit efforts are attempted without

the benefit of approved pharmacotherapy, and when this is the case, the likelihood of one successfully quitting smoking is roughly 1 in 20 [5].

As alluded to earlier, tobacco smoke is a highly addictive drug. Results from the National Household Surveys on Drug Abuse indicate that among regular users of tobacco, alcohol, cocaine, and cannabis, cigarette smokers were more likely to become dependent on cigarettes than were regular users of each of these other types of drugs [9]. As a corollary to this epidemiologic observation, rates of current smoking among alcoholics or cocaine addicts who have successfully recovered from those addictions are three- to fourfold greater than that found in the general population [10,11].

### 2.1. Cigarettes: the model nicotine delivery system

One reason that smoking is so addictive is that the inhaled route of administration is an ideal way to deliver nicotine and other psychoactive components in tobacco smoke to the brain. Nicotine delivered in tobacco smoke readily diffuses into the arterial blood across lung capillaries and then is swiftly distributed into the brain via rapid diffusion across the blood–brain barrier. Thus, nicotine from tobacco smoke reaches the brain within 10–20 s of its inhalation [12]. As a result of its rapid elimination and distribution to peripheral tissues, the rapid decline in brain nicotine concentrations sets up a cycle where the smoker has to readminister the drug frequently. This rapid onset and offset of nicotine's effects in the brain contribute to nicotine's addition potential much like that observed with the smoking of other drugs such as crack cocaine.

### 2.2. Nicotine commandeers nAChRs in the brain reward circuit to reinforce smoking behaviors

Exogenous nicotine from tobacco smoke binds to nicotinic acetylcholine receptors (nAChRs) that are widely distributed throughout the brain and periphery [13]. In

general, stimulation of nAChRs on nerve terminals promotes neurotransmitter release while binding at post-synaptic and somal (neuron cell bodies) nAChRs mediates a small minority of fast excitatory transmission [14]. The nAChRs to which exogenous nicotine from cigarette smoke bind were not intended for this purpose; but rather, were designed to facilitate cholinergic neurotransmission using acetylcholine (ACh) as the primary neurotransmitter (see Fig. 1). Such cholinergic neurotransmission generally relies upon the release of small amounts (i.e. 1 mM) of ACh that gets rapidly degraded by acetylcholinesterase to limit the duration of the signal [14]. However, exogenous nicotine from cigarette smoking collects in the brains of smokers in miniscule amounts (i.e. 0.1 µM) and is not broken down by acetylcholinesterase [15]. Thus, nicotine from tobacco smoke hijacks these nAChRs in ways for which they are not designed to further contribute to the addiction potential of tobacco smoke (see Section 4 below).

Like other drugs of abuse, nicotine's addiction potential is primarily mediated via its actions on the mesocortico-limbic dopamine system [16–18]. This system, schematized in Fig. 1, is comprised of dopamine neurons originating in the ventral tegmental area (VTA) of the midbrain that send their axonal projections rostrally to a region of the ventral striatum known as the nucleus accumbens (NAcc). Dopaminergic projections also extend further rostrally to regions of the cerebral cortex, especially to one area known as the prefrontal cortex (PFC) that plays important roles in executive processing and decision-making [15]. In addition to having bidirectional connectivity with the PFC, the subcortial midbrain dopamine system also has reciprocal linkages with limbic system structures such as the hippocampus (important for memory processing and associative learning) and the amygdala (important for emotional processing) [19]. Thus, given the interconnectivity of these subcortical, cortical, and limbic system structures, each of which are populated with nAChRs, it is not surprising that cigarette smoking and craving for tobacco becomes associated with a host of behaviors and cues involving natural reward learning, memory and emotions [15,19].

While endogenous ACh is required for nicotine to elicit its reinforcing effects [15]; dopaminergic neurotransmission in the mesocorticolimbic reinforcement circuitry is further modulated by several other neurotransmitters other than acetylcholine. Chief among these are glutamate and gamma-aminobutyric acid (GABA) [20,21]. Glutamate, the major excitatory neurotransmitter in the brain, generally acts like an accelerator on the VTA dopaminergic neurons. In contrast, GABA, the major inhibitory neurotransmitter in the central nervous system, mainly functions as the decelerator on midbrain dopamine neurons. Together, these four principal neurotransmitters (i.e. dopamine, ACh, glutamate and GABA) and their receptors form elaborate feed forward and negative feedback loops that are perturbed by nicotine and other intermediary neuromodulators released during tobacco smoking [15].

