

# Varenicline: The newest agent for smoking cessation

LISA A. POTTS AND CANDICE L. GARWOOD

More than a third of the world's adult population smokes cigarettes.<sup>1</sup> Tobacco smoke is a leading cause of death from heart attack, stroke, chronic obstructive pulmonary disease, and cancer.<sup>2</sup> Current guidelines emphasize the importance of tobacco cessation and outline a variety of interventions. Several first-line agents are available to patients who are willing to quit. These include extended-release bupropion and nicotine-replacement therapy (NRT) with gum, lozenge, inhaler, nasal spray, or patch. Clonidine and nortriptyline may be offered as secondline therapies if firstline therapies fail.<sup>3</sup> Varenicline is the first nonnicotine drug therapy developed specifically for use in smoking cessation.

Early research found that cytosine, an alkaloid plant product found in *Cytisus laburnum* L., or golden rain tree, is a partial agonist of the  $\alpha 4\beta 2$  nicotinic acetylcholine receptors. During World War II, the leaves of the golden rain tree were substituted for tobacco, as they were found to curb the craving for nicotine. For decades, cytosine has been used in Eastern Europe as an aid for smoking cessation and has been marketed under the trade name Tabex (Sopharma AD, Sofia, Bulgaria). De-

**Purpose.** The pharmacology, pharmacokinetics, clinical efficacy, safety, dosage and administration, and place in therapy of varenicline are reviewed.

**Summary.** Varenicline is the newest therapy approved by the Food and Drug Administration for smoking cessation and the first in its class targeting the neurobiology of nicotine addiction. Varenicline is selective for the  $\alpha 4\beta 2$  acetylcholine-receptor subtype as a partial agonist, thus conferring its effect in limiting the reinforcing aspect of the addictive nicotine molecule. Varenicline is completely absorbed orally and not affected by food. Steady state is reached within four days of administration. Three Phase III clinical trials of varenicline have been published. Two studies compared varenicline with bupropion in patients over age 18 years who smoked more than 10 cigarettes daily. When the data of the two trials were pooled, varenicline use was associated with significant improvements in the four-week carbon-monoxide-confirmed continuous quit rate (44.2% at weeks 9–12 compared with bupropion (29.7%) and placebo (17.7%) ( $p < 0.0001$

for each comparison). The third trial found that continuous quit rates were also significantly higher in patients treated with varenicline versus placebo. Varenicline is generally well tolerated. Varenicline has been administered concurrently with warfarin, digoxin, transdermal nicotine, bupropion, cimetidine, and metformin without any clinically significant drug interactions.

**Conclusion.** Varenicline, a newly approved agent for smoking cessation, offers a new option to patients who cannot tolerate the adverse effects associated with nicotine-replacement therapy and bupropion. It is also an alternative to consider in patients with contraindications to such therapies.

**Index terms:** Absorption; Anticoagulants; Antidepressants; Antidiabetic agents; Autonomic drugs; Bupropion; Cardiac drugs; Cimetidine; Digoxin; Dosage; Drug comparisons; Drug interactions; Food; Gastrointestinal drugs; Mechanism of action; Metformin; Nicotine; Nicotinic agonists; Pharmacokinetics; Smoking; Toxicity; Varenicline; Warfarin

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spite cytosine's use for smoking cessation, there is little documentation of its efficacy, and most studies evaluating its use were poorly designed.<sup>4</sup> Cytosine has served as a prototype and vehicle for discovery of new drug entities to

be used for smoking cessation. This is the case for varenicline (Chantix, Pfizer). This agent was derived from the cytosine compound to have greater bioavailability and selectivity for  $\alpha 4\beta 2$  receptors as a partial agonist.<sup>5</sup>

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### Pharmacology of nicotine

