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Efficacy and Safety of Varenicline for Smoking Cessation

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ABSTRACT

Effective treatment of nicotine addiction is essential for reducing the substantial current and predicted morbidity and mortality associated with tobacco smoking. Despite the availability of effective treatments for smoking cessation, such as nicotine replacement therapy and bupropion sustained-release (SR), abstinence rates remain less than optimal. Varenicline is the first in a new class of agents for smoking cessation, the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR) partial agonists. Nicotine addiction is mediated by stimulation of central $\alpha_4\beta_2$ nAChRs by nicotine, which causes the release of dopamine, ultimately leading to the pleasurable effects of smoking. As a nAChR partial agonist, varenicline attenuates the craving and withdrawal symptoms that occur with abstinence from nicotine and also reduces the rewarding effects of nicotine obtained from smoking in patients who lapse. Thus, varenicline offers a new therapeutic option for the treatment of nicotine addiction. Clinical trials have demonstrated superior efficacy of this agent over placebo and bupropion-SR for achieving abstinence from smoking, and varenicline has also been shown to significantly delay smoking relapse. As the newest agent approved for smoking cessation, the mechanism of action, efficacy, and safety of varenicline.

KEYWORDS: $\alpha_4\beta_2$ nicotinic acetylcholine receptor; Partial agonist; Smoking cessation; Varenicline

Worldwide, an estimated 1.3 billion people smoke cigarettes and there were an estimated 4.9 million premature deaths in 2000 due to tobacco-related diseases.[1] According to current estimates, if smoking prevalence continues to increase in the developing world, the number of annual deaths attributable to cigarette smoking could reach approximately 10 million by 2030.[1,2] In fact, of all the people in the world today, an estimated 500 million will die from tobacco-related causes.[1] Similarly bleak statistics are applicable for the United States, with >45 million smokers and cigarette smoking–attributable mortality at 440,000 annual deaths,[3,4] or 18.1% of total mortality.[5] Although primary prevention of smoking is an important strategy for the long-term reduction of smoking-attributable morbidity and mortality, the only way to reduce the staggering expected mortality attributable to tobacco dependence is to effectively treat current smokers.

Smoking cessation has been shown to reduce morbidity and mortality related to nicotine addiction and provides both immediate and long-term health benefits such as reducing the risk for lung cancer, other cancers, chronic lung disease, myocardial infarction, and stroke, and decreasing the risk for low birth weight infants when accomplished during the first trimester of pregnancy.[6] Indeed, smoking cessation at age 50 reduces the risk of death from smoking-related causes by half; cessation at age 30 avoids almost all smoking-related mortality.[7]

Unfortunately, tobacco dependence is a chronic disorder that is difficult to treat despite the availability of effective pharmacologic aids, such as nicotine replacement therapy (NRT) and bupropion sustained-release (SR). For these reasons, novel pharmacotherapies are being developed in an attempt to improve long-term abstinence outcomes. Among the most promising of these newer treatments is varenicline, a partial agonist selective for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (nAChR), recently approved by the US Food and Drug Administration (FDA) for use as a smoking cessation aid.

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This article briefly reviews the development and mechanism of action of varenicline, the newest available agent for the treatment of nicotine dependence. Safety and early efficacy data are described and recently published results of phase 2 and 3 trials are reviewed. Recommendations and place in therapy for the use of varenicline as an aid to smoking cessation are discussed.

OVERVIEW OF DEVELOPMENT AND MECHANISM OF ACTION OF VARENICLINE

The positive reinforcing effects of nicotine and the presence of craving and withdrawal symptoms associated with tobacco cessation are important factors that prevent smokers from achieving long-term tobacco abstinence. Addressing both the positive reinforcing effects of nicotine and the withdrawal symptoms with a single drug would be expected to improve the efficacy of tobacco dependence treatment. Varenicline was developed to achieve both of these aims.

A basic understanding of the neurobiologic effects of nicotine is necessary for understanding the mechanism of action of varenicline (a more detailed discussion of the neurobiology of nicotine addiction is given by Benowitz[8] elsewhere in this supplement). The neuronal nAChR are ion channels comprised of α- and β-subunits that form pentameric units.[9] These ligand-gated channels have varying pharmacologic and physical properties and are selectively distributed in the central nervous system (CNS).[10] Among the main functional receptor subtypes found in the CNS ($\alpha_4\beta_2$, $\alpha_3\beta_4$, and α_7), the $\alpha_4\beta_2$ nicotinic receptor has the highest affinity for nicotine.[11] Indeed, the pharmacologic actions of nicotine in the brain, including nicotine's dependence-producing properties, are mediated by the nAChRs,[10] predominantly the $\alpha_4\beta_2$ nicotinic receptor.[12]

The pleasurable effects of nicotine are mediated by the mesolimbic dopaminergic system that consists of the neurons in the ventral tegmental area with projections into the nucleus accumbens and prefrontal cortex.[13,14] The release of dopamine in the nucleus accumbens is a key component of the pleasurable and rewarding (reinforcing) effects of nicotine.[15] The $\alpha_4\beta_2$ nAChRs are located at the presynaptic terminals in the nucleus accumbens and play an important role in dopamine release.[16] Based on this understanding, it was hypothesized that a partial agonist of the $\alpha_4\beta_2$ nAChR (i.e., a compound with a high affinity for the $\alpha_4\beta_2$ nAChRs but less reinforcing effect than the primary agonist, nicotine) would likely attenuate the nicotine withdrawal symptoms and craving and reduce the reinforcing effects of nicotine, while not causing habituation itself.