Nicotine, like other drugs of abuse, leads to a release of dopamine in the NAcc [18,21]. Electrophysiological studies indicate that nicotine stimulates dopaminergic neurons in at least three ways [15,20,21]. First, nAChRs located directly on dopaminergic neurons in the VTA bind exogenous
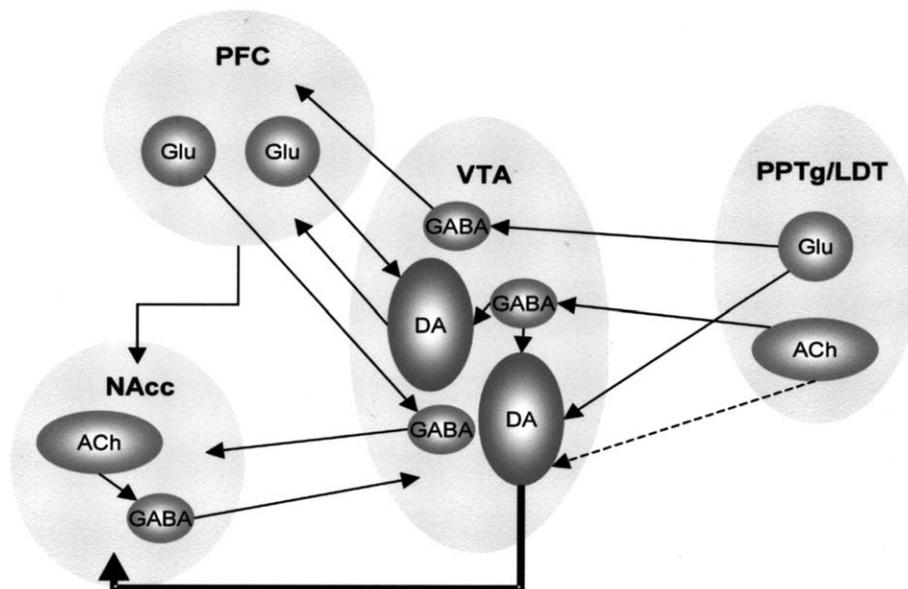


Fig. 1. Nicotine Commandeers the Brain's Reward Circuitry. In this simplified schematic of brain reward center connectivity, reproduced with permission from reference [15], dopamine (DA), acetylcholine (ACh), GABA, and glutamate (Glu) neurons are illustrated in select brain nuclei involved in drug reward. Nicotinic acetylcholine receptors (nAChRs) that usually bind ACh from cholinergic projections originating in the pedunculopontine tegmental and laterodorsal tegmental nuclei (PPTg/LDT) are hijacked by exogenous nicotine in tobacco smoke to reinforce smoking and smoking-related behaviors. See text for further description. VTA, ventral tegmental area; NAcc, nucleus accumbens; PFC, prefrontal cortex. From Fagen, ZM et al. *Ann NY Acad Sci* 1003: 185–195 (2003).

nicotine from tobacco smoke to excite the brain cell to release dopamine. Second, nAChRs located on the terminals of glutamatergic projections synapsing on dopaminergic dendrites bind nicotine from cigarette smoke and release the excitatory neurotransmitter, glutamate, to further stimulate dopamine release. Third, in what appears to be a two-stage process, nAChRs on GABAergic neurons that normally function as the brake on dopamine neurons, are desensitized by chronic exposure to exogenous nicotine, thus, releasing their inhibition of dopaminergic neuronal firing and further stimulating the release of dopamine. Taken together then, nicotine hijacks nAChRs in the mesocorticolimbic dopamine system to reinforce the smoking behavior despite adverse consequences by altering the balance in favor of glutamatergic excitation of dopaminergic neurons at the expense of GABAergic inhibition.

## 3. Therapeutic target #1:

### 3.1. The endocannabinoid system

The mesocorticolimbic dopamine pathway is modulated, in part, by the endocannabinoid system (ECS), a recently discovered modulatory network with exciting implications for the treatment of tobacco dependence. The ECS is comprised of at least two types of cannabinoid receptors which belong to the superfamily of G-protein coupled receptors [22]. The cannabinoid type 1 (CB-1) receptor, found ubiquitously throughout the brain in regions such as the cortex, limbic system and hypothalamus [23], is also located in the gut [24] and on adipocytes [25]. The cannabinoid type 2 (CB-2) receptor is primarily located on immune cells. These receptors bind endogenous ligands (so-called endocannabinoids) that are produced in the brain and body on demand in response to various physiologic demands such as starvation [26]. These endocannabinoids, such as anandamide and 2-arachidonylglycerol (2-AG), are synthesized from lipid cell membranes to serve as signaling molecules that generally inhibit the release of neurotransmitters from presynaptic nerve terminals located in the vicinity near where they are released [27]. Thus, endocannabinoids participate in a retrograde signaling process to modulate the release of dopamine in the mesolimbic dopamine reinforcement center.

Several lines of evidence indicate that endocannabinoids modulate the reinforcing effects of nicotine. In experimental animals, chronic nicotine administration stimulates the production of endocannabinoids in the limbic forebrain region where the NAcc is located [28]. Co-administration of rimonabant, the first selective antagonist of the CB-1 receptor, blocks nicotine self-administration in rodents trained to administer this drug. Furthermore, in vivo microdialysis studies in rodents co-administered rimonabant and nicotine found that the CB-1 antagonist blocked dopamine release in the NAcc [29]. Rimonabant was also found to block conditioned reinforcement in rats trained to lever press in response to nicotine-associated environmental stimuli—an animal model that simulates aspects of cue-induced drug taking in humans [30]. Taken together then, these studies in experimental animals provide evidence that suppression of the ECS may make nicotine less reinforcing.

