

VARENICLINE: NEW TREATMENT WITH EFFICACY IN SMOKING CESSATION

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Summary

Smoking is a significant public health problem, and existing treatments have demonstrated only moderate efficacy in assisting smokers to quit. Varenicline, recently approved by the U.S. Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products as an aid to smoking cessation treatment, has a novel mechanism of action, targeting the specific nicotinic acetylcholine receptor (nAChR) associated

with nicotine-induced behaviors ($\alpha 4\beta 2$ nAChR). It has both agonistic and antagonistic properties that together are believed to account for reduction of craving and withdrawal as well as blocking the rewarding effects of smoking.

The clinical efficacy and tolerability of varenicline has been demonstrated in phase III clinical trials involving more than 2,000 cigarette smokers. At the end of the treatment period in two 12-week, multicenter, randomized, double-blind, placebo-controlled studies, patients receiving varenicline (1 mg twice daily) experienced an increase in the odds of quitting smoking by nearly fourfold compared with those receiving placebo, and almost twofold compared with the odds for patients receiving 150 mg bupropion SR (sustained release) twice daily. In these two trials where patients were

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randomized to either varenicline or bupropion, the efficacy of varenicline was consistently superior at 12 weeks; this result sustained significance at 24 weeks in both studies and up to 52 weeks in one study. Nausea, a common adverse event reported in clinical trials, led to few treatment discontinuations.

Its targeted mechanism of action, superior efficacy and excellent tolerability make varenicline a welcome and useful addition to the therapeutic options for smoking cessation. © 2007 Prous Science. All rights reserved.

Introduction

Despite the well-known health risks associated with cigarette smoking, the prevalence of smoking – and the resultant chronic nicotine dependence – remain high in the United States (1, 2). While the prevalence of smokers has declined from 1998, when it was 24.1%, the decline is insufficient to achieve the national health objective of $\leq 12\%$ prevalence by 2010, with the U.S. Centers for Disease Control and Prevention (CDC) reporting that 20.9% of Americans adults (44.5 million people) were smokers in 2004 (2).

Currently, 1 in 10 people will die from smoking-related illnesses worldwide, and, if unchecked, global smoking-related mortality is expected to rise to 10 million people annually by 2020 (3). In the United States, approximately 438,000 premature deaths occurred each year due to tobacco use between 1997 and 2001 (4). Smoking is a recognized risk factor for cancer and heart and lung diseases (5); however, many of the adverse health effects of smoking are reversible (5). Further, most smokers (70%) in the United States report wanting to stop and many (40.5%) attempt to quit every year, but only 3–5% of those who try to quit on their own are able to stay tobacco-free for up to 12 months (1, 2, 6).

While continued smoking is associated with a steady, progressive increase in health-care utilization, smoking-cessation treatments represent cost-effective health-care interventions (1, 7). Meta-analyses of clinical trials with other agents approved by the U.S. Food and Drug Administration (FDA) for smoking cessation have shown that these therapies (nicotine replacement therapies [NRTs], bupropion) approximately double the odds of achieving abstinence after at least six months of follow-up, with an odds ratio (OR) of 1.77 for abstinence with NRT formulations (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/

lozenges) and an OR of 2.06 with bupropion compared with placebo (8, 9). This discussion reviews the pharmacology, clinical efficacy, tolerability and safety of varenicline tartrate, the agent most recently approved by the FDA for smoking cessation (10).

Nicotine addiction

Nicotine has long been recognized as a primary factor in reinforcing smoking behavior, with nicotine intake resulting in significant changes in the brain that create a desire to smoke (11, 12). Furthermore, the combination of nicotine intake with behavioral rituals and sensory aspects of smoking lead to secondary conditioning that contributes to reinforcement of smoking. The 1988 U.S. Surgeon General's Report emphasized that the pharmacologic and behavioral characteristics associated with smoking are similar to those of other addictive substances such as heroine and cocaine (12).