The structural starting point for varenicline was a naturally occurring plant alkaloid, cytisine. Cytisine selectively binds to and is a partial agonist of the $\alpha_4\beta_2$ nAChR, in that it competitively binds to the receptor and only partially activates it.[17,18] Cytisine has shown limited efficacy when used as an aid to smoking cessation in Eastern European trials; however, most of the studies with this agent have been poorly designed.[19] A recent meta-analysis of 2 double-blind, placebo-controlled trials with $\geq$3 months follow-up demonstrated a pooled odds ratio (OR) for abstinence of 1.83 (95% confidence interval [CI], 1.12 to 2.99) for cytisine compared with placebo.[19] However, the validity of the primary outcome in these 2 studies is questionable, as it was obtained using a mail survey without any biochemical confirmation.

Varenicline was synthesized by performing strategic modifications to benzazephine, a substructure of cytisine, to enhance the binding affinity and selectivity for the $\alpha_4\beta_2$ nAChR subtype while aiming to improve the CNS penetration and efficacy.[20] The partial agonist activity of varenicline at the $\alpha_4\beta_2$ neuronal nAChR promotes a sustained, low level of dopamine release, which reduces withdrawal symptoms. Through its higher affinity, lower efficacy, and relatively long half-life compared with nicotine, varenicline is able to prevent nicotine from occupying and activating the $\alpha_4\beta_2$ nAChRs during a smoking cessation relapse. In this way, varenicline acts functionally as an antagonist at the $\alpha_4\beta_2$ neuronal nAChR, and so has the potential to inhibit the immediate rewarding effects of nicotine from tobacco and reduce smoking satisfaction.[20,21] Following promising results in early human studies, together with a strong theoretical foundation for its use, testing of varenicline began in clinical safety and efficacy trials.

PHASE 2 STUDIES

Design

To establish the safety, efficacy, and appropriate dose of varenicline, 2 multicenter, randomized, double-blind, placebo-controlled phase 2 clinical trials were conducted in cigarette smokers (**Table 1**).[22–26] In both trials, smoking abstinence was determined by self-report and verified by measurement of exhaled carbon monoxide $\leq$10 ppm at weekly visits. Patients were provided with educational material on smoking cessation and up to 10 minutes of smoking cessation counseling at each weekly visit during treatment.

One study involved 638 cigarette smokers randomly assigned to varenicline (0.3 mg daily, 1.0 mg daily, 1.0 mg twice daily), bupropion-SR (150 mg twice daily), or placebo for 7 weeks.[22] Abstinence was assessed during treatment and at weeks 12, 24, and 52. A second study randomized 647 smokers to varenicline (0.5 mg twice daily, 1.0 mg twice daily) or to placebo for 12 weeks.[23] For this study, each varenicline group was divided into subgroups receiving the full dose initially or after titration over 1 week. Continuous abstinence was assessed at each weekly visit during the 12 weeks of treatment, and then at weeks 13, 24, and 52 of the follow-up phase.

Efficacy

In the first study, a dose-response relation for varenicline was observed for smoking cessation (Table 1).[22] The short-term smoking abstinence rates, as defined by the proportion

Table 1 Summary of phase 2 and 3 clinical trials of varenicline for smoking cessation*

Study	N	Treatment Regimen	Active Control	Treatment Period	Follow-up	Primary End Point	CAR at Primary End Point		CAR at 52 Weeks, Varenicline vs. Placebo
							Varenicline vs. Placebo	Varenicline vs. Bupropion	
Phase 2									
Nides et al (2006)[22]	638	0.3 mg qd 1.0 mg qd 1.0 mg bid Placebo	Bupropion-SR 150 mg bid	6 wk + 1 wk of placebo (7 wk in bupropion-SR group)	Up to 52 wk	CAR for any 4 wk during treatment	0.3 mg qd: 1.97 (1.07–3.65) 1.0 mg qd: 2.97 (1.63–5.40) 1.0 mg bid: 4.71 (2.60–8.53)	NR	1.0 mg bid: 14.4% vs. 4.9% (P <0.01)†
Oncken et al (2006)[23]	647	0.5 mg bid‡ 1.0 mg bid‡ Placebo	NA	12 wk	40 wk	CAR for weeks 4–7 and 9–12	1 mg bid: weeks 4–7: 5.86 (3.16–10.90); weeks 9–12: 8.07 (4.42–14.70)	NA	1.0 mg bid: 22.4% vs. 3.9% (P <0.001)†
Phase 3									
Gonzales et al (2006)[24]	1,025	1.0 mg bid Placebo	Bupropion-SR 150 mg bid	12 wk	40 wk	CAR for weeks 9–12	3.85 (2.70–5.50)	1.93 (1.40–2.68)	3.09 (1.95–4.91)
Jorenby et al (2006)[25]	1,027	1.0 mg bid Placebo	Bupropion-SR 150 mg bid	12 wk	40 wk	CAR for weeks 9–12	3.85 (2.69–5.50)	1.90 (1.38–2.62)	2.66 (1.72–4.11)
Tonstad et al (2006)[26]	1,210	1.0 mg bid Placebo	NA	12 wk open label; + additional 12 wk of blinded treatment in abstainers	Up to 52 wk	CAR for weeks 13–24	2.48 (1.95–3.16)	NA	1.34 (1.06–1.69)

CAR = continuous abstinence rate; NA = not applicable; NR = not reported.

Abstinence in all trials was determined by self-report and verified by measurement of exhaled carbon monoxide ≤10 ppm at weekly visits. Patients were provided educational material on smoking cessation and up to 10 minutes of smoking cessation counseling at each weekly treatment visit. Values are given as odds ratios with 95% confidence intervals in parentheses.