These exciting preclinical results led to the development of a phase II proof-of-concept study in humans to determine whether rimonabant might be an aid to smoking cessation in smokers motivated to try to quit smoking. Since the ECS plays an important role in food intake and energy balance [31,32], and since the drug also has anti-obesity effects through both central and peripheral mechanisms [33], it was postulated that rimonabant would also demonstrate the added benefit of limiting post-cessation weight gain that so often is an obstacle to individuals contemplating quitting smoking. Indeed, the findings from this first phase II trial were promising in that smokers treated with rimonabant (40 mg) roughly doubled their odds of quitting smoking compared with placebo. (Anthenelli et al., unpublished data) Moreover, on average, rimonabant-treated quitters gained only 25% of the weight gained by placebo-treated quitters at least in the short term in this 10-week active treatment trial.

The promising phase II trial results paved the way for further phase III clinical trials. Thus, the STRATUS (Studies of Rimonabant and Tobacco Use)—US trial compared fixed dosages of rimonabant 5 versus 20 mg in a randomized, multicenter, double-blind, placebo controlled clinical trial [34]. Seven hundred 84 smokers who were motivated to try to quit smoking were randomized to placebo, rimonabant 5 mg, or rimonabant 20 mg in a 10-week treatment trial. All subjects received brief weekly smoking cessation counseling. Abstinence from smoking was evaluated by self-report, daily diaries, and confirmed by expired breath carbon monoxide (CO) levels $\leq 10$ parts per million (ppm) as well as plasma cotinine concentrations. As was the case in the phase II trial, the primary endpoint was prolonged abstinence during the last four weeks of treatment. Secondary efficacy outcome measures included weight change, safety and tolerability measures.

Consistent with the phase II trial results, the findings from the STRATUS-US trial have not yet been published and can only be summarized here. There were no significant differences across the three groups on demographic or base line smoking characteristics. Compared with placebo, rimonabant 20 mg (but not 5 mg) roughly doubled the odds of quitting smoking and led to an 85% reduction in post-cessation weight gain among these quitters, at least in the short-term in this 10-week treatment trial [34]. The medication was generally well tolerated with relatively few subjects discontinuing treatment due to adverse events.

The combination of positive preclinical and clinical (phase II and III) results make rimonabant a promising agent for the treatment of tobacco dependence. While results regarding the longer term effects of the medication on maintaining smoking abstinence, preventing post-cessation

weight gain, and safety are not yet available, studies determining these parameters are either completed or nearing completion and the results should be available soon. However, when these short-term results are taken together with the Rimonabant in Obesity (RIO)—program results assessing the medication's efficacy and tolerability for the treatment of overweight/obesity and dyslipidemia [35–37], rimonabant might be the first in a class of cardiovascular risk managing agents that simultaneously treats tobacco dependence, post-cessation weight gain, and obesity via ECS suppression.

## 4. Therapeutic target #2:

### 4.1. Nicotinic receptor subtypes

As alluded to above, nicotine in tobacco smoke commandeers the dopamine reward circuitry by binding to nAChRs. These ligand-gated receptors are structurally and functionally diverse as a result of being composed of multiple protein subunits designated alpha ($\alpha$), beta ($\beta$), delta ($\delta$), etc. and it is this structural heterogeneity that distinguishes among neuronal type nicotinic receptors and muscle type nAChRs (i.e. nAChRs in muscle are comprised of $\alpha$, $\beta$, $\delta$ and gamma ($\gamma$) subunits whereas brain nAChRs are made up of either homomeric $\alpha$ pentamers or heteromeric $\alpha/\beta$ subunits) [13,38]. The number and types of subunits that comprise a nAChR affect that receptor's role and function in the brain. Thus, homomeric $\alpha7$ nAChRs are located on glutamatergic terminals synapsing on dopaminergic cell bodies and dendrites, while heteromeric $\alpha/\beta$ nAChRs are found directly on the soma of dopamine neurons and on GABAergic inputs to dopamine brain cells [38]. Since nAChRs are ubiquitously distributed in various brain regions involved in drug reinforcement (i.e. the mesocorticolimbic dopamine pathway), memory and learning (i.e. the hippocampus) and emotional processing (i.e. the amygdala), it is not surprising that nicotine in tobacco smoke affects all these processes.

Electrophysiological studies have demonstrated that chronic or repeated doses of nicotine cause nAChRs to desensitize or become refractory to further ion-gated stimulation [14,21]. Thus, nAChRs exposed to chronic nicotine adapt by becoming desensitized such that the ion pore becomes closed for minutes to hours following the last dose of nicotine. Since desensitized receptors turn over more slowly than do nAChRs in the active state, there is an upregulation of nAChRs in the brains of chronic smokers; the number of nAChRs is increased in an effort to offset the quantities of receptors found in the desensitized or inactive state [14,39].