To understand the pharmacology of varenicline, it is necessary to understand the pharmacology of nicotine and its addiction. Nicotine is distilled from the cigarette as it is smoked and readily absorbed through the alveolar surface of the lung, rapidly reaching circulation through the extensive capillary network within the lung. It is estimated that nicotine rapidly reaches the brain within 11 seconds after inhalation.<sup>6</sup> Nicotine is the primary chemical in tobacco that contributes to tobacco dependency. Nicotine affects many neurotransmitters, but dopamine seems to be most responsible for the major addictive properties of nicotine. Nicotine from tobacco directly stimulates the acetylcholine receptors on dopamine-containing neurons, which are involved in the reinforcing centers of the brain, as a part of the mesolimbic system. The stimulation of these acetylcholine receptors is responsible for the overflow of dopamine in the reward centers of the brain, resulting in extracellular dopamine within the nucleus accumbens and an increased firing of dopaminergic neurons.<sup>7</sup> Many subtypes of acetylcholine receptors are associated with nicotine addiction. Acetylcholine-receptor subtypes, such as  $\alpha 4\beta 2$ , are ligand-gated ion channels found on the dopaminergic neurons and on the  $\gamma$ -aminobutyric acid (GABA)-containing cells. These receptors are thought to play a principal role in the mediation of nicotine addiction.<sup>5,8</sup> Unlike acetylcholine, which is degraded quickly by acetylcholinesterase, nicotine remains active at the  $\alpha 4\beta 2$  receptor sites for a prolonged period of time. While prolonged stimulation by most entities usually causes receptor down-regulation, nicotine stimulation at the acetylcholine receptors causes receptor up-regulation. This up-regulation desensitizes acetylcholine receptors, resulting in physical dependence, tolerance, and withdrawal symptoms,

thereby adding to the propensity for nicotine addiction.<sup>8</sup> Smokers who try to quit unaided experience symptoms of withdrawal, such as depression, insomnia, irritability, anxiety, difficulty concentrating, restlessness, weight gain, increased appetite, and decreased heart rate. Uncomfortable withdrawal symptoms reinforce the desire to smoke, perpetuating the dependency cycle.<sup>9</sup>

### Chemistry and pharmacology of varenicline

Varenicline has a high affinity and high selectivity for binding at the  $\alpha 4\beta 2$  receptor and is the first  $\alpha 4\beta 2$  receptor partial agonist in its class. Varenicline is a highly water-soluble salt, similar in structure to nicotine, composed of a pyridine and pyrrolidine ring. Varenicline has a three-ring configuration with tetrahydro, methano, pyridino, and benzapine components. Varenicline also binds with moderate affinity at the serotonin receptor, in part serving as the mechanistic rationale for the adverse effect of nausea that occurs with the agent.<sup>10</sup>

In vitro studies have shown that varenicline produces 68% of the response seen by the binding of nicotine to  $\alpha 4\beta 2$  receptors. In vivo studies have found the dopamine response to varenicline to be 32–60% of the response to nicotine. With this partial agonist–antagonist profile, the varenicline molecule competitively inhibits nicotine, thereby blocking the effects of nicotine at the  $\alpha 4\beta 2$  receptor site. Therefore, varenicline alleviates the symptoms of nicotine craving and withdrawal through its agonist activity while inhibiting the effects of repeated nicotine exposure by its antagonist activity.<sup>5</sup> Figure 1 illustrates varenicline's mechanism of action at the  $\alpha 4\beta 2$  receptor site as a partial agonist.