*All trials were randomized, double-blind, placebo-controlled.

†OR not reported.

‡Each varenicline group was divided into subgroups receiving the full dose initially or after titration over 1 week.

Adapted from *Arch Intern Med.*[22, 23] and *JAMA.*[24–26]

of subjects achieving 28 consecutive days of abstinence (i.e., continuous abstinence rate [CAR]) any time during the treatment period, was significantly greater with the varenicline 1.0-mg once-daily (37.3%, $P < 0.001$) and 1.0-mg twice-daily (48.0%, $P < 0.001$) doses compared with placebo (17.1%). Bupropion-SR also increased the CAR compared with placebo (33.3%, $P = 0.002$). Similar results were found for the carbon monoxide–confirmed CARs with a dose-response relation being observed. The highest dose, varenicline 1.0 mg twice-daily, increased the CAR compared with placebo from week 4 to weeks 12 (28.8% vs. 10.6%), 24 (20.8% vs. 7.3%), and 52 (14.4% vs. 4.9%) ($P \leq 0.01$ for all comparisons). Compared with placebo, varenicline 1.0 mg twice daily consistently reduced craving scores at all weekly time points through week 6 and demonstrated significantly reduced measures of smoking satisfaction and enjoyment of respiratory tract sensations and increased aversion.

In the second study,[23] varenicline significantly increased the 4-week CAR for week 4 to week 7 of treatment compared with placebo (10.9%); CARs in the 0.5-mg twice-daily nontitrated and titrated groups were 37.2% and 35.4%, respectively ($P < 0.001$), and were 38.8% and 40.8% ($P < 0.001$) for the 1.0-mg twice-daily nontitrated and titrated groups, respectively (Table 1). During week 9 to week 12 of treatment, the 4-week CARs were significantly increased in the varenicline 0.5-mg twice-daily nontitrated and titrated groups (47.3% and 40.8%, respectively, $P < 0.001$) and in the 1.0-mg twice-daily nontitrated and titrated groups (44.2% and 54.6%, respectively, $P < 0.001$) compared with placebo (11.6%). The CARs for weeks 9 to 52 were significantly higher in the pooled varenicline 0.5-mg twice-daily group (18.5%, $P < 0.001$) and the pooled varenicline 1.0-mg twice-daily group (22.4%, $P < 0.001$) compared with placebo (3.9%). Varenicline significantly reduced the urge to smoke, and, in subjects who continued to smoke, reduced the reinforcing effects of smoking.

Adverse Events

The most commonly reported adverse events in varenicline-treated subjects in these phase 2 trials were nausea, abnormal dreams, insomnia, taste perversion, flatulence, dyspepsia, constipation, and headache. Discontinuations due to adverse events ranged from 7% to 14% with varenicline and from 10% to 14% with placebo. In the 7-week phase 2 study that included a bupropion-SR arm, there were fewer discontinuations due to treatment-emergent adverse events with varenicline compared with bupropion-SR (11% to 14% with varenicline vs. 16% with bupropion-SR and 10% for placebo).[21] Also, compared with bupropion-SR 150 mg twice daily, subjects receiving varenicline 1 mg twice daily reported more nausea (21.4% vs. 52%) but less insomnia (45.2% vs. 35.2%) and constipation (13.5% vs. 5.6%).[22] A dose-response relation was demonstrated for the adverse events of nausea, insomnia, abnormal dreams, and taste perversion but not for headache, dyspepsia, or constipation.[22] In the 12-week phase 2 study, nausea was the most common adverse event (reported by 35% of subjects receiving varenicline 1 mg twice daily after dose titration and 16% receiving varenicline 0.5 mg twice daily after titration, compared with 15% of placebo-treated patients).[23] This effect was dose dependent, was lower in patients titrated to target dose, was mild-to-moderate in the majority of subjects, and was usually transient (median duration, ≤12 days).[22,23] Discontinuation due to nausea was low (<5% of subjects in each treatment group).[22,23]

In these phase 2 trials, results of clinical laboratory tests, electrocardiograms, and vital signs demonstrated no safety issues with varenicline. The frequency of clinically significant laboratory test abnormalities was low and similar across the treatment groups.[22,23]

Conclusions from Phase 2 Studies

In the phase 2 studies, efficacy for both short-term and long-term tobacco abstinence with varenicline was demonstrated, with a dose response suggesting an optimal target dose of 1.0 mg twice daily. When combined with results from earlier studies, the phase 2 results with varenicline demonstrate an excellent safety profile. Nausea was the most common adverse event and exhibited a dose-response relation. Sleep disturbances were shown to be less common with varenicline compared with bupropion-SR. These studies prepared the way for the phase 3 clinical trials.

PHASE 3 CLINICAL TRIALS WITH VARENICLINE

Three large phase 3 trials were designed to test the hypothesis that varenicline 1 mg twice daily is safe and efficacious in the treatment of tobacco dependence; 2 of the 3 trials evaluated varenicline as an aid to cessation compared with placebo and bupropion-SR.[24,25] The third trial was designed to determine whether maintenance therapy with varenicline after an initial 12 weeks of varenicline treatment would result in reduced or delayed relapse to smoking compared with varenicline treatment for 12 weeks followed by placebo.[26]

Varenicline as an Aid to Smoking Cessation

The 2 trials evaluating the efficacy and safety of varenicline as an aid to smoking cessation compared with placebo and bupropion-SR were identically designed, double-blind, randomized, placebo-controlled, multicenter trials conducted in the United States (Table 1).[24,25] The main outcome measure in these 2 trials was continuous abstinence from smoking for the final 4 weeks of treatment (weeks 9 to 12); important secondary outcomes included continuous abstinence rates from weeks 9 to 24 and weeks 9 to 52, and 7-day point-prevalence abstinence rates at weeks 12, 24, and 52. Abstinence at each assessment was determined by self-report of "not a puff" since the previous visit and confirmed by exhaled carbon monoxide of not >10 ppm. All subjects received brief office counseling at each visit.

