

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

Zheng-Xiong Xi

National Institute on Drug Abuse,
Intramural Research Program,
Baltimore, MD, USA

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 $\alpha 4 \beta 2$ nicotinic acetylcholine receptors (nAChRs). Varenicline is a novel $\alpha 4 \beta 2$ 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, $\alpha 4 \beta 2$ 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

Correspondence: Zheng-Xiong Xi
National Institute on Drug Abuse,
Intramural Research Program,
Baltimore, MD 21224, USA
Tel +1 443 740 2517
Fax +1 443 740 2781
Email zxi@intra.nida.nih.gov

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 $\alpha_4\beta_2$ 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.^{5,6} 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 Ca^{++} , and are formed from combinations of five subunits.^{8,9} To date, twelve different neuronal nAChR subunits have been cloned, including nine α -subunits ($\alpha 2$ – $\alpha 10$) and three β -subunits ($\beta 2$ – $\beta 4$). Non-neuronal subunits, $\alpha 1$, $\beta 1$, γ , δ , and ϵ , form peripheral nicotinic

receptors at the neuromuscular junction.¹⁰ The neuronal subunits combine with two α - and three β -, 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 Na^+ and 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.^{8–10} This is supported by the finding that blockade of $\alpha 4\beta 2$ nAChRs by dihydro- β -erythroidine (DH β E) 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 DH β E^{17,19} or dramatically decreased on midbrain neurons in $\beta 2$ -knockout mice.^{17,19,20} These data suggest that both the behavioral and DA-releasing effects of nicotine are

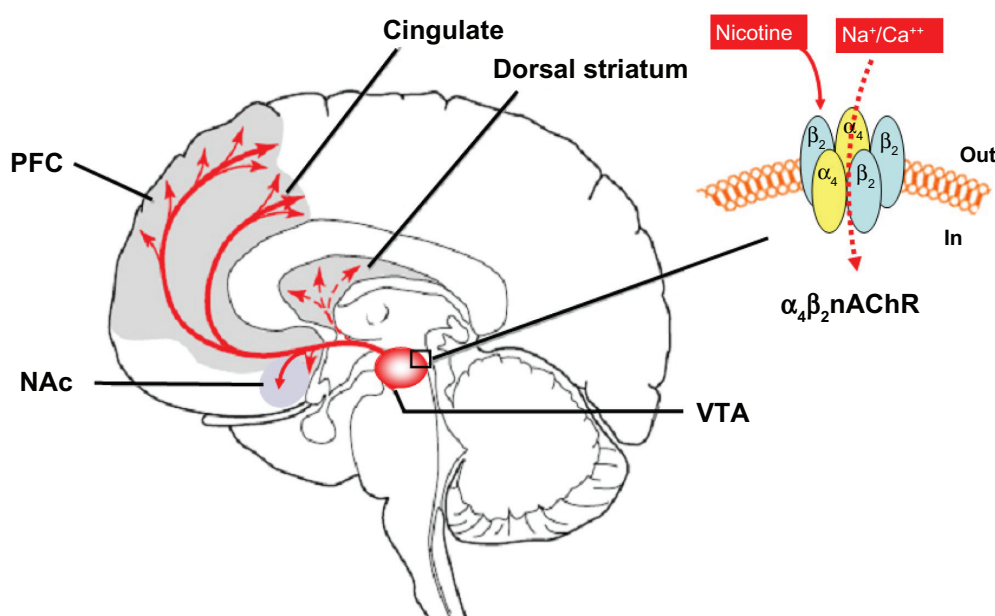


Figure 1 Schematic diagram of the mesolimbic DA projection pathway in human brain, illustrating that nicotine activates $\alpha 4\beta 2$ nAChRs located on DA neurons in the VTA and increases VTA DA neuron activity as well as DA release in the NAc, dorsal striatum, and PFC. Insert: Simplified structure 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 Na^+ and/or 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.^{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^+ influx, which subsequently depolarizes VTA DA neurons and increases DA release in the NAc (Figure 1).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.²² NRT is proven effective in smoking cessation,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.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.²² Surprisingly, mecamylamine in combination with NRT is more effective than NRT alone or mecamylamine alone in smoking cessation.^{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.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.^{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* (Golden Rain).²⁸ Cytisine (Tabex®; Sopharma, Sofia, Bulgaria) has been used in Bulgaria, Germany, Poland, and Russia as a smoking cessation aid since the 1960s.^{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.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.^{28,33} Behavioral studies in experimental animals suggest that cytisine produces low-to-moderate behavioral activation,^{34,35} conditioned place preference,³⁶ and drug discriminative effects.³⁷ In addition, drug-naïve mice also self-administer cytisine intravenously, suggesting that cytisine has certain reinforcing effects.³⁸