Neurobiological substrate of nicotine addiction

Stimulation of mesolimbic dopaminergic neurons is involved in the reinforcing effect of several drugs of abuse, including nicotine (13). These dopaminergic neurons project from the ventral tegmental area to several brain structures, including the nucleus accumbens and prefrontal cortex (14). Although nicotinic acetylcholine receptors (nAChRs) are expressed throughout the central nervous system, it has been demonstrated that nicotine stimulation of dopamine release results from direct activation of the nAChRs in the ventral tegmental area (15). Further, improved understanding of neurophysiology has honed the focus of nicotine-related addictive behaviors to specific nAChRs. Among the neuronal nAChRs that are differentially expressed throughout the nervous system, the $\alpha 4\beta 2$ receptor, the most abundant brain nAChR subtype, has been identified as being central to nicotine addiction (15–21). Nicotine agonist activity at the $\alpha 4\beta 2$ nAChR in the ventral tegmental area affects both upstream and downstream synaptic mechanisms involving functional interactions between dopaminergic and γ -aminobutyric-acid-dependent neural systems, and chronic exposure to nicotine causes nAChR desensitization and upregulation (22–24). Together, these mechanisms are thought to play a key role in nicotine reinforcement or reward and craving

underlying drug-seeking and other addictive behaviors, thus potentially contributing to nicotinic addiction (23, 25, 26).

Varenicline: A new aid to smoking cessation

Pharmacology

It has been suggested that an effective smoking-cessation aid would be one that could reduce craving and withdrawal symptoms while attenuating the nicotine-induced effects of smoking – an effect that could be achieved with a partial agonist agent that has the ability to simultaneously inhibit nicotine-induced dopamine release, thereby reducing reward while sufficiently increasing dopaminergic tone to reduce craving and withdrawal symptoms (27). Varenicline is a selective nAChR partial agonist with specific and potent binding at the $\alpha 4\beta 2$ receptor subtype, displaying selectivity for the $\alpha 4\beta 2$ receptor with binding affinity that is more than 500-fold greater than for the $\alpha 3\beta 4$ subtype and more than 5,000-fold greater than for the $\alpha 7$ subtype (28, 29). With approximately 40–60% the agonist activity of nicotine, varenicline's partial agonist activity is believed to stimulate sufficient dopamine release to reduce tobacco craving and withdrawal *in vivo* (27, 29). Concomitant administration of varenicline and nicotine has been shown to result in dopamine increases that were equivalent to increases observed with varenicline alone and significantly lower than those with nicotine alone, thus confirming its antagonistic effects and the potential clinical utility of its partial agonist action (27, 29). In addition, patient-reported outcomes from clinical trials have supported varenicline's partial agonist activity at the $\alpha 4\beta 2$ nAChR, indicating reduced craving and symptoms of nicotine withdrawal, as well as reduced reinforcing and rewarding effects of smoking (30, 31). Furthermore, varenicline is also a partial agonist at $\alpha 3\beta 2$ and $\alpha 6$ receptors, is a full agonist at $\alpha 7$ receptors, and shows lower potency and high efficacy at $\alpha 3\beta 4$ receptors (28). The partial antagonist effects at $\alpha 3\beta 2$ and $\alpha 6$ receptors may contribute to varenicline's ability to modulate dopamine release, although its affinities for these subtypes are orders of magnitude lower than its affinity for the $\alpha 4\beta 2$ receptor (28, 32).

Pharmacokinetics

Varenicline exhibits linear pharmacokinetics following single-dose (0.1–3.0 mg) and multiple-dose (1, 2, and 3 mg per day) administration (33,

34). In a clinical mass balance study, total excretion of administered varenicline is 88%, with the vast majority excreted unchanged in the urine, indicating that absorption of varenicline is virtually complete and systemic availability is high after oral administration (35); plasma protein binding is low ($\leq 20\%$) (34). Maximum plasma concentrations of varenicline typically occurred within three hours after oral administration (33); steady-state conditions were reached within four days with repeat dosing (34). The oral bioavailability of varenicline is not affected by either coadministration with food or time-of-day dosing (33).

The mean elimination half-life of varenicline is approximately 24 hours (21.4 ± 3.3 hours after single and 26.1 ± 5.5 hours after multiple dosing) (34). Varenicline is minimally metabolized in the liver, with $>90\%$ excreted unchanged in the urine, indicating that renal excretion is the primary route of drug clearance (35). Renal elimination occurs primarily through glomerular filtration with an additional component of active tubular secretion, via the organic cation transporter OCT2 (10).

Varenicline pharmacokinetics are unaffected by mild renal impairment (*i.e.*, creatinine clearance >50 ml/min and ≤ 80 ml/min) (10). Systemic exposure increases 1.5-fold in subjects with moderate renal impairment (*i.e.*, creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) and 2.1-fold in subjects with severe renal impairment (*i.e.*, creatinine clearance <30 ml/min) compared with patients with normal renal function (*i.e.*, creatinine clearance >80 ml/min); it is efficiently removed from circulation by hemodialysis in patients with end-stage renal disease. Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic insufficiency. No clinically meaningful differences in varenicline pharmacokinetics have been reported due to age, race, gender, smoking status or use of certain concomitant medications (10, 33, 36, 37).