Desensitization of nAChRs such as that which occurs in chronic smokers most likely contributes to physiologic dependence on nicotine. That is, smokers become tolerant to nicotine's effects because desensitized nAChRs are inactive and are refractory to further stimulation by exogenous nicotine. Such desensitization of nAChRs allows chronic smokers to take in large amounts of nicotine, which in a non-smoker, would normally lead to adverse effects such as nausea or dizziness [14].

Upregulation of nAChRs in the brains of smokers most likely contributes to the other component of physiological dependence—tobacco withdrawal [14,40]. This uncomfortable state, that usually begins within hours of smoking one's last cigarette, is marked by a characteristic pattern of symptoms and signs that include dysphoric or depressed mood, irritability, insomnia, anxiety, difficulty concentrating, restlessness, decreased heart rate and increased appetite or weight gain [41]. In addition to these complaints, the tobacco withdrawal syndrome is also marked by craving for the drug, and it is this constellation of factors that so often leads smokers to relapse to smoking after they have attempted to abstain.

Nicotine replacement therapy (NRT) substitutes nicotine in the form of gum, patch, spray, inhaler and lozenge in a safer formulation than that found in tobacco smoke. While numerous studies have found NRT to be an effective aid to smoking cessation [42], because of their routes of administration, the available NRTs do not reproduce plasma and brain nicotine concentrations to the extent provided by cigarette smoking [8]. Moreover, full agonism by NRT at nAChRs is nonselective, thus, all types of nAChRs in both the brain and periphery are stimulated and this can contribute to unnecessary side effects such as nausea or tachycardia especially if individuals smoke cigarettes while using NRT products.

### 4.1.1. Selective nAChR agents

Preclinical studies have implicated the $\alpha4\beta2$ subtype of nAChR as most likely playing a central role in the pathophysiology of nicotine dependence. This receptor subtype predominates among all other nicotinic receptor subtypes in the brain, and it has a high affinity for nicotine [43]. Picciotto et al. found that $\beta2$ receptors are necessary for the maintenance of nicotine self-administration in rodent models, as evidenced by $\beta2$ knockout (KO) mice self-administering cocaine, but failing to maintain self-administration when the stimulant was switched to nicotine [44]. In a related fashion, $\alpha4\beta2$ KO mice that are administered nicotine do not manifest increases in striatal DA concentrations as compared to wild type mice [45]. Furthermore, genetically engineered knock-in mutant mice with $\alpha4$ nicotinic subunits rendered hypersensitive to nicotine respond to very low doses of agonist by exhibiting reinforcement after acute nicotine administration; whereas following chronic nicotine administration, these mutant mice exhibit other cardinal features of dependence such as tolerance and sensitization [43].

Since the $\alpha4\beta2$ nAChR subtype appears to play an important role in the development of nicotine dependence, a variety of selective agents targeting this receptor have been

developed for testing in humans as potential aids to smoking cessation. To date, the majority of these compounds have been α4β2 *partial agonists*. These compounds have appeal over full agonists because they have the potential to mitigate both the positive and negative reinforcement associated with tobacco smoking. Thus, in the presence of nicotine from smoking, such agents hold the promise of blocking nicotine-induced reward by having antagonistic blocking effects at α4β2 receptors; whereas in the absence of nicotine, these compounds' agonistic effects should, theoretically, ameliorate nicotine withdrawal much like the full agonists do.

Based on a review of pharmaceutical compounds fitting this profile, it appears that at least three such agents are currently being tested in humans [46,47]. Perhaps the furthest along in development among these agents is varenicline (CP-526,555), an α4β2 partial agonist with phase II-A and II-B trials already completed and with phase III trials completed or underway. While there are scant published data available regarding this compound and its use in clinical trials, the company has released some reports to investors regarding the phase II-A trial that are available in the public domain [48]. Thus, this first proof-of-concept study examined varenicline 0.3–2 mg per day versus bupropion sustained-release (300 mg) in a 3-arm, 7-week, randomized, placebo-controlled clinical trial. According to the results released to date, almost half of varenicline-treated smokers quit smoking compared with 16% of subjects receiving placebo and 33% of smokers administered bupropion SR [48]. Data regarding weight change and side effects are not available; however, when taken with the positive reports of α4β2 partial agonists in animal models of nicotine dependence [47], selective partial agonism of this specific nAChR subtype appears to hold promise.

## 5. Therapeutic target #3:

### 5.1. Selective inhibition of monoamine oxidase (MAO)

In addition to nicotine's effects on dopaminergic neurotransmission in the brain, other components in tobacco smoke also indirectly affect this monoamine neurotransmitter. Monoamine oxidase (MAO) is a mitochondrial flavoenzyme found ubiquitously throughout the brain and body that catalyzes the oxidative deamination of exogenous and endogenous biogenic amines that includes dopamine [49]. MAO exists in two forms, A and B, that are the products of two discrete structural genes located on the X chromosome [50,51]. MAO-A, which is selectively inhibited by clorglyline and newer compounds such as moclobemide, preferentially deaminates norepinephrine, serotonin and epinephrine. MAO-B preferentially deami-nates benzylamine and phenylethylamine, and is selectively inhibited by deprenyl (selegiline) [52]. Dopamine and tyramine are approximately equally catabolized by both

forms of MAO [49,52]. Since inhibition of tyramine breakdown can lead to hypertensive crises in patients treated with non-selective MAO inhibitors (e.g. tranylcy-promine or phenelzine), both reversible inhibitors of MAO-A (e.g. moclobemide) and selective inhibitors of MAO-B (e.g. selegiline) have been developed to try to lessen the potential for this so-called 'cheese effect' [49,53].

