Varenicline for Smoking Cessation: A Review of the Literature

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ABSTRACT

BACKGROUND: Smoking is the leading preventable risk to human health. Various agents have been used to promote smoking cessation, but none has had long-term efficacy. Varenicline, a new nicotinic ligand based on the structure of cytosine, was approved by the US Food amd Drug Administration for use as a smoking cessation aid.

OBJECTIVES: The aims of this review were to provide an overview on the mechanism of action and preclinical and clinical data of the new drug, varenicline, and to discuss the current and future impact of varenicline as a treatment for smoking cessation.

METHODS: MEDLINE, BIOSIS, and Google scholar databases were searched (March 1, 2007–July 1, 2008) using the terms *varenicline, smoking cessation*, and *nicotinic receptors*. Full-text articles in English were selected for reference, and articles presenting the mechanism of action, pharmacokinetics, and data from preclinical and clinical trials were included.

RESULTS: The initial literature search yielded 70 papers. A total of 20 articles fulfilled the inclusion criteria. Varenicline, an $\alpha_4\beta_2$ nicotinic acetylcholine receptor partial agonist, inhibits dopaminergic activation produced by smoking and decreases the craving and withdrawal syndrome that accompanies cessation attempts. In Phase III clinical trials, the carbon monoxide–confirmed 4-week continuous abstinence rates were significantly higher with varenicline than with buproprion sustained release or placebo for weeks 9 through 12. Varenicline has been found to be well tolerated, with nausea being the most commonly reported (28.1%) adverse event.

CONCLUSIONS: Varenicline is the first drug for smoking cessation that has been found to have significant effectiveness in long-term relapse prevention (up to 52 weeks). Varenicline, with its unique profile of agonist and antagonist properties, increased cessation rates (both short- and long-term) compared with both placebo and bupropion sustained release. (*Curr Ther Res Clin Exp*. 2009;70:35–54) © 2009 Excerpta Medica Inc.

KEY WORDS: varenicline, smoking cessation, nicotinic receptors, review.

INTRODUCTION

Cigarette smoking remains the leading preventable cause of disease and premature death in the United States, claiming an estimated 438,000 lives per year.[1] Although 80% of people who smoke cigarettes desire to quit, only 35% attempt to quit, and only 5% are able to quit smoking without an aid.[2] In the mid-1970s there was no effective pharmacologic treatment for tobacco dependence, and few behavioral scientists or pharmaceutical companies were making significant efforts in this area.[3] Thirty years later this situation has changed substantially.

Seven smoking cessation pharmacotherapies are currently approved by the US Food and Drug Adminstration (FDA). Five of these are nicotine replacement products (gum, patch, nasal spray, inhaler, and lozenge).[4] Each delivers nicotine, the agent that is responsible for the development of tobacco dependence, so that the nicotine withdrawal symptoms and the craving for cigarettes are reduced while the patient is quitting smoking. Another approved smoking cessation therapy, bupropion sustained-release (SR), helps in smoking cessation by inhibiting dopamine reuptake in the central nervous system.[5] Bupropion also antagonizes nicotinic acetylcholine receptor function. The primary mechanism of bupropion's effect on smoking cessation is not clear, but it appears to be via reduction of withdrawal symptoms by mimicking nicotine effects on dopamine and noradrenaline.[6] It increases smoking cessation rates compared with both placebo[7] and the nicotine patch.[7,8] Varenicline, a partial nicotine agonist, is the latest addition to the list of drugs approved by the FDA for smoking cessation.[9] The chemical structure of varenicline is (7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3h][3]benzazepine[2R,3R]-2,3-dihydroxybutanedioate) (**Figure 1**).[10]

The purpose of this review was to provide an overview of the clinical trial data of varenicline, with a focus on Phase II and III trials and to discuss the current and future impact of varenicline as a form of smoking cessation therapy.
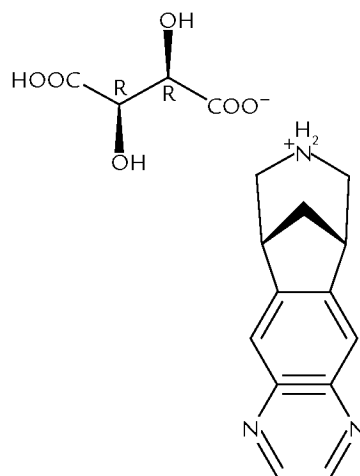

Figure 1. Chemical structure of varenicline.[10]

METHODS

A search was performed using the MEDLINE, BIOSIS, and Google scholar databases (March 1, 2007–July 1, 2008) for literature using the terms *varenicline, smoking cessation*, and *nicotinic receptors*. Full-text articles in English were selected for reference, and articles presenting the mechanism of action, pharmacokinetics, and data from preclinical and clinical trials were included. Reference lists from all retrieved articles were included in the search.