Drug interactions

Varenicline is neither a substrate nor an inhibitor of cytochrome P450 enzymes, and is therefore not expected to be either the cause or subject of drug interactions mediated by P450 activities (10). No clinically meaningful pharmacokinetic drug–drug interactions have been identified to date, including those with narrow therapeutic index drugs digoxin or warfarin; other FDA-approved smoking-cessation therapies (*i.e.*, bupropion, nico-

tine transdermal patch); or renally secreted drugs, such as cimetidine or metformin (10, 37).

Clinical efficacy

The efficacy of varenicline as an aid to smoking cessation has been evaluated in phase II and III clinical trials, including a treatment period of up to 12 weeks and a nontreatment follow-up phase up to one year. In a separate phase III study, the efficacy of an additional 12 weeks of extended therapy was evaluated for relapse prevention.

Phase II studies

The efficacy of varenicline in combination with brief counseling was evaluated in two phase II, placebo-controlled, dose-ranging studies (38, 39). A multicenter, randomized, double-blind, placebo-controlled study evaluated the efficacy and safety of three titrated varenicline doses – 0.3 mg once daily ($n = 128$), 1.0 mg once daily ($n = 128$) or 1.0 mg twice daily ($n = 127$) – and titrated sustained-release (SR) bupropion (150 mg twice daily; $n = 128$) compared with placebo ($n = 127$) in healthy smokers aged 18–65 years (38). Varenicline was administered for six weeks followed by one week of placebo in each of the double-blind varenicline arms; bupropion SR was administered for the seven-week treatment period. Participants were asked to quit smoking on day eight after the baseline visit. The primary endpoint was any four-week carbon-monoxide–confirmed continuous period of abstinence. The four-week abstinence rate was significantly higher in the varenicline 1.0 mg daily group (37.3%; OR, 2.97; 95% confidence interval [CI], 1.63–5.40) and the 1.0 mg twice-daily group (48.0%; OR, 4.71; 95% CI, 2.60–8.53) compared with placebo (17.1%; $p < 0.001$, for both comparisons). The bupropion four-week abstinence rate (33.3%) was also significantly greater than placebo ($p = 0.002$). Varenicline 1.0 mg twice daily significantly reduced craving compared with placebo as assessed by the Minnesota Nicotine Withdrawal Scale (MNWS) and Brief Questionnaire of Smoking Urges (QSU-brief), reduced smoking satisfaction and enjoyment of respiratory tract sensations, and increased aversion *versus* placebo as assessed by the MNWS.

The second study evaluated the efficacy and safety of four varenicline dose regimens in healthy smokers ($n = 647$) aged 18–65 years. Smokers were randomized to 12 weeks of therapy, as follows: varenicline 0.5 mg twice daily, not titrated

($n = 129$); varenicline 0.5 mg twice daily administered as 0.5 mg once daily for 7 days, followed by 0.5 mg twice daily for 11 weeks ($n = 130$); varenicline 1.0 mg twice daily, not titrated ($n = 129$); varenicline 1.0 mg twice daily administered as 0.5 mg once daily for three days, 0.5 mg twice daily for four days, and then 1 mg twice daily for 11 weeks ($n = 130$); or placebo ($n = 129$) (39). All subjects received brief counseling at each weekly clinic visit during the 12-week treatment. Subjects were followed for 40 weeks after the 12-week treatment phase to assess long-term efficacy, and were provided with brief counseling (≤ 10 minutes) at clinic visits and telephone contacts in between visits. A secondary objective was to evaluate the effects of dose titration on nausea and overall tolerability. The primary outcome measures were the carbon-monoxide–confirmed four-week abstinence rates for weeks 4–7 and 9–12, and the rate of continuous abstinence over weeks 9–52 in the combined titrated and nontitrated subjects for each dosing group. As in the first dose-ranging study, the four-week continuous abstinence rates were significantly higher for the varenicline 0.5 mg twice-daily nontitrated (37.2%) and titrated (35.4%) groups and for the varenicline 1.0 mg twice-daily nontitrated (38.8%) and titrated (40.8%) groups compared with placebo (10.9%) ($p < 0.001$, for all comparisons). At week 12, the continuous quit rate was 20.8% of subjects treated with varenicline 0.5 mg twice daily, and 24.0% treated with varenicline 1 mg twice daily *versus* 7% with placebo ($p \leq 0.001$, for all comparisons). There was a higher overall completion rate among subjects treated with varenicline. In addition, reports of nausea were lower for the titrated- compared with the nontitrated-dosing groups, and nausea infrequently led to treatment discontinuations.