Tobacco smoking leads to potent inhibition of both types (A and B) of MAO, and smokers have 30–40% lower MAO-B and 20–30% lower MAO-A activity than non-smokers [49,50,54]. Smoking-induced inhibition of MAO may have important implications for the development and mainten-ance of tobacco dependence, and the return of MAO activity following smoking abstinence may be yet a third therapeutic target for drug development in tobacco smokers.

As alluded to above, while nicotine is the main culprit in producing most of tobacco smoke's addicting effects, it appears that compounds in cigarette smoke other than nicotine are responsible for its MAO inhibitory effects. While the precise compounds have not been identified, it is known that amine/smoke adducts form when biogenic amines are exposed to aqueous extracts of tobacco smoke [49]. Adducts of 1,2,3,4-tetrahydroisoquinoline (THIQ) and 1,2,3,4-tetrahydro-β-carboline (THβC) have been found to act as competitive inhibitors for MAO-A and -B, and it is likely that these and related compounds mediate cigarette smoke's effects on MAO activity [55–57].

Since MAO-A and -B both catabolize dopamine intraneuronally, their potent inhibition by cigarette smoking should potentiate dopaminergic neurotransmission and, thus, further contribute to smoking's reinforcing effects. Ivan Berlin and we have proposed an hypothesis whereby chronic habitual tobacco smoking is best understood by a two component model involving both nicotine and reduced MAO activity [49]. In this 2-component model, the main effect of nicotine is on neurotransmitter and neuromodulator release, while the MAO-inhibiting compounds in tobacco smoke lead to the potentiation of these effects by slowing down the catabolism of dopamine and other neurotransmit-ters (e.g. norepinephrine and serotonin) known to be involved in the addiction process. The involvement of both of these mechanisms might help to explain why nicotine in tobacco products appears to be so addicting, whereas nicotine in pharmacologic replacement therapies so seldom produces a dependence state [49].

Tobacco-related inhibition of MAO activity reverses itself in 3–4 weeks after an individual quits smoking, and former smokers do not exhibit reductions in MAO activity compared with never smokers [58,59]. The return of MAO activity within days to weeks of quitting smoking probably occurs at the least opportune time, however, since the tobacco withdrawal syndrome is most likely characterized by a dopamine (as well as norepinephrine and serotonin) depletion state [60]. Thus, we have hypothesized that the return of MAO activity levels to normal levels following successful smoking cessation most likely contributes to the

tobacco withdrawal syndrome, especially subacute and more protracted withdrawal symptoms and signs, by causing increased catabolism of monoamine neurotransmitters at a time when they are in relatively short supply.

### 5.1.1. Substituting a selective MAOI as a smoking replacement

Several small-scale trials in smokers motivated to try to quit smoking provide evidence that selective MAOIs might be efficacious as adjunctive medications for the treatment of tobacco dependence. In one laboratory study, 15 smokers received the selective MAO-B inhibitor, selegiline (10 mg/day) and placebo in counterbalanced order for two, 4-day periods separated by a 2-week washout period [61]. During the lab sessions, ad lib smoking sessions were conducted after brief enforced periods of abstinence to determine the medication's effects on tobacco withdrawal and response to smoking. The authors found that selegiline decreased craving for tobacco and also reduced the number of cigarettes smoked and smoking satisfaction ratings during the smoking sessions [61].

Two published clinical trials, both using selegiline dosages of 10 mg per day, also provide preliminary evidence that this selective MAOI appears safe for use and increases smoking cessation rates compared with placebo in tobacco dependent smokers. George et al., randomized 40 subjects in an 8-week, double blind placebo controlled study and found that, compared with placebo, selegiline significantly improved weekly point prevalence abstinence rates and smoking cessation rates during the last 4 weeks of the trial (selegiline 30% vs. placebo 5%; $P = 0.07$) [62]. At the 6-month follow-up period, selegiline-treated subjects continued to report higher rates of 7-day point prevalence abstinence (20%) compared with placebo (5%); however, because of the small sample size, this finding also did not reach statistical significance. Selegiline was well tolerated in these smokers, and treatment retention was similar between placebo and drug groups [62].

Using an adjunctive treatment design and a 1-year follow-up period, Biberman et al., reported that adding selegiline to an 8-week course of transdermal nicotine replacement was associated with a doubling of the 52-week continuous abstinence rate in selegiline-treated smokers compared with subjects who received patch therapy and placebo [63]. While this result also did not quite reach statistical significance ($P = 0.08$), the small sample size and lack of a standardized concomitant psychosocial intervention during the trial probably contributed to this. However, when taken together with the findings of Houtsmuller et al. [61], and George et al. [62], these small-scale proof of concept studies provide consistent evidence that selective inhibition of MAO-B may be yet another therapeutic target for the treatment of tobacco dependence.