### Pharmacokinetics

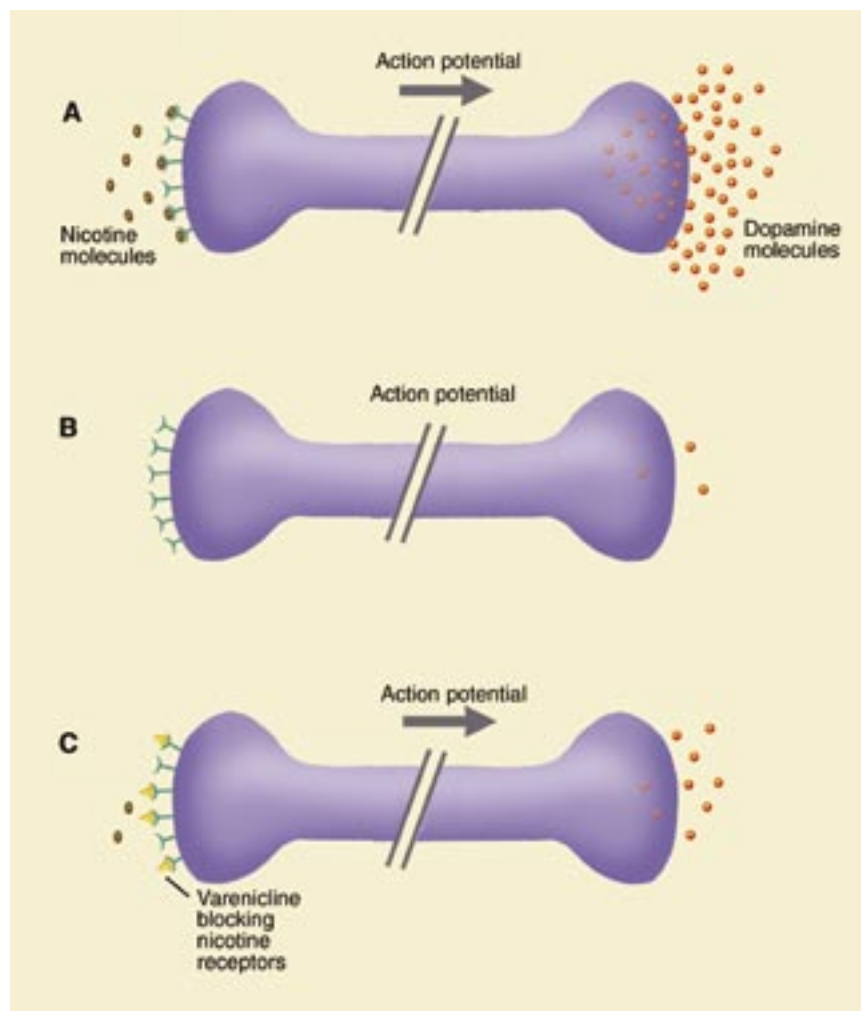
Varenicline is completely absorbed orally and not affected by food.

Steady state is reached within four days of administration. The time to reach maximum concentration is three to four hours. Varenicline exhibits linear kinetics.<sup>10</sup> Varenicline has low protein binding ( $\leq 20\%$ ) and is not metabolized, unlike nicotine, which undergoes hepatic metabolism by cytochrome P-450 (CYP) isoenzyme 2A6.<sup>11</sup> Most of the drug (92%) is excreted unchanged in the urine via glomerular filtration and active tubular secretion via organic cation transporters. Varenicline has a half-life of 24 hours. Mild renal failure does not affect varenicline's area under the concentration–time curve (AUC), though moderate to severe renal failure does increase the AUC 1.5–2-fold. However, this increase in the AUC is not thought to be clinically significant.<sup>10</sup>

### Clinical efficacy

Three Phase III clinical trials of varenicline have been published. Two were randomized, placebo-controlled, double-blind studies, enrolling 1022 and 1023 patients, respectively.<sup>12,13</sup> Patients older than 18 years who smoked over 10 cigarettes daily were randomized to receive one of three treatments: varenicline 1 mg p.o. twice daily, extended-release bupropion 150 mg p.o. twice daily, or placebo. Patients who had previous exposure to bupropion and NRT were excluded. Patients received treatment for 12 weeks and then were followed for an additional 40 weeks. Patients received smoking-cessation literature and brief weekly counseling during the 12 weeks of treatment.<sup>12,13</sup> When the data of the two trials were pooled, varenicline use was associated with significant improvements in the four-week carbon-monoxide-confirmed continuous quit rate (44.2%) at weeks 9–12 compared with bupropion (29.7%) and placebo (17.7%) ( $p < 0.0001$  for each comparison).<sup>14</sup> Individual trial analysis found that 12-week abstinence rates were higher in patients who received varenic-

**Figure 1.** Varenicline's mechanism of action. (A) Nicotine from cigarettes stimulates the production of high levels of dopamine in terminal synapse in the nucleus accumbens. (B) No nicotine present, which induces a state of nicotine withdrawal. (C) Varenicline blocks the nicotine-receptor sites and partially agonizes the receptors, stimulating moderate levels of dopamine in the terminal synapse in the nucleus accumbens. Illustration by Marie Dauheimer, CMI.



cline versus bupropion (43.9% versus 29.8%<sup>13</sup> and 44% versus 29.5%<sup>12</sup>) ( $p < 0.001$  for each comparison). Independently, continuous abstinence rates up to week 52 were significantly improved in only one of the two studies comparing varenicline with bupropion (23% versus 14.6%,  $p = 0.04$ ),<sup>13</sup> but varenicline maintained significant improvements over placebo in both studies (21.9% versus 8.4%,  $p < 0.001$ <sup>12</sup>; 23% versus 10.3%,  $p < 0.004$ <sup>13</sup>).

