Rationale, pharmacology and clinical efficacy of partial agonists of $\alpha_4\beta_2$ nACh receptors for smoking cessation

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Most smokers repeatedly fail in their attempts to stop smoking because of the addictive nature of the nicotine in tobacco products. Nicotine dependence is probably mediated through the activation of multiple subtypes of neuronal nicotinic acetylcholine receptor (nAChR), among which the mesolimbic $\alpha_4\beta_2$ subtype has a pivotal role. Here, we discuss the rationale for and the design of $\alpha_4\beta_2$ nAChR partial agonists as novel treatments for tobacco addiction. Such agents are expected to exhibit a dual action by sufficiently stimulating $\alpha_4\beta_2$-nAChR-mediated dopamine release to reduce craving when quitting and by inhibiting nicotine reinforcement when smoking. Potent and selective $\alpha_4\beta_2$ nAChR partial agonists that exhibit dual agonist and antagonist activity in preclinical models can be identified. The validity of this approach is demonstrated by the clinical efficacy of the $\alpha_4\beta_2$ nAChR partial agonist varenicline, which has significantly better quit rates than do other treatments and offers a new option for smoking cessation pharmacotherapy.

Smoking and tobacco addiction

Despite broad awareness of the health risks to individuals, tobacco smoking is the leading cause of preventable mortality in industrialized countries \cite{1}. Globally, tobacco-attributable mortality is projected to increase to 6.4 million per annum in 2015, and account for 10\% of all deaths \cite{2}. Currently available treatments for nicotine addiction, including nicotine replacement therapy (NRT) and bupropion (Zyban\textsuperscript{\textregistered}), only double the placebo quit rate in clinical trials \cite{3,4}, highlighting the unmet need for more-effective therapies. Even a marginal improvement in quit rate compared with existing therapies will have a significant impact on both individual wellbeing and the public health burden \cite{5,6}.

It is well recognized that smoking is one of the most difficult addictions to overcome: a result of the combination of the reinforcing effects of nicotine, and possibly other substances in tobacco, and the strong behavioral components and environmental cues associated with smoking \cite{7–9}. Cigarettes are particularly addictive because they are readily available and are extremely efficient at delivering the neuroactive components of tobacco to the brain. In essence, cigarettes provide, with each inhalation, individualized control over the amount and frequency of nicotine that is delivered to the brain and, thus, over mesolimbic dopamine (DA) neurotransmission – a crucial element of the response to addictive substances. The rapid and transient increases in DA release in the nucleus accumbens that inhaled nicotine produces will initiate and sustain compulsive substance-seeking behavior and drug dependence in humans, as described for other drugs of abuse. Several studies using genetically modified mice in which the $\alpha_4$ and/or $\beta_2$ subunit of the neuronal nicotinic acetylcholine receptor (nAChR) (Box 1) is deleted provide strong evidence that the nAChR containing these subunits is a key mediator of these nicotinic effects. Consequently, the $\alpha_4\beta_2$ nAChR has become a molecular target for the design of novel smoking-cessation agents, which are the subject of this article.

Although the central role of nicotine in tobacco addiction is not in debate, it is important to emphasize that this addiction is the result of changes in multiple neurotransmitter and receptor systems, coupled with environmental and behavioral secondary reinforcers that support continued smoking. Despite significant progress in knowledge of the dynamics of nAChRs, including receptor activation, desensitization, reactivation and upregulation, the exact role and complex interactions of these neurobiological substrates have not yet been satisfactorily unraveled. A critical evaluation of these underlying mechanisms is beyond the scope of this discussion (for recent reviews, see Refs \cite{10–13}).

In this article, we focus on the hypothesis that activation of $\alpha_4\beta_2$ nAChRs is central to nicotine dependence and we discuss the $\alpha_4\beta_2$ nAChR as a drug target, addressing the rationale, design and development of partial agonists of this receptor subtype as a smoking cessation pharmacotherapy.