RESULTS

SEARCH RESULTS

The initial literature search yielded 70 papers. A total of 20 articles fulfilled the inclusion criteria.

MECHANISM OF ACTION

The dopaminergic neurons located in the midbrain reward center, including the ventral tegmental area (VTA) and substantia nigra pars compacta, play pivotal roles in drug reinforcement, motility, and associative motor learning.[11,12] An increase in the release of dopamine from VTA neurons onto their targets in the nucleus accumbens contributes to drug reinforcement.[13,14]

The midbrain dopaminergic system plays a key role in nicotine dependence.[15] Dopamine antagonists and lesions of dopamine neurons or of the nucleus accumbens have been found to reduce self-administration in rats.[16] When a sufficient concentration of nicotine is carried in the blood to activate $(\alpha_4)3(\beta_2)2$ receptors in the VTA, a burst firing of dopamine neurons occurs. The terminals of these neurons are in the medial shell and core areas of the nucleus accumbens. This stimulation of dopamine neurons causes increased release of extrasynaptic dopamine in the nucleus accumbens.[17]

Attention has now been focused on the specific inhibitors of $(\alpha_4)3(\beta_2)2$ receptors. Varenicline is an $\alpha_4\beta_2$ nicotinic acetycholine receptor partial agonist. It is a synthetic derivative of a natural plant alkaloid, cytisine. Cytisine has been used in Bulgaria since the 1960s as a smoking cessation aid.[18] After the development of varenicline, a review of cytisine was conducted.[19] Cytisine provided a structural starting point for the development of the higher-affinity varenicline. The agonist effect of oral varenicline on dopamine release is 35% to 60% of that observed with nicotine, which is theoretically sufficient to attenuate craving and withdrawal without producing its own dependence syndrome.[20]

Varenicline binds selectively and with high affinity to these receptors, thereby preventing nicotine from binding to the $\alpha_4\beta_2$ receptors (**Figure 2**).[17] In vitro electrophysiologic studies and in vivo neuron chemical studies have found that varenicline, acting as a typical partial agonist, binds to the receptors and stimulates receptor-mediated activity, but at a significantly lower concentration than the full agonist (ie, nicotine).[20–23] The slower release of dopamine with varenicline compared with smoking might also reduce the potential for abuse.[20,24] Varenicline also has a competitive antagonist effect on nicotine due to a substantially higher affinity for the $\alpha_4\beta_2$ receptor.[20] Varenicline blocks the ability of nicotine to activate $\alpha_4\beta_2$ receptors and thus to
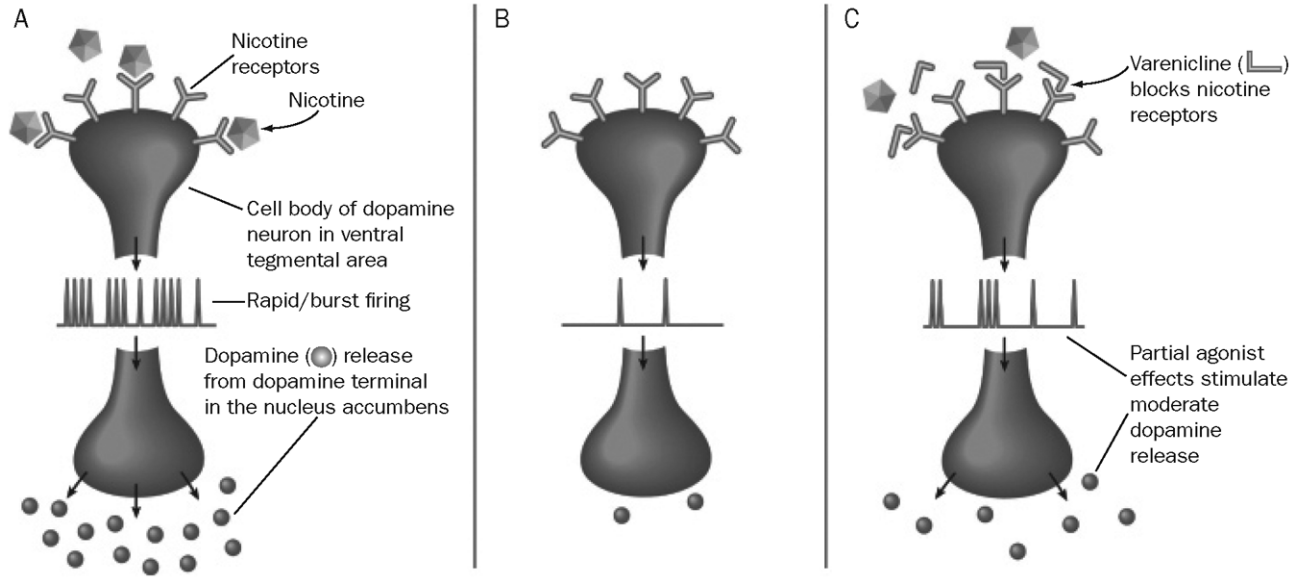
Figure 2. The effects of (A) nicotine from cigarettes, (B) nicotine withdrawal, and (C) varenicline on nicotinic receptors and dopaminergic release. Reprinted with permission.[17]