Phase III studies

Results from the phase II studies were confirmed by two large-scale, identically designed, phase III studies of varenicline in combination with brief counseling for smoking cessation (30, 31). Both studies randomized participants in a blinded fashion to one of three treatment arms (*i.e.*, varenicline titrated to 1 mg twice daily, bupropion SR titrated to 150 mg twice daily, or placebo) for 12 weeks, with 40 weeks of follow-up that also included brief (≤ 10 minutes) counseling sessions during clinic visits and telephone contacts in between clinic visits. A total of 2,052 generally

healthy smokers (≥ 10 cigarettes per day) participated: 696 were randomized to receive varenicline, 671 to bupropion SR, and 685 to placebo (30, 31).

The primary objective of the studies was to evaluate the efficacy and safety of 12 weeks of varenicline *versus* bupropion and placebo for smoking cessation during treatment and follow-up (30, 31). Subjects were asked to attempt to completely stop smoking on day 8 after the baseline evaluation for the study. Smoking-cessation counseling was provided at baseline and each weekly visit during active treatment. Cigarette use was monitored by self-report and expired carbon monoxide. In addition, subjects completed the MNWS and the QSU-brief to assess craving, the MNWS to assess withdrawal symptoms, and the Modified Cigarette Evaluation Questionnaire (mCEQ) to determine the reinforcing effects of smoking. The rate of continuous abstinence for the last four weeks of study treatment (weeks 9–12) confirmed by exhaled carbon monoxide was the primary endpoint. Continuous abstinence from weeks 9–24 and 9–52 were secondary endpoints (30, 31). Subject demographics were similar be-

tween groups at baseline in both studies. The mean age was approximately 42–45 years, and most subjects were Caucasian and had smoked for 24 years or longer. The mean score on the Fagerstrom Test for Nicotine Dependence ranged from 5.16 ± 2.19 to 5.39 ± 2.21 (30, 31). Results for the primary endpoint, the rate of continuous abstinence during weeks 9–12, were practically identical in the two studies (Fig. 1) and significantly superior to bupropion and placebo. In the first study, the continuous abstinence rate during weeks 9–12 was 44.0% in the varenicline group *versus* 17.7% for placebo (OR, 3.85; 95% CI, 2.70–5.50; $p < 0.001$) and 29.5% for bupropion SR (OR, 1.93; 95% CI, 1.40–2.68; $p < 0.001$) (30). In the second study, the continuous abstinence rate for weeks 9–12 was 43.9% in the varenicline group *versus* 17.6% for placebo (OR, 3.85; 95% CI, 2.69–5.50; $p < 0.001$) and 29.8% for bupropion SR (OR, 1.90; 95% CI, 1.38–2.62; $p < 0.001$) (31). Carbon-monoxide-confirmed continuous abstinence rates weeks 9–52 for the groups in the two studies were 21.9% and 23.0% for varenicline, 16.1% and 14.6% for