Role of $\alpha_4\beta_2$ nAChRs in nicotine dependence

Recent insights into the molecular mechanisms that underlie nicotine dependence have revealed unique
opportunities for developing more-efficacious treatments for tobacco addiction. Upon smoking, inhaled nicotine enters the brain within seconds, reaching maximal concentrations within 2 min [14,15], and acts on nAChRs located on DA and GABA neurons in the mesolimbic system in the ventral tegmental area (VTA) (Figure 1). Nicotine can both activate and desensitize these receptors, depending on the concentration and duration of exposure (Box 1). Activation of nAChRs on mesolimbic DA neurons leads to DA release, whereas the desensitization of nAChRs on GABA neurons is thought to attenuate the GABA-mediated inhibitory drive. In addition, nicotine interacts with nAChRs on glutamate neurons that regulate the activity of DA and GABA neurons in the VTA. The differential activation and desensitization of nAChR subtypes on these neurons result in stimulated DA release in the nucleus accumbens (Figure 1), which initiates a physiological response that strongly contributes to the reinforcing effects of nicotine [11,12,16,17].

Although nicotine can interact with several nAChR subtypes in the mesolimbic pathway, such as $\alpha_4$, $\alpha_4^*$, and $\alpha_7$-containing nAChRs [18], there is convincing evidence that activation of mesolimbic nAChRs containing $\alpha_4$ and/or $\beta_2$ subunits – either as $\alpha_4\beta_2$ or more complex ($\alpha_4\beta_2^*$) combinations – has a pivotal role in the reinforcing effects of nicotine. For instance, preclinical studies in transgenic mice have shown that elimination of either the $\alpha_4$ or $\beta_2$ subunit attenuates the pharmacological and behavioral effects of nicotine [19,20], and targeted expression of $\beta_2$ subunits in the VTA of $\beta_2$-knockout mice reinstates nicotine-seeking behavior and nicotine-induced DA release [21]. Recent clinical evidence that selective partial agonists of $\alpha_4\beta_2$ nAChRs are efficacious smoking-cessation agents provides further validation of the role of $\alpha_4\beta_2$ nAChRs in tobacco addiction.

Between cigarettes, brain nicotine levels gradually decrease, triggering several processes that contribute to the cycle of craving and urge to smoke that maintains nicotine dependence. It is believed that the rapidly recurring and transitory increases in mesolimbic DA levels following repeated exposure to, and withdrawal from, nicotine transmit salient reward and aversive signals to higher cortical centers, facilitating the learning and associations that lead to physical dependence, which is characterized by both somatic and psychoactive symptoms [7,22–24].

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**Box 1. Neuronal nAChRs: activation and desensitization**

Neuronal nAChRs are pentameric ligand-gated ion channels assembled from five of the 11 different $\alpha$ and $\beta$ subunits that have been identified in mammals. They consist of either five $\alpha$ subunits or a combination of $\alpha$ and $\beta$ subunits (e.g. $\alpha_4\beta_2$, the predominant subtype form in the mammalian brain), forming a central ion-conducting channel. According to the allosteric theory [49,50], these channels can be open (‘activated’), closed (‘resting’) or desensitized to regulate the passage of cations across the cell membrane. The transition into and out of the open mode can be monitored at the level of the individual receptors or populations of receptors (Figure I), using a variety of electrophysiology, ion flux or imaging methods.

The proportion of receptors in each mode is determined by the concentration and intrinsic activity of the agonist and by the duration of agonist binding. In the absence of agonist, the receptors strongly favor the closed mode, whereas agonist binding shifts the equilibrium from the closed to the open and desensitized modes. In the open mode, cations flow down their respective electrochemical gradients, depolarize the membrane and elicit an excitatory signal in neurons. However, agonist-bound receptors prefer the desensitized mode; in the continued presence of agonists such as nicotine, an increasingly greater fraction of receptors will become desensitized over time. For most ligand-gated ion channels, the binding of a full agonist favors the open mode more strongly than does the binding of a partial agonist. Thus, at a given level of receptor occupancy, partial agonists enable fewer ions to cross the cell membrane, resulting in a smaller excitatory signal and less DA release than are caused by full agonists (Figure II). It has been well established that long-term exposure to nicotine can modify the function and expression of $\alpha_4\beta_2$ nAChRs through diverse mechanisms, including receptor desensitization, posttranslational modifications and receptor upregulation, all of which could have a role in nicotine addiction [51,52]. For instance, prolonged exposure to low levels of agonist can desensitize nAChRs, resulting in inhibition of nAChR function. Consistent with this, it has been shown that, at low concentrations, (partial) agonists can act as antagonists at $\alpha_4\beta_2$ nAChRs [35,53,54].