stimulate the central nervous meso limbic dopaminergic system. It inhibits dopaminergic activation and simultaneously provides relief from craving and withdrawal symptoms that accompany smoking cessation.[20] Varenicline has been found to be a full agonist at the α_7-homomeric receptors.[23] Several experimental studies have found that α_7-homomeric nicotinic receptors in the VTA are involved in the acute effect of nicotine on dopamine release in the nucleus accumbens.[25,26] The combination of the actions on $\alpha_4\beta_2$ and α_7 receptors may explain the mechanism of action of varenicline as a smoking cessation aid.

PHARMACOKINETICS

The pharmacokinetics of varenicline have been studied in various preclinical and Phase I trials.[20,27] The metabolism and disposition of varenicline was examined in rats, mice, monkeys, and humans after oral administration.[27] The majority of varenicline was unchanged in the circulation of all these species, and metabolites were primarily excreted in the urine. A large percentage of varenicline was excreted as unchanged parent drug (84%, 90%, 75%, and 81% of the dose in rats, mice, monkeys, and humans, respectively). Metabolites observed in excreta arose via N-carbamoyl glucuronidation and oxidation. These metabolites were also observed in the circulation, in addition to metabolites that arose via N-formylation and formation of a novel hexose conjugate. Metabolites observed in humans were also observed in other animal species, and there was no readily observable difference between smokers and nonsmokers.[27]

In a Phase I, double-blind, placebo-controlled, single-dose, dose-escalation study, the clinical pharmacology of single doses of varenicline in healthy smokers and nonsmokers under fed and fasted conditions was determined. The subjects were administered oral doses of varenicline ranging from 1 to 10 mg. All subjects had quantifiable plasma concentrations of varenicline up to 120 hours postdose.[28] Over this dose range, T_{max} occurred at 1.50 to 4.25 hours after administration and the mean $t_{1/2}$ of the decay phase ranged from 14.4 to 19.5 hours. Dose-proportional increases were observed in C_{max} and $AUC_{0-\infty}$ from 0.1 to 3 mg only; at higher doses there was no further increase in C_{max} or $AUC_{0-\infty}$. All 4 subjects given the 10-mg dose vomited shortly after dosing, which may have affected C_{max} and $AUC_{0-\infty}$ estimates. Smoking restriction produced no detectable change in the pharmacokinetic profile of varenicline.[28]

In another double-blind, placebo-controlled, multiple-dose, dose-escalation study of the pharmacokinetics of varenicline in healthy subjects who smoked, 4 dose levels were studied (1, 2, and 3 mg QD, and 1 mg BID).[29] The T_{max} of varenicline was achieved at 2 to 4 hours after administration for each regimen after both single and multiple doses of varenicline. Plasma varenicline concentrations were detectable from 96 to 144 hours after QD dosing with 1 and 2 mg and up to 144 hours after 3 mg QD and 1 mg BID. The individual $t_{1/2}$ values ranged from 16 to 27 hours after a single administration and from 18 to 43 hours after repeat administrations. Steady-state conditions were reached by day 4. The overall mean (SD) accumulation factor after once-daily dosing with 1, 2, and 3 mg was 1.94 (0.31) and after BID dosing it was 2.85 (0.73). The pharmacokinetics of varenicline were not time- or concentration-

