Preclinical pharmacology, efficacy, and safety of varenicline in smoking cessation and clinical utility in high risk patients

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Abstract: Smoking is still the most prominent cause of preventable premature death in the United States and an increasing cause of morbidity and mortality throughout the world. Although the current treatments such as nicotine replacement therapy (NRT) and bupropion are effective, long-term abstinence rates are low. Mechanism studies suggest that the pleasurable effects of smoking are mediated predominantly by nicotine, which activates the brain reward system by activation of brain α4β2 nicotinic acetylcholine receptors (nAChRs). Varenicline is a novel α4β2 nAChR partial agonist and has been found to be even more effective than NRT or bupropion in attenuating smoking satisfaction and in relieving craving and withdrawal symptoms after abstinence. Thus, varenicline has been recently approved to be a first-line medication for smoking cessation in the United States and European countries. Varenicline is generally well tolerated in healthy adult smokers, with the most commonly reported adverse effects being nausea, insomnia, and headache. However, growing postmarketing data has linked varenicline to an increase in neuropsychiatric symptoms such as seizures, suicidal attempts, depression, and psychosis as well as serious injuries potentially relating to unconsciousness, dizziness, visual disturbances, or movement disorders. Therefore, new safety warnings are issued to certain high risk populations, such as patients with mental illness and operators of commercial vehicles and heavy machinery. In particular, pilots, air traffic controllers, truck and bus drivers have been banned from taking varenicline.

Keywords: nicotine, varenicline, α4β2 nicotinic acetylcholine receptor, nAChRs, partial agonist, smoking cessation

Introduction

It is estimated that about 1.3 billion people smoke cigarettes worldwide and about 500 million people die annually from tobacco-related diseases.1–3 In the United States (US), about 45 million adults (~20%) smoke cigarettes or are exposed to secondhand smoking, resulting in about 18% of total mortality and 440,000 annual premature deaths.1–2 The annual economic cost of smoking in the US is about 200 billion dollars. Smoking cessation has shown to significantly reduce the risk of many smoking-related diseases such as lung cancer, chronic lung diseases, myocardial infarction, and stroke as well as decrease morbidity and mortality related to tobacco use.3

However, tobacco dependence is a chronic relapse disorder that is difficult to treat.3 Despite the availability of effective pharmacologic aids, such as nicotine replacement therapy (NRT) and bupropion sustained-release, these treatments only help 5%–15% of people to maintain long-term abstinence from smoking.4–6 Craving and withdrawal symptoms after tobacco cessation are the most important reasons to prevent smokers
from achieving long-term tobacco abstinence. For these reasons, novel pharmacotherapies are being developed in an attempt to improve long-term abstinence outcomes. Among the most promising of treatments is varenicline, a novel partial $\alpha_\beta_2$ nicotinic acetylcholine receptors (nAChR) agonist, which has recently been approved by the US Food and Drug Administration (FDA) as a smoking cessation aid. Varenicline has been found to be even more effective than placebo, NRT or bupropion in clinical trials.\(^6\)\(^7\) In this article, we review the mechanism-based medication development strategies, preclinical pharmacology, efficacy, and safety profiles of varenicline in the treatment of cigarette smoking in humans.