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**Figure I.** Time course of the current evoked by the agonist nicotine (black diamond) in HEK cells expressing $\text{h} \alpha_4\beta_2$ nAChRs (patch clamp), with a schematic representation of the corresponding transitions among the three functional modes of the nAChRs.
dynamic array of responses probably contributes to both the reinforcing effects of nicotine and the craving symptoms upon smoking cessation, but it is not known exactly how changes in transmitter release and receptor dynamics interact to cause craving and to suppress craving between cigarettes and during smoking, respectively.

This article is based on the hypothesis that led to the development of partial agonists of \( \alpha_4\beta_2 \nAChR \) as effective smoking-cessation agents: that is, that smoking regulates the rapid increase and decrease in levels of nicotine in the brain that result in \( \alpha_4\beta_2 \)-nAChR-mediated neurobiological changes that lead to reinforcement and craving.

**Why \( \alpha_4\beta_2 \nAChR \) partial agonists for smoking cessation?**

Given the central role of \( \alpha_4\beta_2 \nAChR \) in the reinforcement and maintenance of nicotine dependence, modulating the activity of these receptors would be expected to have therapeutic benefits. Specifically, partial agonists of \( \alpha_4\beta_2 \nAChR \) that enhance the activity of these receptors sufficiently to blunt craving and withdrawal, but without associated abuse potential, are attractive options. Furthermore, high-affinity partial agonists of \( \alpha_4\beta_2 \nAChR \) would have the additional potential benefit of preventing nicotine from activating \( \alpha_4\beta_2 \nAChR \), thereby blocking its reinforcing effects. These considerations prompted the search for ligands that act as partial agonists at the \( \alpha_4\beta_2 \) subtype of \( \nAChR \) as novel treatments for smoking cessation.

By definition, partial agonists act as agonists with a smaller maximal effect at full receptor occupancy than does the full agonist (i.e., they have lower intrinsic functional activity). Additionally, partial agonists with high binding affinity act as antagonists of co-administered agonists and suppress their effects. By mimicking some of the agonist rewarding effects of nicotine, partial agonists of the \( \alpha_4\beta_2 \nAChR \) will, theoretically, relieve craving and withdrawal when quitting. Furthermore, during smoking, the presence of a partial agonist will reduce reinforcement by diminishing the repetitive nicotine-induced phasic DA increases that are mediated by \( \alpha_4\beta_2 \nAChR \) (Figure 2).

In theory, the combination of these effects would reduce smoking in the short term and could be expected, over a period of months, to attenuate the salient cues associated with nicotine-based positive reinforcement, thus facilitating the extinction of behaviors associated with smoking and, ultimately, the achievement of long-term abstinence.
Agonist and antagonist combinations: a proof of concept for partial agonists

Rational approaches to pharmacotherapy for nicotine addiction would include direct activation of $\alpha_4\beta_2$ nAChRs with an agonist to reduce craving and withdrawal symptoms when quitting, or blockade of $\alpha_4\beta_2$ nAChRs with an antagonist to reduce reinforcement and reward from smoking. The first approach, represented by nicotine replacement therapy (NRT), uses nicotine as an agonist in safe delivery forms by eliminating the smoke that causes tobacco-related illnesses. NRT is effective [3] at reducing craving and withdrawal associated with quitting; however, users are still theoretically able to obtain additional reinforcement during NRT because of a rapid and steep rise in nicotine peak levels when smoking during treatment [14] [Figure 1b(ii)], coupled with the sensory cues that further maintain tobacco dependence [8].