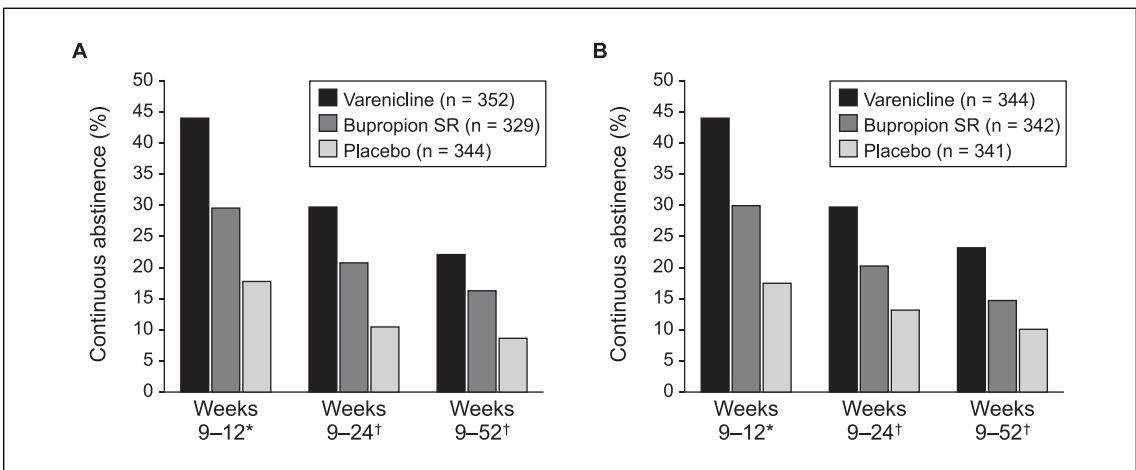


Fig. 1. Continuous abstinence rates in the phase III studies (A) Gonzales *et al.* (30) and (B) Jorenby *et al.* (31). The numbers (n) shown in the key are the denominators used for all three periods. Bupropion SR = sustained-release bupropion. A: All comparisons $p < 0.001$ except varenicline *versus* bupropion SR at weeks 9–24 ($p = 0.007$), varenicline *versus* bupropion SR at weeks 9–52 ($p = 0.057$) and bupropion SR *versus* placebo at weeks 9–52 ($p = 0.001$). *Abstinence confirmed by measurement of exhaled carbon monoxide. †Clinic and telephone visits: Abstinence confirmed by measurement of exhaled carbon monoxide at clinic visits. B: For weeks 9–12: varenicline *versus* placebo, $p < 0.001$; varenicline *versus* bupropion SR, $p < 0.001$; and bupropion SR *versus* placebo, $p = 0.001$. For weeks 9–24: varenicline *versus* placebo, $p < 0.001$; varenicline *versus* bupropion SR, $p = 0.003$; and bupropion SR *versus* placebo, $p = 0.01$. For weeks 9–52: varenicline *versus* placebo, $p < 0.001$; varenicline *versus* bupropion SR, $p = 0.004$; and bupropion SR *versus* placebo, $p = 0.08$. Reproduced from refs. 30 (A) and 31 (B) with permission from the American Medical Association © 2006. All rights reserved.

bupropion, and 8.4% and 10.3% for placebo, respectively (30, 31). At week 52, the ORs for abstinence were 3.09 (95% CI, 1.95–4.91; $p < 0.001$) (30) and 2.66 (95% CI, 1.72–4.11; $p < 0.001$) (31) for varenicline *versus* placebo and 1.46 (95% CI, 0.99–2.17; $p = 0.057$) (30) and 1.77 (95% CI, 1.19–2.63; $p = 0.004$) (31) for varenicline *versus* bupropion.

Subgroup analysis

Pooled analysis of results, based on all subjects from these two phase III trials who took at least one dose of randomized study medication, demonstrated that varenicline significantly improved abstinence *versus* placebo in men (weeks 9–12: OR, 3.69; 95% CI, 2.73–5.0; $p < 0.0001$; weeks 9–52: OR, 2.73; 95% CI, 1.86–4.01; $p < 0.0001$) as well as women (weeks 9–12: OR, 4.74; 95% CI, 3.36–6.67; $p < 0.0001$; weeks 9–52: OR, 3.87; 95% CI, 2.45–6.12; $p < 0.0001$) (40). These data suggest improvements in smoking cessation achieved with varenicline are not gender-specific, and varenicline is an effective smoking-cessation treatment for both men and women.

Extended therapy

Another phase III trial was designed to evaluate the efficacy of an additional 12 weeks of treatment with varenicline for relapse prevention, following successful abstinence after the first 12 weeks of open-label treatment (41). Among the

64.1% ($n = 1,236$) of subjects who did not smoke a single puff of a cigarette during the last seven days of the 12-week open-label period, 1,210 were randomized in a double-blind fashion to either a further 12-week course of varenicline 1 mg twice daily ($n = 603$) or placebo ($n = 607$). The primary endpoint was carbon-monoxide-confirmed continuous abstinence during weeks 13–24; a key secondary endpoint was continuous abstinence during weeks 13–52. During weeks 13–24, 70.5% of subjects randomized to varenicline were smoke-free, compared with 49.6% of subjects randomized to placebo (OR, 2.48; 95% CI, 1.95–3.16; $p < 0.001$). At week 52, 43.6% of subjects in the varenicline arm *versus* 36.9% in the placebo arm were continuously abstinent from week 13 (OR, 1.34; 95% CI, 1.06–1.69; $p = 0.02$). Figure 2 illustrates the seven-day point prevalence of abstinence throughout the study; as indicated, the difference between varenicline and placebo was significant at weeks 24 (OR, 2.82; 95% CI, 2.18–3.64; $p < 0.001$) and 52 (OR, 1.33; 95% CI, 1.06–1.67; $p = 0.01$).