**Mechanism of tobacco dependence**

The mechanisms underlying tobacco addiction are not completely understood. Accumulating evidence indicates that nicotine is the major addictive component in tobacco.\(^7\) Nicotine binds to central and peripheral nAChRs. Acetylcholine (Ach) is an endogenous neurotransmitter that binds to and activates both nAChRs and muscarinic acetylcholine receptors. Neuronal nAChRs are ligand-gated ion channels with high permeability to $\text{Ca}^{++}$, and are formed from combinations of five subunits.\(^8\)\(^9\) To date, twelve different neuronal nAChR subunits have been cloned, including nine $\alpha$-subunits ($\alpha_2$–$\alpha_{10}$) and three $\beta$-subunits ($\beta_2$–$\beta_4$). Non-neuronal subunits, $\alpha_1$, $\beta_1$, $\gamma$, $\delta$, and $\varepsilon$, form peripheral nicotinic receptors at the neuromuscular junction.\(^10\) The neuronal subunits combine with two $\alpha$- and three $\beta$-, or five $\alpha_7$-subunits to form nAChRs (Figure 1).\(^10\)\(^11\) Both the $\alpha_4\beta_2$ and $\alpha_7$ subtypes of nAChRs are the most abundant subtypes in the brain and are localized on presynaptic terminals, somatodendrites, and postsynaptic cells.\(^8\)\(^9\) Activation of presynaptic nAChRs by Ach or nicotine potentiates neurotransmitter release, while activation of postsynaptic nAChRs increases excitability of postsynaptic cells by increasing influx of $\text{Na}^+$ and $\text{Ca}^{++}$ via nAChR channels.\(^10\)\(^12\)

One third of the $\alpha_4\beta_2$ nAChRs are located on the dopamine (DA) cells in the mesolimbic DA system (Figure 1).\(^13\)\(^14\) This system originates from DA neurons in the ventral tegmental area (VTA) in the midbrain and projects to the forebrain nucleus accumbens (NAc) and the prefrontal cortex (PFC).\(^15\) The $\alpha_4\beta_2$ nAChR subtype has been thought to play a vital role in mediating nicotine reward.\(^8\)\(^9\)\(^10\) This is supported by the finding that blockade of $\alpha_4\beta_2$ nAChRs by dihydro-β-erythroidine (DHβE) inhibits nicotine self-administration in rats.\(^16\) Genetic deletion of $\alpha_4$ or $\beta_2$ subunits largely abolishes nicotine binding to mouse brain and inhibits nicotine self-administration and nicotine-induced increases in NAc DA.\(^17\)\(^18\) Similarly, nicotine-mediated currents from VTA (DA) neurons are also inhibited by DHβE\(^17\)\(^19\) or dramatically decreased on midbrain neurons in $\beta_2$-kockout mice.\(^17\)\(^19\)\(^20\) These data suggest that both the behavioral and DA-releasing effects of nicotine are

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**Figure 1** Schematic diagram of the mesolimbic DA projection pathway in human brain, illustrating that nicotine activates $\alpha_4\beta_2$ nAChRs located on DA neurons in the VTA and increases VTA DA neuron activity as well as DA release in the NAc, dorsal striatum, and PFC. Insert: Simplified structure of $\alpha_4\beta_2$ nAChR (ion channel) located on surface of VTA DA neurons. Activation of $\alpha_4\beta_2$ nAChR opens the receptor ion channel, causing influx of $\text{Na}^+$ and/or $\text{Ca}^{++}$ and depolarization of VTA DA neuron.

**Abbreviations:** DA, dopamine; NAc, nucleus accumbens; nAChR, nicotinic acetylcholine receptors; PFC, prefrontal cortex; VTA, ventral tegmental area.
mediated predominantly by activation of $\alpha 4\beta 2$ nAChRs in the mesolimbic DA system.\textsuperscript{8,9,17,21} As stated above, the $\alpha 4\beta 2$ nAChR is a receptor ion channel with high affinity to nicotine. High concentrations of nicotine binds to the $\alpha 4\beta 2$ receptor, causing the ion channel opening and Na\textsuperscript{+} influx, which subsequently de polarizes VTA DA neurons and increases DA release in the NAc (Figure 1).\textsuperscript{21}