The second approach has been exemplified by treatment with the nonselective nAChR antagonist mecamylamine, the use of which was one of the earliest suggestions for smoking cessation pharmacotherapy [25]. Mecamylamine reduced subjective nicotine experiences in a dose-dependent manner [26] but produced inconsistent effects, increasing cigarette consumption in some studies, and its side
effects compromised compliance [27]. Rose and Levin [28] proposed a combination of these two approaches using the co-administration of nicotine and mecamylamine, hypothesizing that an agonist–antagonist mixture, when interacting in an appropriate ratio at $\alpha_4\beta_2$ nAChRs, would not only prevent withdrawal symptoms but also attenuate the reinforcing effects of nicotine. In initial small clinical trials using transdermal nicotine and oral mecamylamine, this combination achieved higher abstinence rates than did transdermal nicotine alone [29], providing conceptual validation of the mixed agonist–antagonist approach. However, the major practical challenge of maintaining a narrow agonist:antagonist ratio while administering two separate compounds with different pharmacokinetic and metabolic profiles remained. Nevertheless, this experiment defined the clear therapeutic objective of delivering dual agonist–antagonist $\alpha_4\beta_2$-selective action for smoking cessation. Could this be better achieved by combining these properties into a single molecule (i.e. an $\alpha_4\beta_2$-nAChR partial agonist) [Figure 1b(iii)]? Such an approach has the potential to provide an optimal ratio of agonist and antagonist, avoid the pitfalls associated with managing the exposure of two separate, nonselective compounds and achieve an optimized balance of partial agonist activity and duration of action.

**Design of $\alpha_4\beta_2$ nAChR partial agonists: clues from nature**

Cytisine (Figure 3), which is a plant alkaloid that has been used for >40 years in Eastern Europe as a smoking cessation agent (see later), provided early support for the partial agonist theory. In 1994, evidence revealed cytisine to be a
partial agonist of nAChRs [30], providing a rationale for its reported efficacy. Direct chemical modifications of cytisine did not lead to viable drug candidates (i.e. R≠H), but combining knowledge from morphine substructural studies with structural elements of other nicotinic agents led to partial agonist profiles and, ultimately, to varenicline [31–34]. Dianicline is a structurally related α4β2 nAChR partial agonist in Phase III [36].

The discovery and neuropharmacology of α4β2 nAChR partial agonists

Although the pharmacological characteristics of partial agonists are easily formulated, the actual identification of a partial agonist with the desired profile presents a formidable challenge. The characterization of nAChR partial agonists became more practical only in the 1990s, with the application of functional in vitro assays – most notably patch clamp and fluorescence imaging plate reader (FLIPR) methodology – to ion channels expressed in oocytes or mammalian cell lines. This enabled the evaluation of the whole spectrum of functional efficacies of partial agonists. Screening strategies to identify compounds with the desired properties of α4β2 nAChR partial agonists have been described [33–36]. Figure 4 summarizes a typical screening strategy – including receptor binding, electrophysiology, and in vitro and in vivo DA-release assays – before the compound is tested in animal models that can predict efficacy for smoking cessation (Box 2). In most of these assays, exemplified by data for varenicline (Figure 4), the effects of the partial agonist alone and in combination with nicotine are compared with the effects of nicotine. This provides a measurement of the partial agonist activity of a compound per se and of its antagonist activity in the presence of nicotine because potent partial agonists have comparable effects in the absence and the presence of nicotine.

The ideal partial agonist has a high binding affinity and achieves high free levels in the brain because these parameters determine whether sufficient levels of DA are released to relieve craving and whether the partial agonist can act as an antagonist of nicotine. With peak brain levels of ~300 nM [15] and a Kᵢ for α4β2 nAChRs of ~2 nM [35], nicotine can readily displace compounds with either poor binding affinity or low brain concentrations. The free levels of varenicline in the brain (equivalent to its free plasma levels of ~30 nM) [37] and its high α4β2-nAChR-binding affinity Kᵢ of 0.1 nM [35] are sufficient to prevent nicotine levels in smokers from fully activating α4β2 nAChRs. However, high-affinity compounds with poor brain penetration, such as cytisine, or low-affinity compounds such as dianicline [36] might be less effective at competing with nicotine for α4β2 nAChRs and could be expected to display only agonist activity (i.e. efficacy comparable to NRT), without sufficiently potent antagonist activity. Finally, no clinical data are available regarding the optimal agonist:antagonist ratio for smoking cessation treatment but, in our search for partial agonists, we assumed that 30–70% efficacy relative to nicotine would provide an optimal range. We reasoned that compounds

![Figure 3](image-url)
with higher intrinsic activity could produce dependence liability comparable to that of nicotine – although their brain penetration rates might be a more critical factor than relative efficacy – and that compounds with low intrinsic activity would act as antagonists and could precipitate withdrawal without relieving craving.