dependent upon repeat dosing. There was an apparent decrease (~50%–90%) in both mean plasma nicotine and conitine concentrations compared with baseline after administration of the 2- and 3-mg QD doses and the 1-mg BID dose of varenicline. Similar decreases (~60%–80%) in the mean number of cigarettes smoked per day were observed with the 2- and 3-mg QD doses. The study did not show any change in renal elimination with the QD or BID regimen. Estimates of renal clearance were similar across treatments and study days, indicating that varenicline elimination was not altered with repeat dosing.

After oral administration of varenicline, absorption is complete and systemic bioavailability is high.[27] Bioavailability of oral varenicline is unaffected by food or by the time of administration.[28] The elimination $t_{1/2}$ of varenicline is ~24 hours.[21] T_{max} is reached in 3 to 4 hours after oral administration. Over the recommended dose range, varenicline exhibits linear pharmacokinetics after single or repeated doses.[28] Varenicline is not highly protein bound (20%) in plasma. Varenicline is almost exclusively excreted by the kidneys in humans.[21] It is not known whether varenicline is excreted in breast milk (Table I).

The pharmacokinetics of varenicline are unaffected in patients with hepatic insufficiency; however, patients with impaired renal function may be at an increased risk of toxic reactions as the drug is excreted exclusively by the kidneys.[30] The manufacturer of the drug has instructed that the patients with severe renal impairment should receive a reduced initial dose.[10]

In a double-blind, placebo-controlled, parallel-group study, the single- and multiple-dose pharmacokinetics and tolerability of varenicline were observed in elderly smokers.[31] Twenty-four healthy male and female volunteers aged >65 years who had smoked ≥10 cigarettes per day for ≥1 year were enrolled. Two groups, each consisting of 12 eligible volunteers, were randomized in a 2:1 ratio to receive varenicline or placebo: in group 1, varenicline 1 mg QD was administered for 7 days, and in group 2, varenicline 1 mg BID on days 1 through 6 and a single dose on day 7 was administered. Varenicline plasma concentrations were higher on day 7 than after a single administration, indicating accumulation of varenicline upon repeat dosing. Maximum plasma concentrations were achieved within 2 to 3 hours following single or repeat

Table I. Pharmacokinetics of varenicline.[27–29]

Bioavailability	High, unaffected by food or time of administration
Plasma protein binding	<20%
T_{max}	3–4 hours
Time to C_{ss}	4 days
Metabolism	Minimal hepatic metabolism
Active metabolites	N-formyl conjugate, N-carbamoyl glucoronide, N-hexose conjugate, and an unidentified metabolite
Elimination	Renal, 92% unchanged
Elimination $t_{1/2}$	~24 hours

C_{ss} = steady-state concentration.

oral administration with each dose regimen. Steady state conditions developed within 4 days of repeated administration. The steady state minimum plasma concentrations pooled from days 4 to 8 averaged ~3.3 ng/mL after 1 mg QD and 6.0 ng/mL after 1 mg BID dosing. Adverse events were reported by 4 participants (50%) receiving varenicline 1 mg QD, 3 (38%) receiving BID treatment, and 5 (62%) in the placebo group. The most commonly reported adverse event was nausea: 2 in group 1, 1 in group 2, and 1 in the placebo group. There was no evidence of concentration- or time-dependent changes in varenicline pharmacokinetics following repeated once or twice daily administration for 7 consecutive days. According to the authors, no dose adjustment is necessary based on age alone.[31] The drug is not recommended for patients aged <18 years, as no studies have been conducted in this age group.[10]

DOSE

The recommended dose of varenicline is 1 mg BID after a 1-week titration period (starting with 0.5 mg QD, then 0.5 mg BID, and then 1 mg BID). The initial dose titration reduced the incidence of nausea.[32,33] Varenicline should be started 7 days before the date identified for smoking cessation.