The 2 trials yielded consistent results. The primary outcome of continuous abstinence from weeks 9 to 12 was approximately 44% in the varenicline group compared with approximately 30% in the bupropion-SR group and 18% in the placebo group (Table 1 and **Figure 1**). Thus, after 12 weeks of treatment, there was nearly a 4-fold increase in the odds of tobacco abstinence with varenicline compared with placebo and nearly a doubling of the odds of quitting with varenicline compared with bupropion-SR for the primary endpoint (Figure 1). In **Figure 2**, the continuous abstinence rates through week 52 are demonstrated. Again, a significant difference was shown between varenicline and placebo with abstinence rates ranging from 22% to 23% with varenicline compared with 8% to 10% with placebo. Bupropion-SR demonstrated 52-week continuous abstinence rates of approximately 15% to 16%. Thus, in these 2 trials, varenicline showed significantly increased odds of quitting compared with both placebo and bupropion-SR in the short term (over 12 weeks), was significantly better than placebo after 1 year, and tended toward improved abstinence compared with bupropion-SR at 1 year.[24,25]

The 7-day point-prevalence abstinence outcome was also interesting in both of these studies. One of the studies demonstrated a significant increase in point-prevalence abstinence at weeks 12, 24, and 52 with varenicline compared with both bupropion-SR and placebo,[25] while the second study showed a similar advantage for varenicline over placebo and bupropion-SR at weeks 12 and 24, but failed to reach a statistically significant difference for varenicline compared with bupropion-SR at week 52 (**Figure 3**).[24] Both studies demonstrated a gradually increasing 7-day point-prevalence abstinence rate from the target quitting date up to approximately weeks 6 to 8 with varenicline (Figure 3).[22,23] A possible interpretation of this result is that quitting activity increased through a cumulative effect of varenicline over the course of several weeks following the target quit date.

The results of these 2 studies showed that many measures of craving, withdrawal, and smoking satisfaction were significantly diminished in subjects treated with varenicline compared with placebo (**Figure 4**). Although statistical comparisons were not carried out for varenicline versus bupropion-SR for these measures, numerical differences appear to generally favor varenicline. The partial agonist activity of varenicline at the $\alpha_4\beta_2$ nAChR explains its ability to mitigate craving and withdrawal following abstinence from nicotine. Also, by occupying the receptor and preventing full stimulation by nicotine, this agent also acts as a partial antagonist at the $\alpha_4\beta_2$ nAChR, an effect demonstrated by the reduced satisfaction from smoking before quitting or following relapse observed in these phase 3 trials. These effects may explain the efficacy of varenicline when used for smoking cessation and are consistent with its known mechanism of action.

Adverse Events. These studies demonstrated that varenicline is safe at the dosage of 1 mg twice daily. The most common adverse event due to varenicline was nausea, which occurred in approximately 29% of participants (Table 2). However, the majority of cases of nausea were reported as mild or moderate, and permanent discontinuation of treatment due to nausea was minimal at about 2.5%. The other most common adverse events related to varenicline were headache, insomnia, and abnormal dreaming. The complaints of abnormal dreams tended to be mild and were not a common reason for study discontinuation. Fewer complaints of insomnia occurred with varenicline (14%) compared with bupropion-SR (21%); nausea was not a significant complaint in patients treated with bupropion-SR. In these 2 studies, discontinuation of treatment due to adverse events was more common with bupropion-SR (14%) than with varenicline (9.5%).[24,25]

Varenicline for Relapse Prevention

The third phase 3 trial evaluated the effect of 24 weeks of therapy with varenicline to delay or prevent smoking relapse after successful cessation (Table 1).[26] In this randomized, placebo-controlled trial conducted at multiple medical centers in 7 countries, subjects were treated with open-label varenicline 1 mg twice daily (following 1 week of dose titration) for 12 weeks. All subjects who were confirmed abstinent during the final week of treatment were eligible for randomization to continue treatment with either varenicline 1 mg twice daily or placebo for an additional 12 weeks. The primary end points were continuous abstinence from weeks 13 to 24 and from weeks 13 to 52.

A total of 1,927 smokers were recruited and treated with 12 weeks of open-label varenicline 1 mg twice daily. Of these, 1,236 (64.1%) subjects were confirmed abstinent during week 12 of therapy and were eligible for randomization; 1,210 (62.8%) subjects were randomized to additional varenicline or placebo for 12 weeks. CARs were significantly better in the varenicline-treated subjects than in the placebo group at both the week 24 and week 52 follow-up visits (Table 1 and **Figure 5**). The continuous abstinence rate from weeks 13 to 24 in varenicline-treated subjects was 70.5% compared with 49.6% in placebo-treated subjects (OR, 2.48; $P < 0.001$). Likewise, the CAR for weeks 13 through 52 in varenicline-treated subjects was 43.6% compared with 36.9% with placebo (OR, 1.34; $P = 0.02$). The time to first lapse was significantly longer in the varenicline-treated group, with a median time of 198 days (postrandomization to double-blind treatment) compared with 87 days in placebo-treated patients ($P < 0.001$).