Impact on withdrawal symptoms and rewarding/reinforcing effects of smoking

The MNWS was used to assess craving and withdrawal after varenicline treatment in both phase II (38, 39) and all three phase III studies (30, 31, 41). In addition, in the two identically designed phase III trials, the QSU-brief was administered to assess craving and the mCEQ to assess the rein-

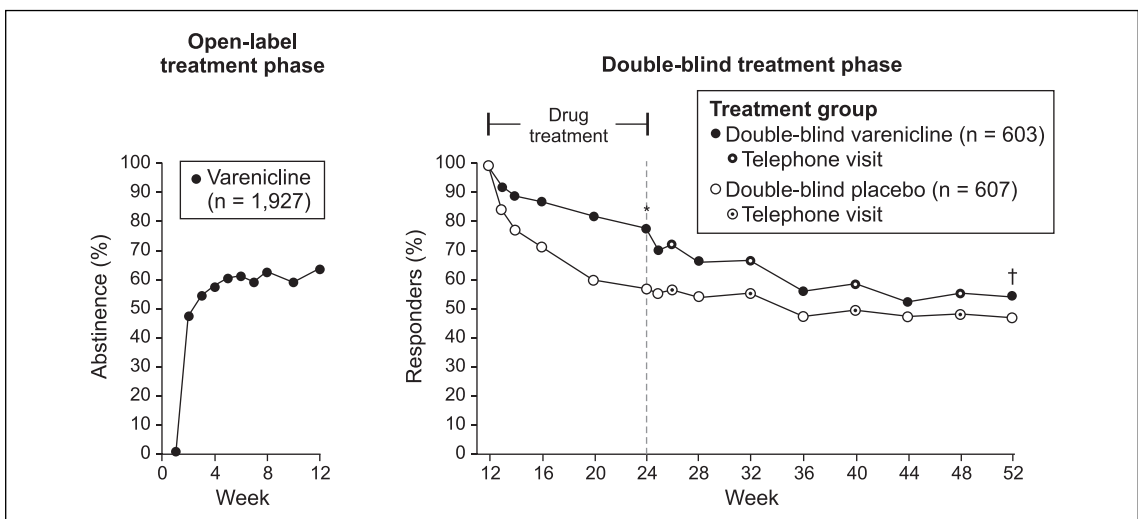


Fig. 2. Seven-day point prevalence of abstinence; * $p < 0.001$; † $p = 0.01$. Reproduced from ref. 41 with permission from the American Medical Association © 2006. All rights reserved.

forcing effects of smoking (30, 31). Varenicline reduced the urge to smoke compared with placebo, as assessed by the MNWS, in all three phase III trials (30, 31, 41). In the two identically designed phase III trials with a bupropion arm, bupropion also significantly reduced the urge to smoke (30, 31); however, the effect size of the difference from

placebo for varenicline was approximately twice that of bupropion in one trial (30). Similarly, both varenicline and bupropion significantly decreased craving compared with placebo as measured by the QSU-brief (30, 31); however, the effect size of the difference from placebo for varenicline was approximately twice that of bupropion in one trial