Clinical efficacy: do partial agonists of α₄β₂ nAChRs work?
As noted, the potential benefits of dual agonist and antagonist action, as proposed by Rose and Levin [28], were originally examined by simultaneous nAChR agonist (NRT) and antagonist (mecamylamine) administration
Box 2. Predicting smoking cessation efficacy with animal models

Animal models used in nicotine research [55] can identify compounds that: (i) animals perceive as being nicotine like; (ii) decrease nicotine self-administration; (iii) are significantly less reinforcing than nicotine; and (iv) do not produce withdrawal symptoms upon discontinuation. (i) Drug discrimination assesses the ability of an animal to detect the subjective effects of centrally acting drugs (i.e. whether a test compound feels more like saline or more like a reference agent, in this case nicotine). Because this procedure does not allow ‘in-between’ responses, partial agonists from various drug classes can fully substitute for the reference compound, as has been shown for varenicline [36]. (ii) Nicotine self-administration procedures are good translational models for the reinforcing effects of tobacco [56–58]. Intake that is essentially unrestricted, similar to that of a smoker, can be observed when nicotine is obtained after a fixed number of lever presses, enabling animals to establish their own patterns of intake. Acute pretreatment with nicotine agonists (nicotine), antagonists (mecamylamine and erysodine) and partial agonists (varenicline and dianicline) decreases nicotine self-administration by ~50% – similar to the effect of substituting saline for nicotine [35,36,59]. (iii) The reinforcing properties of a compound are assessed by requiring an increasing number of lever presses (‘raised costs’) to obtain each subsequent nicotine injection; in this paradigm, the reinforcement strength is reflected by the effects of substituting a drug for nicotine. For instance, the substitution of increasing doses of varenicline significantly increased responding at only one dose, compared with saline substitution, in contrast to three doses of nicotine [35]. It is important to note that acute saline substitution for nicotine causes only a 50% reduction in responding, which indicates that some self-administration is maintained by secondary reinforcements associated with the self-administration session, such as signaling lights and pump noise (perhaps analogous to the feel of a cigarette in the hand and other contextual cues associated with smoking). It takes several sessions of saline substitution for animals trained to self-administer nicotine to cease lever-pressing behavior completely, illustrating the complex nature of the primary and secondary reinforcing effects of nicotine [60]. (iv) Withdrawal symptoms can be assessed by the sudden discontinuation of chronic drug administration and by noting withdrawal signs, either through observations or through monitoring disruptions in operant behavior.

Two small studies showed that mecamylamine augmented the efficacy of NRT; however, there are no published data from larger studies confirming these results, and the combination has not yet become an established treatment for smoking cessation [29]. Interestingly, the antidepressant bupropion, which is an accepted first-line pharmacotherapy for smoking cessation [40], has also recently been shown to have antagonist activity at the α4β2 nAChR [41,42].

A recently published systematic review of clinical data for partial agonists of nicotinic receptors in smoking cessation [43] included cytisine and varenicline. A third α4β2 nAChR partial agonist, dianicline [36], is – like varenicline – the product of rational drug design for smoking cessation. Preliminary Phase II data indicated significantly higher end-of-treatment quit rates than those seen with placebo: 19% and 16% for 80 mg and 40 mg, respectively, compared with 8% for placebo [44]. Phase III clinical trials are in progress.

Cytisine is available in Eastern Europe in 1.5-mg tablets, under the trade name Tabex® (Sophrma, Sofia, Bulgaria). Recommended dosing begins with six tablets daily, taken every 2 h, tapering to 1–2 tablets daily over 25 days (http://www.tabex.net/41814_packageinsert.phtml). Although most of the clinical trials conducted between 1967 and 1987 do not conform to current standards of study design and conduct for smoking cessation trials, the data collectively indicate that cytisine is effective for smoking cessation [45]. In pooled data from three randomized placebo-controlled studies (one with long-term follow-up), self-reported responder rates are approximately twice those occurring with placebo (Table 1), which is similar to the treatment effect achieved with NRT [3]. It is possible that the efficacy of cytisine is limited by poor brain penetration, as discussed earlier.