**Medication strategies for the treatment of nicotine addiction**

Modulating nAChRs can be achieved using nAChR agonists, antagonists, or partial agonists. Full agonists, such as NRT, mimic the effects of nicotine by activating the receptor, therefore reducing withdrawal symptoms during nicotine abstinence.\textsuperscript{22} NRT is proven effective in smoking cessation,\textsuperscript{23} although it does not produce complete abstinence because the smoker is still physically dependent on the effects of smoking. Antagonists, such as mecamylamine, compete with nicotine or ACh for occupancy of the receptors.\textsuperscript{24} Therefore, a full antagonist may fully block the pharmacological action of nicotine, such as nicotine reward. However, antagonists are prone to induce withdrawal symptoms by themselves.\textsuperscript{22} Surprisingly, mecamylamine in combination with NRT is more effective than NRT alone or mecamylamine alone in smoking cessation.\textsuperscript{25,26} This could be due to a functional effect of the agonist NRT (reduction of the withdrawal syndromes) in combination with the effect of the antagonist mecamylamine (attenuation of the reinforcing effects of nicotine). This finding suggests that the development of a nicotine partial agonist such as cytisine and varenicline may be optimal in the treatment of nicotine dependence because partial agonists display the properties of both agonists and antagonists. Partial agonists occupy the receptors, but only partially activate them. As a consequence, the action of a partial agonist is dependent on the receptor occupancy.\textsuperscript{27} In cigarette smokers, a partial agonist would mostly work as an antagonist during smoking (ie, high nicotine occupancy), but as an agonist during abstinence or withdrawal (ie, low nicotine occupancy). Thus, the rewarding effects of smoking would decrease substantially but not disappear completely, whereas withdrawal symptoms and craving episodes would occur less frequently during drug abstinence due to the release of a low-to-moderate level of DA produced by a partial agonist itself.\textsuperscript{28–30}

**Cytisine – an unnoticed smoking cessation drug since the 1960s**

Cytisine has a molecular structure somewhat similar to that of nicotine and varenicline (Figure 2). Cytisine is a natural insecticide present in plants called *Cytisus laburnum* (Golfen Rain).\textsuperscript{28} Cytisine (Tabex<sup>®</sup>; Sopharma, Sofia, Bulgaria) has been used in Bulgaria, Germany, Poland, and Russia as a smoking cessation aid since the 1960s.\textsuperscript{29–32} Despite its widespread use in Eastern and Central Europe, cytisine has remained largely unnoticed elsewhere, possibly due to limited access to the non-English literature.\textsuperscript{32} In addition, the underlying mechanisms have remained unclear until the 1990s when it was reported that cytisine is a partial agonist of nAChRs with high affinity for $\alpha 4\beta 2$ receptors.\textsuperscript{28,33} Behavioral studies in experimental animals suggest that cytisine produces low-to-moderate behavioral activation,\textsuperscript{34,35} conditioned place preference,\textsuperscript{36} and drug discriminative effects.\textsuperscript{37} In addition, drug-naive mice also self-administer cytisine intravenously, suggesting that cytisine has certain reinforcing effects.\textsuperscript{38}

**Preclinical pharmacology of varenicline**

Varenicline as a smoke-cessation aid was developed by Pfizer in 1997, largely based on cytisine described above.\textsuperscript{39,40}
In vitro binding assays indicate that varenicline has higher binding affinity ($K_i = 0.15 \text{nM}$) to α4β2 nAChRs than cytisine ($K_i = 0.23 \text{nM}$) or nicotine ($K_i = 1.6 \text{nM}$). It has 500–20,000-fold selectivity for α4β2 receptors over other nAChR subtypes (Table 1).\(^{39,41}\) In vitro functional patch clamp studies in HEK cells expressing nAChRs show that varenicline is a partial agonist with 45% of nicotine’s maximal efficacy at α4β2 nAChRs.\(^{39}\) In neurochemical models varenicline has significantly lowered (40%–60%) efficacy than nicotine in stimulating \(^{[125]}\text{I}\) DA release from rat brain slices in vitro, and in increasing DA release from rat NAc in vivo.\(^{39}\) When combined with nicotine, varenicline effectively attenuates the nicotine-induced DA release, consistent with partial agonism.\(^{39}\)