Preclinical pharmacology of varenicline

Varenicline as a smoke-cessation aid was developed by Pfizer in 1997, largely based on cytisine described above.^{39,40}

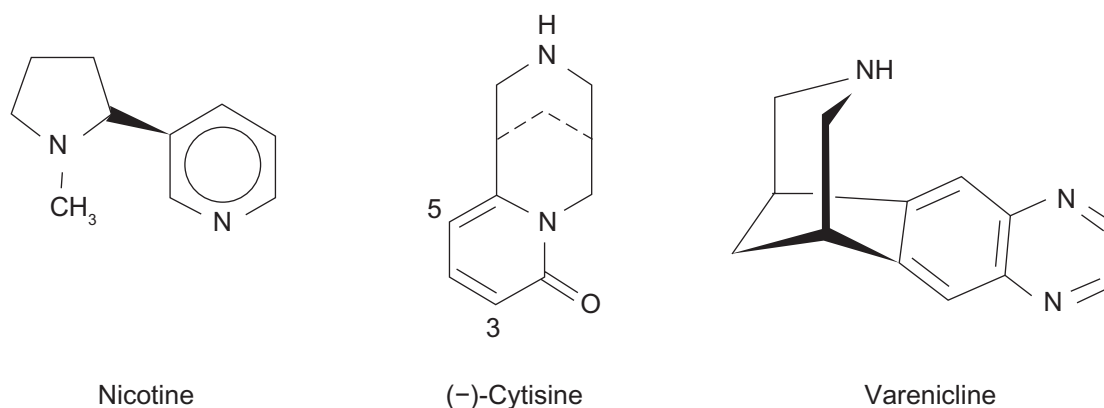


Figure 2 Chemical structures of nicotine, cytisine, and varenicline.

In vitro binding assays indicate that varenicline has higher binding affinity ($K_i = 0.15$ nM) to $\alpha 4\beta 2$ nAChRs than cytosine ($K_i = 0.23$ nM) or nicotine ($K_i = 1.6$ nM). It has 500–20,000-fold selectivity for $\alpha 4\beta 2$ 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 $\alpha 4\beta 2$ nAChRs.³⁹ In neurochemical models varenicline has significantly lowered (40%–60%) efficacy than nicotine in stimulating [³H]-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.⁴³ 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 $\alpha 4\beta 2$ nAChR partial agonist, varenicline is also a full $\alpha 7$ nAChR agonist.⁴⁶ To determine which receptor subtype underlies the action of varenicline, we have recently investigated the effects of $\alpha 4\beta 2$ or $\alpha 7$ 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 DH β E (a selective $\alpha 4$ -containing nAChR antagonist), but not by methyllycaconitine (a selective $\alpha 7$ nAChR antagonist), suggesting an effect mediated by activation of $\alpha 4\beta 2$ receptors.⁴² This suggestion is further supported by findings that SIB-1765F, another selective $\alpha 4\beta 2$ nAChR agonist, produced a dose-dependent enhancement of BSR, while pretreatment with SIB-1765F also attenuated nicotine-enhanced BSR. In contrast, the selective $\alpha 7$ receptor agonist, ARR-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 $\alpha 7$ receptors nor pharmacological blockade of $\alpha 7$ 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 $\alpha 4\beta 2$, rather than the $\alpha 7$ 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, cytosine, and varenicline at human brain nAChRs^{28,29,41}

	$\alpha 4\beta 2^a$ (K_i , nM)	$\alpha 3\beta 4^b$ (K_i , nM _i)	$\alpha 7^c$ (K_i , nM)	$\alpha 1\beta 1\gamma\delta^d$ (K_i , nM)	Functional activity at $\alpha 4\beta 2^e$
Nicotine	1.6	530	6,300	6,300	–
Cytosine	0.23	840	4,200	250	56%
Varenicline	0.15	83.2	616.6	3,388.4	45%

Notes: ^a[³H]-Nicotine, ^b[³H]-Epibatidine, ^c[¹²⁵I]- α -Bungarotoxin, ^d[¹²⁵I]- α -Bungarotoxin, ^e% Response of 10 μ M cytosine or varenicline relative to 10 μ M (–)-nicotine.