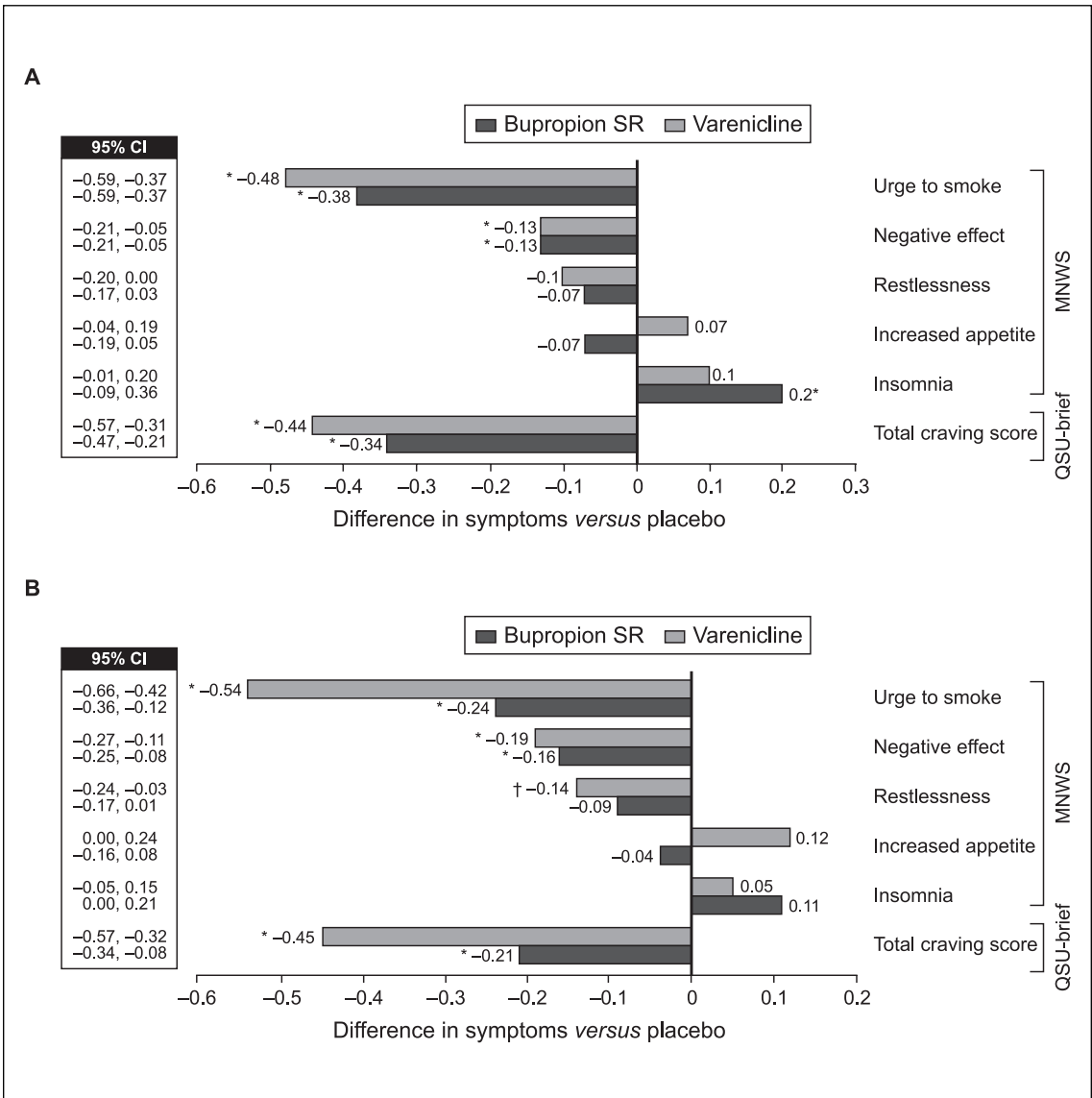


Fig. 3. Impact of varenicline on withdrawal, craving and smoking reinforcement in phase III trials (A) Gonzales *et al.* (30) and (B) Jorenby *et al.* (31). CI = confidence interval; bupropion SR = sustained-release bupropion; MNWS = Minnesota Nicotine Withdrawal Scale; QSU-brief = Brief Questionnaire of Smoking Urges; * $p \leq 0.001$; † $p = 0.01$. Reproduced from refs. 30 (A) and 31 (B) with permission from the American Medical Association © 2006. All rights reserved.

(30). The mCEQ scores demonstrated that varenicline significantly reduced smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations, and the effect of smoking on immediate relief of craving compared with placebo in the two identically designed phase III trials, while bupropion significantly reduced psychological reward *versus* placebo in both trials – with an effect size about half that of varenicline – and smoking satisfaction in one (30, 31). Figure 3 illustrates the results of these trials.

Safety profile

In phase II (38, 39) and III (30, 31, 41) placebo-controlled studies, varenicline was generally well-tolerated. Table I presents the adverse events reported in the two identical phase III studies. The most common adverse events associated with varenicline were gastrointestinal (*e.g.*, nausea, flatulence, constipation) and neurologic (*e.g.*, insomnia, headache, abnormal dreams). Few participants discontinued drug treatment due to nausea, a common adverse event for varenicline (30, 31, 38, 39). In the phase II dose-titration study, titration reduced the overall incidence of nausea (39). The

treatment discontinuation rate due to adverse events in patients dosed with 1 mg twice daily ranged from 8.6–21.7% for varenicline *versus* 7.3–17.4% for placebo (30, 31, 38, 39). In the two identical phase III trials, weight gain among those who completed the treatment period and remained abstinent for weeks 9–12 ranged from 2.37–2.89 kg in varenicline-treated participants, 1.88–2.12 kg among bupropion-treated participants, and 2.92–3.15 kg in placebo group participants (30, 31).

Conclusions

Smoking cessation is now well-recognized as an important means of reducing global morbidity and mortality. Increased understanding of the neurobiologic basis for nicotine addiction, the principle addictive component of cigarettes, has contributed to the development of a new and effective therapy for smoking cessation. Varenicline targets the $\alpha 4\beta 2$ nAChR with partial agonist and antagonist properties, which are believed to contribute to reduced craving and withdrawal as well as blockade of the reinforcing effects of smoking associated with treatment.