In animal models of addiction (Table 2), varenicline significantly inhibits nicotine self-administration,\(^{39}\) nicotine-enhanced brain stimulation reward,\(^{42}\) and nicotine priming, but not nicotine-associated cue-induced reinstatement of drug-seeking behavior.\(^{41}\) Varenicline itself does not induce reinstatement of nicotine seeking when administered as a priming injection.\(^{43}\) Varenicline partially substitutes for nicotine in self-administration testing in animals and partially generalizes to nicotine in the drug discrimination preclinical animal paradigm,\(^{39,44}\) suggesting that it may have some abuse potential, but lower than that of nicotine. In addition, varenicline also enhanced the basal locomotor activity in drug-naïve rats by itself, while pretreatment with varenicline attenuated acute nicotine-induced hyperlocomotion and repeated nicotine-induced behavioral sensitization.\(^{45}\)

In addition to being an α4β2 nAChR partial agonist, varenicline is also a full α7 nAChR agonist.\(^{46}\) To determine which receptor subtype underlies the action of varenicline, we have recently investigated the effects of α4β2 or α7 receptor agonists or antagonists on varenicline-enhanced electrical brain-stimulation reward (BSR). We found that systemic administration of nicotine or varenicline produced significant BSR enhancement, while pretreatment with varenicline dose-dependently attenuated nicotine-enhanced BSR. The BSR-enhancing effect produced by varenicline was blocked by mecamylamine (a full nAChR antagonist) and DHβE (a selective α4-containing nAChR antagonist), but not by methyllycaconitine (a selective α7 nAChR antagonist), suggesting an effect mediated by activation of α4β2 receptors.\(^{42}\) This suggestion is further supported by findings that SIB-1765F, another selective α4β2 nAChR agonist, produced a dose-dependent enhancement of BSR, while pretreatment with SIB-1765F also attenuated nicotine-enhanced BSR. In contrast, the selective α7 receptor agonist, AR-17779, altered neither BSR itself nor nicotine-enhanced BSR, at any dose tested.\(^{42}\) These findings are consistent with other reports that neither deletion of α7 receptors nor pharmacological blockade of α7 receptors alters the nicotine-produced discriminative stimulus effect.\(^{47–49}\) Together, these data suggest that the pharmacotherapeutic effects of varenicline on nicotine’s action are mediated by activation of the α4β2, rather than the α7 nAChR subtype.

The bioavailability of varenicline is high and is unaffected by the time of dosing or administration with food.\(^{50}\) After serial measurements, varenicline followed first-order kinetics, with an elimination $T_{1/2}$ of ∼24 h after single and multiple doses.\(^{50,51}\) Steady-state levels were achieved within four days with repeated oral dosing.\(^{51}\) Pharmacokinetic assays in healthy adult smokers indicated that varenicline did not undergo significant hepatic metabolism. Varenicline is <20% plasma protein bound. Its clearance is predominantly renal, with >90% excreted unchanged in the urine. Elimination of varenicline by the kidney primarily involves glomerular filtration and active tubular secretion via the renal organic cation transporter hOCT2.\(^{51,52}\)

**Therapeutic efficacy in humans**

Following promising results in preclinical studies, together with a strong theoretical foundation for its use, testing of varenicline began in clinical safety and efficacy trials. Table 3 summarizes the results of the ten clinical trials with varenicline since it was approved by the US FDA in 2006. These trials were conducted in Australia, Canada, Europe, Japan, South Korea, China, Thailand, Singapore, and the US, and enrolled both male and female subjects.

### Table 1  
In vitro binding affinity and functional activity of nicotine, cytisine, and varenicline at human brain nAChRs\(^{28,29,41}\)

<table>
<thead>
<tr>
<th></th>
<th>α4β2* (K, nM)</th>
<th>α3β4* (K, nM.)</th>
<th>α7* (K, nM)</th>
<th>α1β1γδ* (K, nM)</th>
<th>Functional activity at α4β2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine</td>
<td>1.6</td>
<td>530</td>
<td>6,300</td>
<td>6,300</td>
<td>–</td>
</tr>
<tr>
<td>Cytisine</td>
<td>0.23</td>
<td>840</td>
<td>4,200</td>
<td>250</td>
<td>56%</td>
</tr>
<tr>
<td>Varenicline</td>
<td>0.15</td>
<td>83.2</td>
<td>616.6</td>
<td>3,388.4</td>
<td>45%</td>
</tr>
</tbody>
</table>