Table 2 Behavioral effects of cytosine and varenicline in animal models related nicotine addiction

Animal models	Cytosine	Varenicline
Locomotor behavior	↑ Locomotion by itself ^{34,35}	↑ Locomotion by itself ⁴⁵ ↓ Nicotine-induced hyperactivity ⁴⁵ ↓ Nicotine-induced sensitization ⁴⁵
Self-administration (SA)	Naïve mice self-administer cytosine ³⁸	↓ Nicotine SA ³⁹ No effect on food taking ³⁹ Supports low SA by itself ^{39,43}
Brain-stimulation reward (BSR)	–	↑ BSR by itself ⁴² ↓ Nicotine-enhanced BSR ⁴²
Reinstatement	–	↓ Nicotine-induced reinstatement ⁴³ But not on cue-induced reinstatement ⁴³ No reinstatement by itself ⁴³
Condition place preference (CPP)	Intra-VTA cytosine produces CPP ³⁶	–
Drug discrimination (DD)	Producing DD by itself Partially substitutes nicotine in DD ³⁷	Fully substitutes nicotine in DD ³⁹
Dopamine (DA) in the nucleus accumbens	–	↑ DA by itself ³⁹ ↓ Nicotine-enhanced DA ³⁹

(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,⁵³ and the others reported data to 52 weeks.^{54–62} 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 to bupropion,^{55,57,58} and one trial reported significantly higher CARs with varenicline compared with NRT (Table 3).⁶² In a relapse-prevention study, CARs were significantly improved at 24 weeks with varenicline relative to placebo (70.5% vs 49.6%).⁵⁹

Nides et al⁶³ conducted a pooled data analysis from the Phase III trials by Gonzales et al⁵⁷ and Jorenby et al⁵⁸ 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 al⁶⁴ conducted a similar analysis of pooled data from the same two Phase III trials^{57,58} 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 al⁶⁵ conducted a systemic review and meta-analysis of the efficacy and tolerability of varenicline for

Table 3 Clinical efficacy (CARs) of varenicline in human clinical trials

	Varenicline dose	CARs (%) (Week 12)	CARs (%) (Week 24)	CARs (%) (Week 52)
Nides et al ⁵⁵ (n = 638)	Placebo	10.6	7.3	4.9
	0.3 mg/d, 6 wks	16.7	9.5	7.9
	1 mg/d, 6 wks	15.1	9.5	5.6
	1 mg, bid, 6 wks	28.8**	20.8**	14.4**
	Bupropion:	19.8*	10.3	6.3
	150 mg, bid, 6 wks			
Oncken et al ⁵⁶ (n = 1,210)	Placebo	11.6	—	3.9
	0.5 mg/d, 12 wks (Titrated)	40.8***	—	Pooled (Titrated and Nontitrated):
	0.5 mg, bid, 12 wks (Nontitrated)	47.3***	—	18.5***
	1 mg, bid, 12 wks (Titrated)	54.6***	—	Pooled (Titrated and Nontitrated):
	1 mg, bid (Nontitrated)	44.2***	—	22.4***
Gonzales et al ⁵⁷ (n = 1,025)	Placebo	17.7	10.5	8.4
	1 mg, bid, 12 wks	44.0***	29.5***	21.9***
	Bupropion:	29.5***	20.7***	16.1***
	150 mg, bid			
Jorenby et al ⁵⁸ (n = 1,027)	Placebo	17.6	13.2	10.3
	1 mg, bid, 12 wks	43.9***	29.7***	23***
	Bupropion:	29.8***	20.2**	14.6
	150 mg, bid, 12 wks			
Tonstad et al ⁵⁹ (n = 1,210)	Placebo	—	49.6	36.9
	1 mg, bid, 12 wks	—	70.5***	43.6*
Tsai et al ⁵³ (n = 250)	Placebo	32.3	21.8	
	1 mg, bid, 12 wks	59.5***	46.8***	
Nakamura et al ⁶⁰ (n = 619)	Placebo	39.5	29.5	23.3
	0.25 mg, bid, 12 wks	54.7*	33.6	27.3
	0.5 mg, bid, 12 wks	55.5**	35.2	28.9
	1 mg, bid, 12 wks	65.4***	37.7	34.6
Niaura et al ⁶¹ (n = 320)	Placebo	11.6	9	7.7
	0.5–2 mg/d, 12 wks	40.1***	28***	22.3***
Aubin et al ⁶² (n = 757)	NRT, 21 mg/d, 6 wks	42.2	26.6	19.8
	1 mg, bid, 12 wks	55.6###	32.2	25.9#
Wang et al ⁶⁷ (n = 333)	Placebo	—	31.6	25
	1 mg, bid, 12 wks	—	50.3***	38.2**

Notes: *** $P < 0.05$, ** $P < 0.01$, * $P < 0.001$, compared to placebo; # $P < 0.05$, ### $P < 0.001$, compared to NRT.

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

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.^{5,54} 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.^{78,79}

Conclusions

Varenicline (Chantix®; Pfizer, New York, NY), an $\alpha 4\beta 2$ 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 manufactures 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.

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