## 6. Discussion

As summarized in Table 2, in this paper we have highlighted three novel therapeutic targets for the treatment of tobacco addiction that we believe hold great future promise for smokers motivated to try to quit smoking. With the exception of selegiline, which is FDA-approved for the adjunctive treatment of Parkinson's Disease when used with levodopa/carbidopa, all of the drugs discussed in this article are investigational medications that have not been approved by the US FDA or other regulatory agencies. Thus, although the phase II and, in the case of the CB-1 blocker, rimonabant, phase III trials we have discussed have been positive, it remains to be seen whether the long-term safety and efficacy of these agents will be demonstrated, and the reader is urged to place these findings in the proper perspective. The reader should also be mindful that, to our knowledge, the rimonabant and varenicline results discussed herein have not yet, as of the time of this writing, undergone the scrutiny of independent scientific peer review, a critical step in the evaluation of any investigational medication. However, these same cautionary statements apply to other compounds being developed for this indication [8], and the investigational medications we have highlighted have substantial preclinical and clinical evidence behind them to warrant enthusiasm.

In addition to the three novel mechanisms of action and corresponding agents we have described in this article, several other nicotine and non-nicotine medications are being developed to help tobacco dependent men and women quit smoking. New nicotine replacement medications such as the nicotine straw are being developed to improve adherence by making the medications easier to use, and nicotine vaccines are also under development [8]. Other agents targeting the α7 nicotinic receptor subtype such as

Table 2
Promising therapeutic targets for new drug development in the treatment of tobacco dependence

| Therapeutic target | Prototypic agents | Proposed mechanism of action |
|---|---|---|
| Smoking-induced overactivation of the endocannabinoid system (ECS) | Rimonabant (SR141716) | Cannabinoid type 1 (CB-1) receptor blockade suppresses nicotine-induced EC release that contributes to tobacco smoking's reinforcing effects; added advantage of curbing post-cessation weight gain |
| α4β2 Nicotinic Receptor Subtype | Varenicline (CP-526, 555) | Partial agonism at α4β2 nAChRs ameliorates nicotine withdrawal and blocks smoking's reinforcing effects |
| Selective MAO-B inhibition | Selegiline (l-deprenyl) | Forestalls return of MAO-B activity after smoking cessation that contributes to subacute and protracted nicotine withdrawal |

GTS-21 (DMXBA, anabaseine) are being developed both as possible aids to smoking cessation and as cognitive enhancers [8,64,65]. Finally, a whole host of agents are being tested in various animal models to evaluate their potential as therapeutic agents for tobacco dependence [66]. Thus, there is much optimism that within the next few years we will have several new medications available in our treatment armamentarium to combat this pernicious disease.

## References

[1] Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. J Am Med Assoc 2004;291(10): 1238–45.

[2] World Health Organization. The World Health Report 2002: Reducing risks, promoting healthy life. 1–94. 2002. Geneva Switzerland: World Health Organization.

[3] Centers for Disease Control and Prevention. State-specific prevalence of current cigarette smoking among adultsUnited States, 2003. MMWR Morb Mortal Wkly Rep, 2004;53(44):1035–1037.

[4] Mackay J, Eriksen M. The tobacco atlas. Brighton, United Kingdom: Myriad Editions Limited; 2002.

[5] Fiore MC, Bailey WC, Cohen SJ, et al. Clinical practice guideline Treating tobacco use and dependence. Rockville, MD: US Department of Health and Human Services; 2000.

[6] Rigotti NA. Clinical practice. Treatment of tobacco use and dependence. N Engl J Med 2002;346(7):506–12.

[7] George TP, O'Malley SS. Current pharmacological treatments for nicotine dependence. Trends Pharmacol Sci 2004;25(1):42–8.

[8] Foulds J, Burke M, Steinberg M, Williams JM, Ziedonis DM. Advances in pharmacotherapy for tobacco dependence. Expert Opin Emerg Drugs 2004;9(1):39–53.

[9] Kandel D, Chen K, Warner LA, Kessler RC, Grant B. Prevalence and demographic correlates of symptoms of last year dependence on alcohol, nicotine, marijuana and cocaine in the US population. Drug Alcohol Depend 1997;44(1):11–29.

[10] Kalman D, Hayes K, Colby SM, Eaton CA, Rohsenow DJ, Monti PM. Concurrent versus delayed smoking cessation treatment for persons in early alcohol recovery. A pilot study. J Subst Abuse Treat 2001;20(3): 233–8.

[11] Burling TA, Salvio MA, Seidner AL, Ramsey TG. Cigarette smoking in alcohol and cocaine abusers. J Subst Abuse 1996;8(4):445–52.

[12] Zevin S, Gourlay SG, Benowitz NL. Clinical pharmacology of nicotine. Clin Dermatol 1998;16(5):557–64.

[13] Dani JA. Overview of nicotinic receptors and their roles in the central nervous system. Biol Psychiatry 2001;49(3):166–74.