**Notes:** \(^{[125]}\text{I}\)-nicotine, \(^{[125]}\text{I}\)-Epibatidine, \(^{[125]}\text{I}\)-α-Bungarotoxin, \(^{[125]}\text{I}\)-α-Bungarotoxin, % Response of 10 μM cytisine or varenicline relative to 10 μM (−)-nicotine.
Table 2 Behavioral effects of cytisine and varenicline in animal models related nicotine addiction

<table>
<thead>
<tr>
<th>Animal models</th>
<th>Cytisine</th>
<th>Varenicline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locomotor behavior</td>
<td>↑ Locomotion by itself&lt;sup&gt;34,35&lt;/sup&gt;</td>
<td>↑ Locomotion by itself&lt;sup&gt;46&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>↓ Nicotine-induced hyperactivity&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>↓ Nicotine-induced sensitization&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-administration (SA)</td>
<td>Naïve mice self-administer cytisine&lt;sup&gt;28&lt;/sup&gt;</td>
<td>↓ Nicotine SA&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No effect on food taking&lt;sup&gt;33&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supports low SA by itself&lt;sup&gt;39&lt;/sup&gt;</td>
</tr>
<tr>
<td>Brain-stimulation reward (BSR)</td>
<td>–</td>
<td>↑ BS R by itself&lt;sup&gt;40&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reinstatement</td>
<td></td>
<td>↓ Nicotine-enhanced BSR&lt;sup&gt;46&lt;/sup&gt;</td>
</tr>
<tr>
<td>Condition place preference (CPP)</td>
<td>Intra-VTA cytisine produces CPP&lt;sup&gt;36&lt;/sup&gt;</td>
<td>↓ Nicotine-induced reinstatement&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug discrimination (DD)</td>
<td>Producing DD by itself</td>
<td>But not on cue-induced reinstatement&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Partially substitutes nicotine in DD&lt;sup&gt;37&lt;/sup&gt;</td>
<td>No reinstatement by itself&lt;sup&gt;43&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dopamine (DA) in the nucleus accumbens</td>
<td>–</td>
<td>↑ DA by itself&lt;sup&gt;39&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td>↓ Nicotine-enhanced DA&lt;sup&gt;39&lt;/sup&gt;</td>
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</table>

(age range, 18–75 years) with no major comorbidities in the past year. The primary end point in most of the studies was efficacy, which was assessed primarily in terms of the continuous abstinence rate (CAR) or continuous quit rate (CQR) based on subjective reporting and confirmation by exhaled carbon monoxide (CO) measurement (≥10 ppm). The second end points included the urge to smoke, withdrawal symptoms, and the reinforcing effects of nicotine. In addition, odds ratio (OR) meta-analysis was also used to measure the comparative efficacy and abstinence rates for various smoking cessation medications in some of those clinical trials.

One of the trials reported follow-up data to 24 weeks,<sup>53</sup> and the others reported data to 52 weeks.<sup>54–62</sup> During treatment with oral varenicline titrated to 1 mg twice per day (bid), CO-confirmed CQRs or CARs at week 12 ranged from 28.8% to 65.4%, at week-24 from 20.8% to 70.5%, and at week-52 from 14.4% to 43.6%. In all these trials, varenicline 1 mg bid was associated with significantly higher CARs or CQRs compared with placebo at either week 12, week 24, or week 52 when compared with placebo. Three trials reported significantly higher CARs or CQRs with varenicline 1 mg bid compared with bupropion,<sup>55,57,58</sup> and one trial reported significantly higher CARs with varenicline compared with NRT (Table 3).<sup>62</sup> In a relapse-prevention study, CARs were significantly improved at 24 weeks with varenicline relative to placebo (70.5% vs 49.6%).<sup>59</sup>

Nides et al<sup>63</sup> conducted a pooled data analysis from the Phase III trials by Gonzales et al<sup>57</sup> and Jorenby et al<sup>63</sup> to explore the relative efficacy of varenicline, bupropion, and placebo for smoking cessation. Pooled CARs for weeks 9 through 12 were significantly greater for varenicline compared with bupropion and placebo (44.0%, 29.7%, and 17.7%, respectively; both comparisons P < 0.001).