Adverse Events. The safety and tolerability of varenicline in this study were extremely favorable. Similar to the previously described phase 3 trials, the most common adverse event reported in the varenicline-treated subjects was nausea. Although approximately 30% of participants described nausea as an adverse event during the open-label varenicline treatment phase, only approximately 3% discontinued treatment due to nausea during this phase, and only 1.2% of varenicline-treated patients reported nausea as an adverse event during the additional 12-week, double-blind treatment

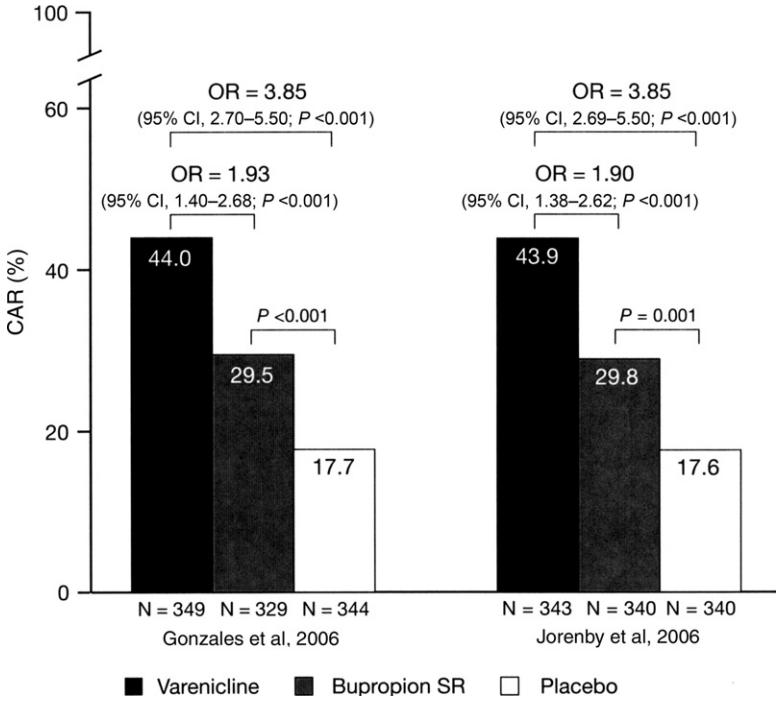

Figure 1 Carbon monoxide–confirmed continuous abstinence rates (CARs) from weeks 9 to 12 in 2 identical phase 3 trials of varenicline as an aid to smoking cessation. CI = confidence interval; OR = odds ratio. (Adapted from *JAMA*.[24,25])

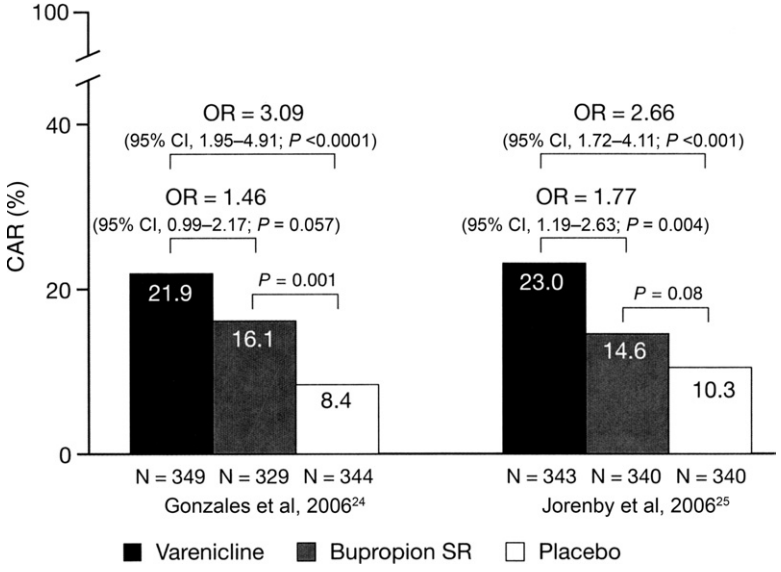

Figure 2 Carbon monoxide–confirmed continuous abstinence rates (CARs) from weeks 9 to 52 in 2 identical phase 3 trials of varenicline as an aid to smoking cessation. CI = confidence interval; OR = odds ratio. (Adapted from *JAMA*.[24,25])

phase.[26] During the second 12-week course of treatment with varenicline, no adverse events occurred more often in the varenicline group than in the placebo group.[26]

Conclusions from Phase 3 Studies

Taken together, these large phase 3 trials confirmed the efficacy of varenicline over bupropion-SR and placebo as an aid to smoking cessation. Varenicline also demonstrates the ability to maintain abstinence and to delay relapse significantly better than placebo when provided for up to 24 weeks of treatment. The overall safety and tolerability of varenicline is excellent. Based on the findings of the phase 2 and 3 clinical trials, varenicline was approved in 2006 by the FDA for use as a smoking cessation aid and for extended treatment in successful quitters to increase the likelihood of long-term abstinence.