[14] Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. Pharmacol Biochem Behav 2001;70(4):439–46.

[15] Fagen ZM, Mansvelder HD, Keath JR, McGehee DS. Short- and long-term modulation of synaptic inputs to brain reward areas by nicotine. Ann NY Acad Sci 2003;1003:185–95.

[16] Dani JA. Roles of dopamine signaling in nicotine addiction. Mol Psychiatry 2003;8(3):255–6.

[17] Picciotto MR, Corrigall WA. Neuronal systems underlying behaviors related to nicotine addiction: neural circuits and molecular genetics. J Neurosci 2002;22(9):3338–41.

[18] Pontieri FE, Tanda G, Orzi F, Di Chiara G. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 1996;382(6588):255–7.

[19] Kelley AE. Memory and addiction: shared neural circuitry and molecular mechanisms. Neuron 2004;44(1):161–79.

[20] Mansvelder HD, Keath JR, McGehee DS. Synaptic mechanisms underlie nicotine-induced excitability of brain reward areas. Neuron 2002;33(6):905–19.

[21] Mansvelder HD, De Rover M, McGehee DS, Brussaard AB. Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction. Eur J Pharmacol 2003; 480(1–3):117–23.

[22] Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology, XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54(2):161–202.

[23] Westlake TM, Howlett AC, Bonner TI, Matsuda LA, Herkenham M. Cannabinoid receptor binding and messenger RNA expression in human brain: an in vitro receptor autoradiography and in situ hybridization histochemistry study of normal aged and Alzheimer's brains. Neuroscience 1994;63(3):637–52.

[24] Carai MA, Colombo G, Gessa GL. Rapid tolerance to the intestinal prokinetic effect of cannabinoid CB1 receptor antagonist, SR 141716 (Rimonabant). Eur J Pharmacol 2004;494(2–3):221–4.

[25] Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003;63(4):908–14.

[26] De Petrocellis L, Cascio MG, DiMarzo V. The endocannabinoid system: a general view and latest additions. Br J Pharmacol 2004; 141(5):765–74.

[27] Diana MA, Marty A. Endocannabinoid-mediated short-term synaptic plasticity: depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). Br J Pharmacol 2004;142(1):9–19.

[28] Gonzalez S, Cascio MG, Fernandez-Ruiz J, Fezza F, Di Marzo V, Ramos JA. Changes in endocannabinoid contents in the brain of rats chronically exposed to nicotine, ethanol or cocaine. Brain Res 2002; 954(1):73–81.

[29] Cohen C, Perrault G, Voltz C, Steinberg R, Soubrie P. SR141716, a central cannabinoid (CB(1)) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. Behav Pharmacol 2002;13(5–6):451–63.

[30] Cohen C, Perrault G, Griebel G, Soubrie P. Nicotine-associated cues maintain nicotine-seeking behavior in rats several weeks after nicotine withdrawal: reversal by the cannabinoid (CB(1)) receptor antagonist, rimonabant (SR141716). Neuropsychopharmacology 2004.

[31] Cota D, Marsicano G, Tschop M, et al. The endogenous cannabinoid system affects energy balance via central orexigenic drive and peripheral lipogenesis. J Clin Invest 2003;112(3):423–31.

[32] Horvath TL. Endocannabinoids and the regulation of body fat: the smoke is clearing. J Clin Invest 2003;112(3):323–6.

[33] Ravinet TC, Arnone M, Delgorge C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. Am J Physiol Regul Integr Comp Physiol 2003;284(2):R345–R53.

[34] Dale LC, Anthenelli RM. Rimonabant as an aid to smoking cessation in smokers motivated to quit: results from a US multicenter study-STRATUS US Trial. Paper presented at the Annual Meeting of the American College of Cardiology, New Orleans, Louisiana, March 2004.

[35] Despres JP. Rimonabant in obesity (RIO)-lipids trial results. Paper presented at the Annual Meeting of the American College of Cardiology, New Orleans, Louisiana, March 2004.

[36] Van Gaal L. RIO-Europe: a randomized double-blind study of weight reducing effect and safety of rimonabant in obese patients who are without comorbidities. Paper presented at the European Society of Cardiology Congress, Munich, Germany, August 2004.

[37] Pi-Sunyer X. Effect of rimonabant on weight reduction and weight maintenance: RIO-North America Trial. Paper presented at the Annual Meeting of the American Heart Association, New Orleans, Louisiana, November 2004.

[38] Picciotto MR. Nicotine as a modulator of behavior: beyond the inverted U. Trends Pharmacol Sci 2003;24(9):493–9.

[39] Kelley AE. Nicotinic receptors: addiction's smoking gun? Nat Med 2002;8(5):447–9.

[40] O'Dell LE, Bruijnzeel AW, Ghozland S, Markou A, Koob GF. Nicotine withdrawal in adolescent and adult rats. Ann NY Acad Sci 2004;1021:167–74.

[41] Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry 1986;43:289–94.

[42] Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2004;(3):CD000146.

[43] Tapper AR, McKinney SL, Nashmi R, et al. Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. Science 2004;306(5698):1029–32.