West et al<sup>64</sup> conducted a similar analysis of pooled data from the same two Phase III trials<sup>57,58</sup> to evaluate the effects of varenicline, bupropion, and placebo on craving and withdrawal symptoms among smokers. They used the Minnesota Nicotine Withdrawal Scale (MNWS) to score craving and withdrawal symptoms in abstinent smokers (n = 612) and the Modified Cigarette Evaluation Questionnaire (mCEQ) to score the reinforcing effects of smoking in nonabstinent smokers (n = 1,115). They found that among all participants, cravings (urge to smoke) were significantly reduced with varenicline or bupropion compared with placebo (both P < 0.001) and with varenicline compared with bupropion (P = 0.008). Overall, varenicline or bupropion significantly inhibited negative withdrawal syndromes (depression, irritability, anxiety, difficulty concentrating, and insomnia) compared with placebo. In addition, they also found that varenicline-treated patients had significantly lower pleasurable effects of smoking compared with those treated with bupropion and placebo, as assessed by mCEQ scores for smoking satisfaction, psychological reward and enjoyment of respiratory tract sensations.

Cahill et al<sup>65</sup> conducted a systemic review and meta-analysis of the efficacy and tolerability of varenicline for...
smoking cessation in seven placebo-controlled trials, one relapse-prevention trial, and one open-label trial comparing varenicline with NRT. The nine trials covered 7,267 participants, 4,744 of whom used varenicline. The pooled ORs for CAR for varenicline versus placebo at six months or longer was 2.33 (95% confidence interval [CI]: 1.95–2.80), for varenicline versus bupropion at one year was 1.52 (95% CI: 1.22–1.88), and for varenicline versus NRT at one year was 1.31 (95% CI: 1.01–1.71). These data suggest that varenicline is even more effective than bupropion or NRT.

Mills et al66 conducted large-scale pooled data analysis from nine trials with varenicline (n = 5,192), 101 clinical trials with NRT (n = 31,321), and 31 trials with bupropion (n = 11,118) in order to compare treatment effects across interventions. They found that the pooled ORs for smoking cessation at four weeks post-target quit data with varenicline, NRT, and bupropion were 3.16, 2.25, and 2.05, respectively (P < 0.001, compared to placebo). Two trials evaluated head to head comparisons of varenicline and bupropion, and found a pooled OR 1.86 (P < 0.001). Indirect comparison between