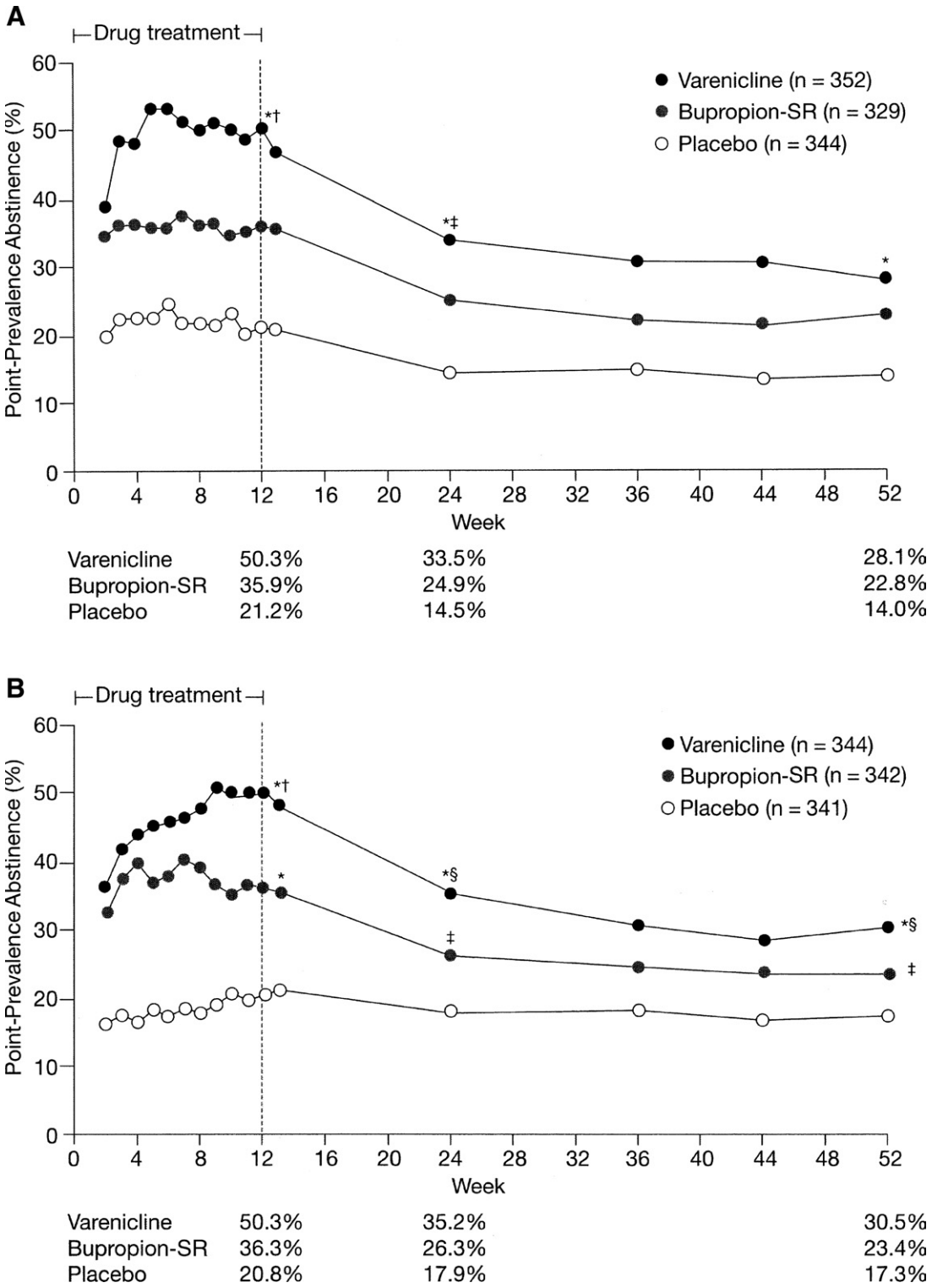

Figure 3 Carbon monoxide–confirmed 7-day point prevalence abstinence rates in identical phase 3 trials of varenicline as an aid to smoking cessation by (*A*) Gonzales and colleagues[24] ($^{*}P < 0.001$ vs. placebo; $^{\dagger}P < 0.001$ vs. bupropion-SR; $^{\ddagger}P = 0.01$ vs. bupropion-SR) and (*B*) by Jorenby and colleagues[25] ($^{*}P < 0.001$ vs. placebo; $^{\dagger}P < 0.001$ vs. bupropion-SR; $^{\ddagger}P \leq 0.05$ vs. placebo; $^{\S}P \leq 0.05$ vs. bupropion-SR). (Adapted with permission from *JAMA*.[24,25])

VARENICLINE: PLACE IN THERAPY

Varenicline is the first in a new class of agents for smoking cessation, the $\alpha_4\beta_2$ nAChR partial agonists. Thus, varenicline offers a new therapeutic option for patients trying to achieve smoking cessation. Consistent with its mechanism of action, this agent appears to offer improvement over placebo and bupropion-SR for nicotine craving and withdrawal measures, and for reducing smoking satisfaction and