[44] Picciotto MR, Zoli M, Rimondini R, et al. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 1998;391(6663):173–7.

[45] Marubio LM, Gardier AM, Durier S, et al. Effects of nicotine in the dopaminergic system of mice lacking the alpha4 subunit of neuronal nicotinic acetylcholine receptors. Eur J Neurosci 2003;17(7):1329–37.

[46] Rueter LE, Anderson DJ, Briggs CA, et al. ABT-089: pharmacological properties of a neuronal nicotinic acetylcholine receptor agonist for the potential treatment of cognitive disorders. CNS Drug Rev 2004;10(2):167–82.

[47] Cohen C, Bergis OE, Galli F, et al. SSR591813, a novel selective and partial alpha4beta2 nicotinic receptor agonist with potential as an aid to smoking cessation. J Pharmacol Exp Ther 2003;306(1):407–20.

[48] CNNmoney. Pfizer unveils anti-smoking drug. CNNmoney 2004.

[49] Berlin I, Anthenelli RM. Monoamine oxidases and tobacco smoking. Int J Neuropsychopharmacol 2001;4(1):33–42.

[50] Berlin I, Said S, Spreuz-Varoquaux O, Olivares R, Launay JM, Puech AJ. Monoamine oxidase A and B activities in heavy smokers. Biol Psychiatry 1995;38(11):756–61.

[51] Shih JC, Chen K, Ridd MJ. Monoamine oxidase: from genes to behavior. Annu Rev Neurosci 1999;22:197–217.

[52] Lenders JW, Eisenhofer G, Abeling NG, et al. Specific genetic deficiencies of the A and B isoenzymes of monoamine oxidase are characterized by distinct neurochemical and clinical phenotypes. J Clin Invest 1996;97(4):1010–9.

[53] Berlin I, Said S, Spreux-Varoquaux O, et al. A reversible monoamine oxidase A inhibitor (moclobemide) facilitates smoking cessation and abstinence in heavy, dependent smokers. Clin Pharmacol Ther 1995;58:444–52.

[54] Fowler JS, Logan J, Wang GJ, et al. Low monoamine oxidase B in peripheral organs in smokers. Proc Natl Acad Sci USA 2003;100(20):11600–5.

[55] Bembenek ME, Abell CW, Chrisey LA, Rozwadowska MD, Gessner W, Brossi A. Inhibition of monoamine oxidases A and B by simple isoquinoline alkaloids: racemic and optically active 1,2,3,4-tetrahydro-,e,4-dihydro-, and fully aromatic isoquinolines. J Med Chem 1990;33(1):147–52.

[56] Glover V, Liebowitz J, Armando I, Sandler M. beta-Carbolines as selective monoamine oxidase inhibitors: in vivo implications. J Neural Transm 1982;54(3–4):209–18.

[57] Mendez-Alvarez E, Soto-Otero R, Sanchez-Sellero I, Lopez-Rivadulla LM. Inhibition of brain monoamine oxidase by adducts of 1,2,3,4-tetrahydroisoquinoline with components of cigarette smoke. Life Sci 1997;60:1719–27.

[58] Rose JE, Behm FM, Ramsey C, Ritchie Jr JC. Platelet monoamine oxidase, smoking cessation, and tobacco withdrawal symptoms. Nicotine Tob Res 2001;3(4):383–90.

[59] Anthenelli RM, Tipp J, Li TK, et al. Platelet monoamine oxidase activity in subgroups of alcoholics and controls: results from the Collaborative Study on the Genetics of Alcoholism. Alcohol Clin Exp Res 1998;22:598–604.

[60] Watkins SS, Koob GF, Markou A. Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. Nicotine & Tobacco Research 2000;2:19–37.

[61] Houtsmuller EJ, Thornton JA, Stitzer ML. Effects of selegiline (L-deprenyl) during smoking and short-term abstinence. Psychopharmacology (Berl) 2002;163(2):213–20.

[62] George TP, Vessicchio JC, Termine A, Jatlow PI, Kosten TR, O'Malley SS. A preliminary placebo-controlled trial of selegiline hydrochloride for smoking cessation. Biol Psychiatry 2003;53(2):136–43.

[63] Biberman R, Neumann R, Katzir I, Gerber Y. A randomized controlled trial of oral selegiline plus nicotine skin patch compared with placebo plus nicotine skin patch for smoking cessation. Addiction 2003;98(10):1403–7.

[64] Martin LF, Kem WR, Freedman R. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. Psychopharmacology (Berl) 2004;174(1):54–64.

[65] Kitagawa H, Takenouchi T, Azuma R, et al. Safety, pharmacokinetics, and effects on cognitive function of multiple doses of GTS-21 in healthy, male volunteers. Neuropsychopharmacology 2003;28(3):542–51.

[66] Cryan JF, Gasparini F, van Heeke G, Markou A. Non-nicotinic neuropharmacological strategies for nicotine dependence: beyond bupropion. Drug Discov Today 2003;8(22):1025–34.

[67] Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. Cochrane Database Syst Rev 2004;(3):CD000058.