<table>
<thead>
<tr>
<th>Varenicline dose</th>
<th>CARs (%) (Week 12)</th>
<th>CARs (%) (Week 24)</th>
<th>CARs (%) (Week 52)</th>
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<tr>
<td>Nides et al55</td>
<td>Placebo</td>
<td>10.6</td>
<td>7.3</td>
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<td></td>
<td>0.3 mg/d, 6 wks</td>
<td>16.7</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>1 mg/d, 6 wks</td>
<td>15.1</td>
<td>9.5</td>
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<tr>
<td></td>
<td>1 mg, bid, 6 wks</td>
<td>28.8***</td>
<td>20.8***</td>
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<td>Bupropion:</td>
<td>150 mg, bid, 6 wks</td>
<td>19.8*</td>
<td>10.3</td>
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<td>Oncken et al56</td>
<td>Placebo</td>
<td>11.6</td>
<td>–</td>
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<tr>
<td></td>
<td>0.5 mg/d, 12 wks</td>
<td>40.8***</td>
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<tr>
<td></td>
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<td>47.3***</td>
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<td>(Nontitrated)</td>
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<tr>
<td></td>
<td>1 mg, bid, 12 wks</td>
<td>54.6***</td>
<td>–</td>
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<tr>
<td></td>
<td>(Titrated)</td>
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<td>44.2***</td>
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<tr>
<td></td>
<td>(Nontitrated)</td>
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<td>17.7</td>
<td>10.5</td>
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<td>44.0***</td>
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<td>Bupropion:</td>
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<td>Jorenby et al58</td>
<td>Placebo</td>
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<td>13.2</td>
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<td>29.7***</td>
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<td>1 mg, bid, 12 wks</td>
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<td>21.8</td>
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<td>54.7**</td>
<td>33.6</td>
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<td>35.2</td>
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<td></td>
<td>1 mg, bid, 12 wks</td>
<td>65.4***</td>
<td>37.7</td>
</tr>
<tr>
<td>Niaura et al61</td>
<td>Placebo</td>
<td>11.6</td>
<td>9</td>
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<tr>
<td></td>
<td>0.5–2 mg/d, 12 wks</td>
<td>40.1***</td>
<td>28***</td>
</tr>
<tr>
<td>Aubin et al62</td>
<td>NRT, 21 mg/d, 6 wks</td>
<td>42.2</td>
<td>26.6</td>
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<td></td>
<td>1 mg, bid, 12 wks</td>
<td>55.6***</td>
<td>32.2</td>
</tr>
<tr>
<td>Wang et al67</td>
<td>Placebo</td>
<td>–</td>
<td>31.6</td>
</tr>
<tr>
<td></td>
<td>1 mg, bid, 12 wks</td>
<td>50.3***</td>
<td>–</td>
</tr>
</tbody>
</table>

Notes: ***P < 0.05, **P < 0.01, *P < 0.001, compared to placebo; #P < 0.05, ###P < 0.001, compared to NRT.
varenicline and NRT was OR 1.56 (P < 0.001), and between varenicline and bupropion OR 1.40 (P = 0.01).

Taken together, all these clinical data suggest that varenicline is superior to placebo, NRT, and bupropion for achieving abstinence from smoking in the short-term. Varenicline not only significantly attenuates the craving and withdrawal symptoms that occur during abstinence from smoking, but also significantly reduces the rewarding effects of nicotine and delay smoking relapse. Thus, varenicline, as the newest agent approved for smoking cessation, offers a new therapeutic option for the treatment of nicotine addiction.

**Tolerability**

Varenicline is generally well tolerated, with the most commonly reported adverse effects being nausea (28.8%, 9.9%, and 9.1%), insomnia (14.2%, 21.5%, and 12.6), and headache (14.2%, 11.1%, and 12.4) when compared to bupropion or placebo.54

**Nausea**

Mild to moderate nausea was the most frequently reported adverse effect (overall incidence, 24.4%–52.0%) that occurred at a higher rate in varenicline group than in placebo groups. Most episodes of nausea began in the first week of treatment and lasted for a median duration of ≤12 days. Dose titration appeared to reduce the overall incidence of nausea.56 There was a low incidence of nausea (13.4%) in varenicline-treated patients in the self-regulated flexible dosing study.61 In clinical trials, rates of treatment discontinuation due to nausea were generally <5% in varenicline-treated patients.54

**Insomnia**

Insomnia was another commonly reported adverse effect (14.0%–37.2%) associated with varenicline in the clinical trials.54,55 In general, insomnia occurred during the first four weeks of treatment with varenicline and became less common as treatment continued. In one extended treatment study,67 the incidence of insomnia was 19.1% with varenicline and 9.5% with placebo, suggesting that insomnia may be a common symptom of nicotine withdrawal during smoking-cessation attempts.

**Headache**

Other common adverse effects include headache, abnormal dreams, sleep disturbance, dizziness, dry mouth, increased appetite, weight gain, and constipation, which generally occurred at rates twice those with placebo.55–67 These adverse events were mild-to-moderate and transient, occurring predominantly during the first four weeks of therapy. The rates of discontinuation of varenicline treatment due to these adverse effects were <2% of participants.