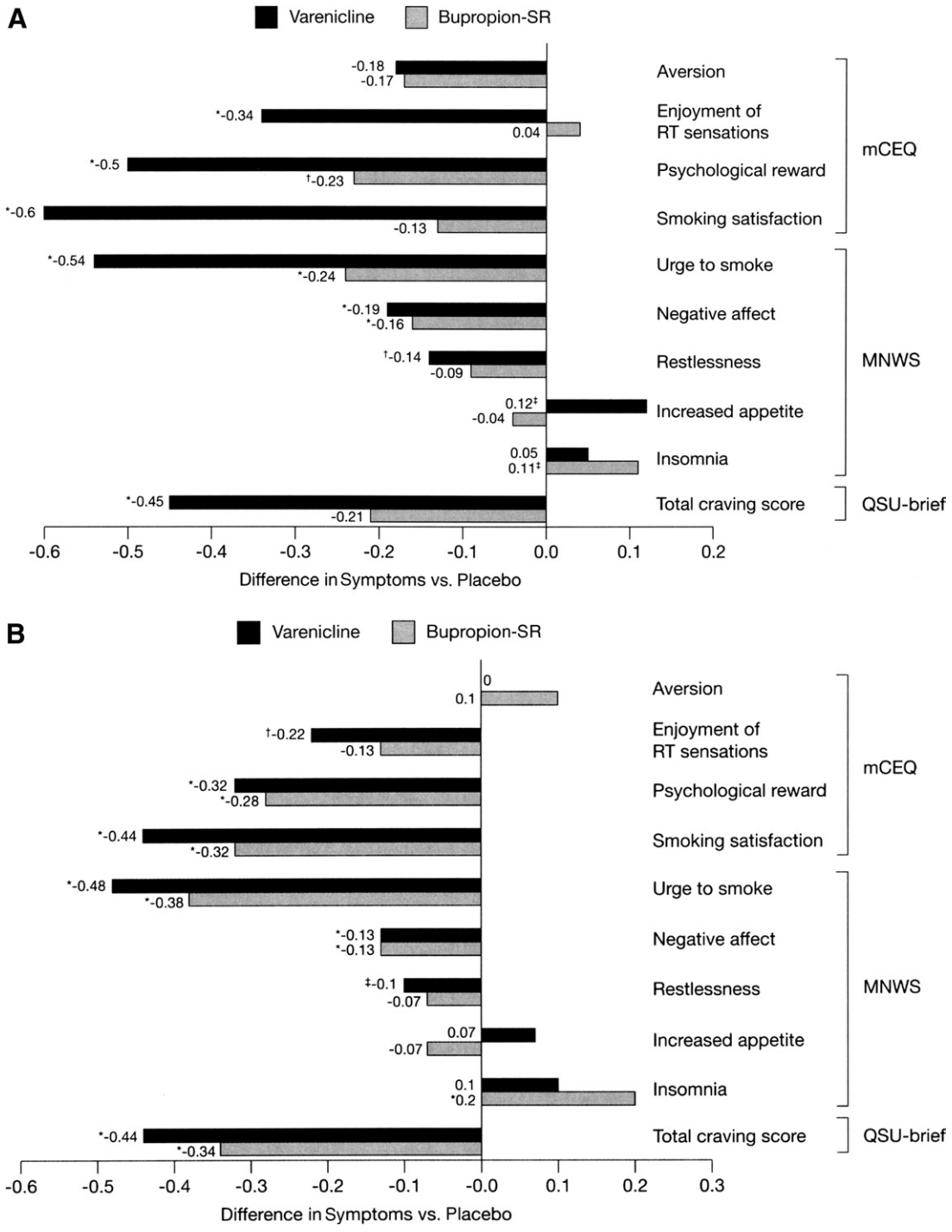

Figure 4 Measures of withdrawal and craving using the Minnesota Nicotine Withdrawal Scale (MNWS) and Brief Questionnaire of Smoking Urges (QSU-brief) and measures of the reinforcing effects of smoking (in participants who smoked) using the Modified Cigarette Evaluation Questionnaire (mCEQ). Charts are based on repeated-measures analysis of data for week 1 through week 7 in phase 3 trials of varenicline for smoking cessation by (*A*) Gonzales and colleagues[24] and (*B*) Jorenby and colleagues.[25] $^{*}P \leq 0.001$; $^{\dagger}P \leq 0.01$; $^{\ddagger}P < 0.05$. RT = respiratory tract. (Adapted from *JAMA*.[24,25])

reward in subjects who lapse. These pharmacologic differences between varenicline and other available agents may explain the improved abstinence rates observed with this agent.

In addition, varenicline significantly delays and may prevent long-term smoking relapse.[26] Importantly, this finding was observed in the long-term maintenance trial with varenicline despite the strict outcome criteria of carbon monoxide–confirmed continuous abstinence used in that trial, in which smokers are not considered abstinent if they had even 1 puff (rather than point prevalence of abstinence often used in other trials, in which lapses do not count

Table 2 Most common adverse events in phase 3 clinical trials with varenicline for smoking cessation*

	Gonzales et al (2006)[24]			Jorenby et al (2006)[25]		
	Varenicline 1 mg bid (n = 349)	Bupropion-SR 150 mg bid (n = 329)	Placebo (n = 344)	Varenicline 1 mg bid (n = 343)	Bupropion-SR 150 mg bid (n = 340)	Placebo (n = 340)
Nausea†	98 (28.1)	41 (12.5)	29 (8.4)	101 (29.4)	25 (7.4)	33 (9.7)
Mild	70 (71.4)	27 (65.9)	22 (75.9)	72 (71.3)	14 (56.0)	30 (90.9)
Moderate	26 (26.5)	12 (29.3)	5 (17.2)	25 (23.8)	10 (40.0)	3 (9.1)
Severe	2 (2.0)	2 (4.9)	2 (6.9)	5 (5.0)	1 (4.0)	0 (0)
Headache	54 (15.5)	47 (14.3)	42 (12.2)	44 (12.8)	27 (7.9)	43 (12.6)
Insomnia	49 (14.0)	72 (21.9)	44 (12.8)	49 (14.3)	72 (21.2)	42 (12.4)
Abnormal dreams‡	36 (10.3)	18 (5.5)	19 (5.5)	45 (13.1)	20 (5.9)	12 (3.5)
Flatulence	20 (5.7)	14 (4.3)	10 (2.9)	20 (5.8)	7 (2.1)	8 (2.4)
Constipation	19 (5.4)	23 (7.0)	13 (3.8)	31 (9.0)	22 (6.5)	5 (1.5)

*Values given as numbers with percentages in parentheses.
†Values may not total 100% because of rounding.
‡Self-described by the participants as any change in dreaming, such as vivid dreams or increased frequency of dreaming.
Adapted from *JAMA*.[24,26]