Varenicline (Pfizer: CP526555) was taken into full clinical development because it combined high binding affinity at α4β2 nAChRs and 40–60% partial agonist activity with good oral bioavailability and predictable pharmacokinetics (highly absorbed, low plasma protein binding, almost completely renally excreted as unchanged varenicline, with an elimination half-life of ~24 h [37,46]). Varenicline, as CHANTIX™, was approved by regulatory agencies as an aid to smoking cessation treatment in the USA in May 2006 and, subsequently, as CHAMPIX™ in the EU; it has now been approved for marketing in >40 countries. Efficacy at smoking cessation has been demonstrated in four clinical trials that followed post-treatment

Table 1. Smoking cessation efficacy of α4β2 nAChR partial agonists in randomized controlled clinical trials

<table>
<thead>
<tr>
<th>α4β2 nAChR partial agonist</th>
<th>Odds ratio (95% CI)</th>
<th>Criterion</th>
<th>Refs</th>
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<tbody>
<tr>
<td>(number of trials*)</td>
<td>vs placebo</td>
<td></td>
<td></td>
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<tr>
<td><strong>End-of-treatment smoking cessation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Varenicline (2)</td>
<td>3.69 (2.88, 4.72)</td>
<td>CO-confirmed continuous abstinence during the last four weeks of the 12-week treatment period</td>
<td>∈</td>
</tr>
<tr>
<td>Cytisine (3)</td>
<td>1.93 (1.21, 3.06)</td>
<td>Point prevalence of self-reported abstinence at 3–8 weeks</td>
<td>[46]</td>
</tr>
<tr>
<td><strong>Long-term abstinence</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Varenicline (4)</td>
<td>3.22 (2.43, 4.27)</td>
<td>CO-confirmed continuous abstinence in weeks 9–52</td>
<td>[43]</td>
</tr>
<tr>
<td>Cytisine (1)</td>
<td>1.77 (1.30, 2.40)</td>
<td>Point prevalence of self-reported abstinence at two years</td>
<td>[43]</td>
</tr>
</tbody>
</table>

*Abbreviations: CI, confidence interval; CO, carbon monoxide.
*Number of clinical trials contributing data for meta-analysis.
smoking status to the end of one year [43]. Two Phase III trials compared 12-week treatment with varenicline (1 mg twice daily), 150 mg of sustained-release bupropion twice daily or placebo [47,48]. For varenicline, rates of end-of-treatment smoking cessation [measured as carbon monoxide (CO)-confirmed continuous abstinence during the last four weeks of the treatment period] and long-term abstinence (measured as continued abstinence from the last four weeks of treatment to the end of one year) were approximately three times those occurring with placebo (Table 1) and 1.5–1.9 times those caused by bupropion [47,48]. Compared with placebo, varenicline significantly reduced craving (urge to smoke) and negative effects associated with nicotine withdrawal. Varenicline also reduced smoking satisfaction, psychological reward and enjoyment of respiratory-tract sensations, as reported by individuals who smoked during treatment [47,48].

Concluding remarks

Treatment of tobacco addiction with partial agonists of α4β2 nAChRs offers a novel and well-validated pharmacotherapeutic approach. Mechanistically, these agents target the receptors that are believed to mediate the reinforcing effects of nicotine and, to some extent, mimic the agonist effects of nicotine sufficiently to reduce craving when quitting. Furthermore, partial agonists with sufficiently high receptor-binding affinity and free concentration in the brain will act as antagonists in the presence of nicotine, attenuating its reinforcing effects when smoking. Treatment of tobacco addiction with partial agonists builds on early experiments with agonist–antagonist combinations and on historical anecdotal data regarding the moderate effectiveness of the alkaloid cytisine. This approach has conferred robust clinical efficacy in the case of varenicline, which is now marketed as an aid to smoking cessation treatment. This novel treatment option is a welcome addition to available pharmacotherapies of nicotine dependence, providing improvement in abstinence rates that should provide a substantial public and individual health benefit.

Disclosure statement

Varenicline is a product of Pfizer and is marketed as CHANTIXTM (USA) and CHAMPIXTM (Europe and elsewhere). H.R., J.W.C., L.K.C., R.S.H. and K.E.W. are employees of Pfizer and own Pfizer stock. S.M.S. has received grants from and is a consultant for several pharmaceutical companies, including Pfizer, for which he is on the speakers’ bureau.

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