A third Phase III study had a 12-week open-label period where 1206 patients were treated with varenicline 1 mg p.o. twice daily. Those who remained abstinent at the end of the 12 weeks were enrolled in a second phase of blinded randomization to varenicline 1 mg p.o. twice daily or placebo for an additional 12 weeks. The continuous quit rates for weeks 13–24 of the trial were 70.5% and 49.6% for varenicline and placebo, respectively ( $p < 0.001$ ). For weeks

13–52, the continuous quit rates were 43.6% and 36.9% for varenicline and placebo, respectively ( $p = 0.02$ ).<sup>15</sup>

### Safety

Varenicline is generally well tolerated. Mild to moderate nausea and vomiting are the most common adverse effects, occurring in approximately 30% of patients.<sup>10</sup> Dropout rates due to adverse events in the two bupropion comparison studies were 10.5% and 8.6% for varenicline, 12.6% and 15.2% for bupropion, and 7.3% and 9% for placebo.<sup>12,13</sup> Other common adverse effects observed in over 10% of participants included headache, insomnia, and abnormal dreams. Adjusting the dosage over one week and taking it after a meal with a full glass of water helped to decrease these effects.<sup>8,10,14</sup> There are currently no known contraindications to varenicline therapy.<sup>10</sup>

### Drug interactions

Varenicline has been administered concurrently with warfarin, digoxin, transdermal nicotine, bupropion, cimetidine, and metformin without any clinically significant drug interactions.<sup>10</sup> Increased rates of nausea were reported when varenicline was given with NRT versus NRT alone.

### Dosage and administration

Varenicline was approved for smoking-cessation treatment on May 11, 2006, under the trade name Chantix (Pfizer). A cost comparison of currently available smoking-cessation therapies appears in Table 1. Varenicline is available in 0.5- and 1-mg tablets. The labeling information recommends adjusting the dosage from 0.5 mg once daily for days 1–3 to 0.5 mg twice daily for days 4–7, with a final dosage of 1 mg twice daily. Varenicline should be initiated one week before the patient's set "quit date." Varenicline is indicated for 12 weeks of treatment, and patients who have stopped smoking by the end of that time should receive

Table 1.  
**Cost Comparison of Currently Available Smoking-Cessation Therapies**

Drug	Cost (\$)/30-Day Supply <sup>a</sup>	Availability Status
Varenicline	106.99	Prescription
Bupropion	69.98	Prescription
Nicotine patch	120	Nonprescription
Nicotine gum	46.61–50.43 (108 pieces)	Nonprescription
Nicotine nasal spray	99.97 (3 bottles)	Prescription
Nicotine inhaler	136.99	Prescription
Nicotine lozenge	56.99 (108 pieces)	Nonprescription

<sup>a</sup>Prices obtained from www.drugstore.com in November 2006.

an additional 12 weeks of therapy. As the half-life of varenicline is long (approximately 24 hours), steady state is reached only after at least four days of therapy.<sup>10</sup> This would make varenicline a less-than-ideal therapy for patients who must abstain from smoking quickly, as is the case for many hospitalized patients.

**Place in therapy**

The data for varenicline look promising. The marginal benefit that varenicline has demonstrated over bupropion and its unsubstantiated benefit after discontinuation could limit its use. Yet, varenicline may be an option for those patients who concurrently smoke with cessation therapy, since varenicline is a non-nicotine drug and will antagonize the effects of nicotine. However, smoking during varenicline use does increase nausea. It is also important to consider the patient’s motivation to

quit and utilize behavioral therapies. Varenicline may be useful therapy in the patient who does not tolerate or wishes to avoid the adverse effects of bupropion or who has contraindications to such therapy (e.g., seizures).

**Conclusion**

Varenicline, a newly approved agent for smoking cessation, offers a new option to patients who cannot tolerate the adverse effects associated with NRT and bupropion. It is also an alternative to consider in patients with contraindications to such therapies.

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