Table I: Adverse events in the phase III studies of varenicline* (30, 31).

Adverse event	Varenicline		Bupropion SR		Placebo	
	(n = 349) (ref. 30)	(n = 343) (ref. 31)	(n = 329) (ref. 30)	(n = 340) (ref. 31)	(n = 344) (ref. 30)	(n = 340) (ref. 31)
Gastrointestinal disorders						
Nausea	98 (28.1)	101 (29.4)	41 (12.5)	25 (7.4)	29 (8.4)	33 (9.7)
Dry mouth	23 (6.6)	19 (5.5)	29 (8.8)	26 (7.6)	19 (5.5)	11 (3.2)
Flatulence	20 (5.7)	20 (5.8)	14 (4.3)	7 (2.1)	10 (2.9)	8 (2.4)
Constipation	19 (5.4)	31 (9.0)	23 (7.0)	22 (6.5)	13 (3.8)	5 (1.5)
Dyspepsia	NR	19 (5.5)	NR	10 (2.9)	NR	12 (3.5)
Vomiting	NR	18 (5.2)	NR	7 (2.1)	NR	6 (1.8)
Psychiatric disorders						
Insomnia	49 (14.0)	49 (14.3)	72 (21.9)	72 (21.2)	44 (12.8)	42 (12.4)
Abnormal dreams†	36 (10.3)	45 (13.1)	18 (5.5)	20 (5.9)	19 (5.5)	12 (3.5)
Irritability	21 (6.0)	NR	17 (5.2)	NR	20 (5.8)	NR
Sleep disorder	20 (5.7)	16 (4.7)	13 (4.0)	23 (6.8)	13 (3.8)	9 (2.6)
Anxiety	NR	15 (4.4)	NR	18 (5.3)	NR	13 (3.8)
Nervous system disorders						
Headache	54 (15.5)	44 (12.8)	47 (14.3)	27 (7.9)	42 (12.2)	43 (12.6)
Dizziness	21 (6.0)	22 (6.4)	19 (5.8)	25 (7.4)	20 (5.8)	24 (7.1)
Fatigue	NR	25 (7.3)	NR	13 (3.8)	NR	22 (6.5)
Nasopharyngitis	20 (5.7)	NR	17 (5.2)	NR	18 (5.2)	NR

Bupropion SR = sustained-release bupropion; NR = not reported. *Treatment-emergent adverse events were defined as adverse events that began or increased in severity during study drug treatment or up to seven days after the last dose. Reported events occurred at 5% or more for varenicline and at a higher frequency than reported for placebo. †Self-described as any change in dreaming, such as vivid dreams or increased frequency of dreaming.

Phase III clinical trials in more than 2,000 cigarette smokers have demonstrated the efficacy and tolerability of varenicline, increasing the odds of quitting at the end of treatment approximately fourfold (ORs: 3.85 and 3.85) compared with that of placebo, and nearly twofold (ORs: 1.90 and 1.93) compared with bupropion (30, 31). Further, after one year, approximately one in five patients who received a 12-week course of varenicline remained smoke-free, and a maintenance study demonstrated that among patients who quit at the end of 12 weeks, an additional 12-week course of treatment with varenicline resulted in a greater likelihood of maintaining abstinence at the end of the year (41). This finding is in contrast to that from two trials of extended therapy with bupropion for relapse prevention after initial cessation, which did not show significant long-term benefit (9). Phase III studies also demonstrated that varenicline treatment results in beneficial effects on craving, reward and withdrawal symptoms (30, 31). Data from a pooled analysis suggest that improvements in smoking cessation with varenicline are not gender-specific (40), and analysis of other baseline characteristics by treatment groups in phase III trials have not demonstrated significant differences, indicating the potential value of varenicline for smoking cessation in a diverse population of smokers (30).

These efficacy results are almost double those reported in clinical trials with other pharmacotherapies used for smoking cessation. A meta-analysis of clinical trials report the OR for abstinence with NRT formulations (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) compared with placebo is 1.77, and bupropion has been shown to approximately double the odds of cessation *versus* placebo (OR, 2.06) when used as the sole pharmacotherapy (8, 9). Meta-analyses of clinical trials with other frequently used pharmacologic treatments have demonstrated similar efficacy for the tricyclic antidepressant nortriptyline (OR, 2.79) and antihypertensive agent clonidine (OR, 1.89) (9, 42).

Varenicline is generally well-tolerated, with nausea as the most common adverse event. The targeted mechanism of action, superior efficacy and tolerability of varenicline make it an excellent and welcome addition to the therapeutic options for treatment of smoking cessation.

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