**Utility in high risk people**

Since the approval of varenicline in May 2006, post-marketing surveillance suggests an association between varenicline and increased risk of erratic behavior, agitation, suicidal attempt, depression, psychosis, and severe injuries.68 While some of the behavioral and mood changes may be associated with nicotine withdrawal, some occurred in people who continued smoking while on the medication. The Institute for Safe Medication Practices (ISMP), an independent safety group, analyzed all adverse effects since the approval for marketing and found that varenicline accounted for more reports of serious adverse effects than any other drug in the US.69,70 Accordingly, the following people are thought to be high-risk to the use of varenicline.

**Patients with mental illnesses**

In the fourth quarter report of 2007,71 the FDA reported that among the total 988 serious injuries related to varenicline from 2006 to December 2007, there were 227 reports of suicidal attempt or behavior, 397 cases of possible psychosis, and 525 reports of hostility or aggression within days to weeks of initiating varenicline therapy for smoking cessation. Based on these reports, in November 2007, the FDA issued an early alert about the safety of varenicline, emphasizing the need for screening for pre-existing psychiatric illness before using varenicline and the importance of monitoring/reporting of mood or behavior changes.71 In May 2008, the FDA updated the previous Public Health Advisory and required that all patients should be observed and report to their physicians immediately for any mood or behavior changes, or worsening of preexisting psychiatric illness, during or upon discontinuation of varenicline therapy.72 This safety concern in such high-risk patients was further emphasized in more recent clinical reports.73–76 For example, about 5% patients (from the total 2,682 patients since December 2006) in the UK reported psychiatric effects during treatment with varenicline, including sleep disorder (43, 1.6%), anxiety (33, 1.2%), depression (29, 1.0%), abnormal dreams (26, 1.0%), mood change (17, 0.6%), and suicidal events (n = 5).77

**Commercial vehicle drivers**

and heavy machinery operators

In addition to those psychiatric effects described above, in the fourth quarter report of 2007,71 the FDA also reported 372...
movement disorders, 173 serious accidental injuries (including 28 traffic accidents and 77 falls), at least 148 reports of visual disturbances, 224 reports of potential cardiac rhythm disturbances, 338 moderate to severe skin reactions, and numerous reports of drowsiness that may affect patients’ ability to drive or operate machinery. Based on these reports, the ISMP issued immediate safety concerns related to varenicline use among operators of vehicles and heavy machinery as well as in any setting in which alertness and motor control are required to avoid serious injury. In May 2008, the Federal Motor Carrier Safety Administration and Federal Aviation Administration announced that pilots, air-traffic controllers, and truck and bus drivers are barred from taking smoking-cessation drug.

Conclusions

Varenicline (Chantix®, Pfizer, New York, NY), an α4β2 nAChR partial agonist, is the first in a new class of agents for smoking cessation. In the updated clinical practice guideline from the US Public Health Service, varenicline is recommended as a well-tolerated and effective first-line treatment option for smoking cessation. We should note that the majority of published clinical trials of the efficacy and tolerability of varenicline have generally excluded smokers with comorbid conditions (ie, psychiatric disorders, cardiovascular diseases), obese patients, adolescents, pregnant women, and light smokers (<10 cigarettes/d), which may reduce the generalization of the results to the broad population of smokers. To date, almost all clinical trials have been sponsored by the manufacturers of varenicline, suggesting that potential clinician bias may also affect the results even when double-blind procedures are used. Thus, more clinical-trials and postmarketing data are needed to confirm its efficacy, safety, and tolerability. Given the growing evidence suggesting a possible association between varenicline and increased psychiatric symptoms and other severe injuries potentially relating to unconsciousness, the FDA has issued special warning for the use of varenicline in patients with pre-existing psychiatric illnesses, and the Federal Motor Carrier Safety Administration and Federal Aviation Administration have banned the use of varenicline in pilots, air-traffic controllers, and truck and bus drivers.

Acknowledgments

This work was supported by the Intramural Research Program of the National Institute on Drug Abuse (NIDA) and National Institutes of Health (NIH), USA.

Disclosure

The author reports no conflicts of interest in this work.

References


46. Mihalak KB, Carroll FI, Lu etje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. *Mol Pharmacol*. 2006;70:801–805.