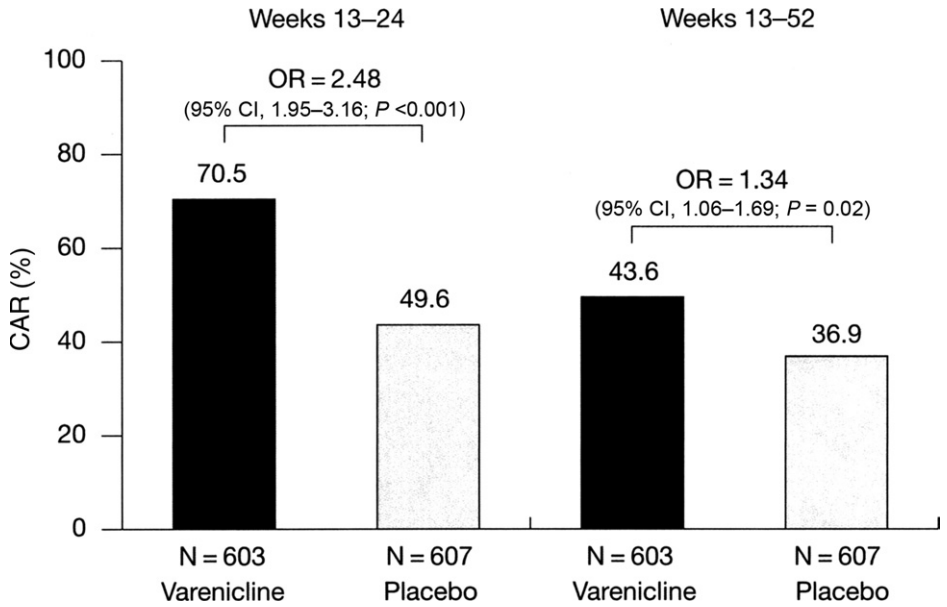

Figure 5 Carbon monoxide–confirmed continuous abstinence rates (CARs) for phase 3 long-term maintenance of abstinence study of varenicline versus placebo. CI = confidence interval; OR = odds ratio. (Adapted from *JAMA*.[26])

against abstinence). This finding is especially meaningful considering the general lack of effective treatments available for relapse prevention.[27] Bupropion-SR may possess a similar characteristic to improve long-term abstinence, but the data are somewhat unclear. A study of bupropion-SR for extended treatment (52 weeks) showed that point prevalence abstinence rates were significantly improved with bupropion-SR at the end of treatment (52 weeks) and up to week 78, but failed to demonstrate a difference in CARs relative to placebo after week 24.[28] In that study, bupropion-SR delayed but did not significantly prevent smoking relapse over the duration of the 2-year study.[28] In a more recent study, extended treatment with bupropion-SR (25 weeks) failed to demonstrate improvement over placebo for maintaining long-term abstinence from smoking.[29]

The average daily cost of therapy with varenicline in the United States is comparable to bupropion-SR and most NRTs, and should not create a significant barrier to treatment. Although retail drug costs vary greatly depending on the region of the country and type of pharmacy, the average daily cost for varenicline is about US$4 to $5 and is similar for generic bupropion (about $3 per day) and NRTs (which may cost $3 to $6 per day depending on amount used and whether used as monotherapy or in combination therapy with other NRTs or bupropion).[30] As with virtually any drug therapy in the United States, insurance coverage for

any tobacco dependence treatment is quite variable. However, when long-term smoking-abstinence rates are considered, varenicline appears to be a cost-effective treatment for tobacco use and dependence. An analysis from the United Kingdom reaches a similar conclusion. In a study analyzing the effectiveness of varenicline for reimbursable prescription in the United Kingdom a 12-week course of varenicline is cited at costing £164, compared with about £120 to £150 for NRT and £80 for the full 8-week course of bupropion-SR. In considering the comparative efficacy of varenicline—the study's conclusion was that varenicline—being about 20 to 30 times more cost-effective than the UK's National Institute for Clinical Excellence (NICE) upper limit for funding—should be reimbursed on at least an equal basis with bupropion and NRT prescriptions by the UK National Health Service (NHS) Primary Care Trusts.[31]

SUMMARY

Tobacco use continues to be the most important cause of preventable premature death in the United States and an increasing cause of morbidity and mortality throughout the world. Effective therapy for current smokers is needed to reduce the substantial predicted morbidity and mortality related to smoking. Currently recommended treatments are efficacious, but long-term abstinence rates are less than optimal. Varenicline, a novel $\alpha_4\beta_2$ nAChR partial agonist, is efficacious for the treatment of tobacco dependence. The phase 3 trials with this agent suggest that it may be more efficacious than the only other non-nicotine medication approved for tobacco dependence, bupropion-SR. Longer-term therapy for up to 24 weeks also appears to delay or prevent relapse compared with treatment for only 12 weeks, a significant finding in the field of smoking relapse prevention for which other available therapies have not demonstrated a similar benefit. The safety profile of varenicline is excellent, with the most commonly occurring adverse event, nausea, typically mild and well tolerated by most individuals. However, new safety warnings were added to the varenicline label in early 2008 because of post-marketing reports of neuropsychiatric symptoms including agitation, depression and suicidality in patients who were smoking and among those who were abstinent. A causal connection between varenicline use and these symptoms has not been established. Monitoring patients for these symptoms is advised for all varenicline prescribers.[32] Efforts aimed at increasing short-term abstinence and reducing relapse rates over the longer term are important for the goal of reducing smoking prevalence throughout the world. Varenicline adds significantly to our armamentarium of treatment options and should be considered a first-line therapy for smokers who are motivated to quit.

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