DRUG INTERACTIONS

Since varenicline is not a substrate for the cytochrome P450 family of metabolizing enzymes, it is expected to interact with few drugs.[29] The safety of the combination of bupropion and varenicline has not yet been reported, and the safety and efficacy of varenicline with other smoking cessation therapies are yet to be established.[10] Varenicline was not found to have any clinically significant interactions with digoxin, cimetidine, metformin,[30] or warfarin.[34]

VARENICLINE CLINICAL TRIAL DATA

The literature search for clinical trials yielded 8 papers.[4,32,35–40] Six double-blinded, randomized, controlled trials evaluated varenicline for smoking cessation. One open-label randomized trial compared varenicline with nicotine replacement therapy (NRT) but without a placebo arm.[40] One trial evaluated varenicline as an aid to relapse prevention[37] (Table II).

Clinical Efficacy

A Phase II, randomized, double-blind, placebo- and active-controlled, multicenter, parallel-group study was conducted to select the optimal dose for larger-scale Phase III trials and to assess the efficacy and tolerability of 3 different doses of varenicline administered for 6 weeks.[35] Subjects were healthy smokers aged 18 to 65 years. They were required to have smoked an average of 10 cigarettes per day during the previous year without abstinence of >3 months. The primary efficacy measure was the continuous quit rate (CQR) for any 4-week period, which was defined as abstinence for any 28-day period during the treatment phase. The secondary efficacy measures included the carbon monoxide (CO)-confirmed (≤10 ppm) 4-week CQR for weeks 4 to 7, as well as CQRs from week 4 to weeks 12, 24, and 52. Craving was assessed using the

Table II. Overview of clinical trials used in this review.

Trial	Design	Dose	Subjects	Objectives
Jorenby et al[4]	Phase III, randomized, double-blind, placebo-controlled; consisted of a 12-week treatment period with follow-up to week 52	Varenicline 1 mg BID (titrated as 0.5 mg/d for days 1–3, 0.5 mg BID for days 4–7, then 1 mg BID through week 12) Bupropion SR 150 mg/d for days 1–3, then 150 mg BID through week 12 Placebo	Aged 18–75 years, smoked ≥10 cigarettes/d during the previous year without a period of abstinence >3 months	Primary end point: exhaled CO-confirmed 4-week CAR for weeks 9–12 Secondary end points: (1) CAR from weeks 9–24 and from weeks 9–52; (2) 7-day point prevalence abstinence rates at weeks 12, 24, and 52
Oncken et al[32]	Phase II, randomized, double-blind, placebo-controlled, multicenter clinical trial	Varenicline 0.5 mg BID nontitrated Varenicline 0.5 mg BID titrated Varenicline 1 mg BID nontitrated Varenicline 1 mg BID titrated Placebo	Aged 18–65 years, in general good health, smoked ≥10 cigarettes/d during the previous year without a period of abstinence >3 months	Primary end point: exhaled CO-confirmed CQR for weeks 4–7 and 9–12 during treatment and CARs for weeks 9–52 for each dose relative to placebo Secondary end points: during the treatment period, CO-confirmed 7-day point prevalence abstinence and changes in the MNWS and the mCEQ

Table II (continued).

Trial	Design	Dose	Subjects	Objectives
Nides et al[35]	Phase II, randomized, double-blind, parallel-group, multicenter, placebo- and active-controlled clinical trial	Varenicline 0.3 mg/d Varenicline 1.0 mg/d Varenicline 1.0 mg BID Bupropion SR 150 mg BID Placebo	Aged 18–65 years, in general good health, smoked an average of 10 cigarettes/d during the previous year without a period of abstinence >3 months	Primary end point: exhaled CO-confirmed CQR for any 4 weeks Secondary end points: CQRs from weeks 4–7 and weeks 4–12, 24, and 52
Gonzales et al[36]	Phase III, randomized, double-blind, parallel-group, multicenter, placebo- and active-treatment controlled trial with a 12-week treatment phase and blinded poststudy drug follow-up to week 52	Varenicline 1 mg BID (titrated as 0.5 mg/d for days 1–3, 0.5 mg BID for days 4–7, 1 mg BID through week 12) Bupropion SR 150 mg/d for days 1–3, then 150 mg BID through week 12 Placebo	Aged 18–75 years, smoked ≥10 cigarettes/d, had <3 months of smoking abstinence in the past year	Primary end point: exhaled CO-confirmed 4-week CAR for weeks 9–12 Secondary end points: (1) CARs from weeks 9–24 and from weeks 9–52; (2) 7-day point prevalence abstinence rates at weeks 12, 24, and 52
Tonstad et al[37]	52-Week, randomized, open-label (first 12 weeks) and then double-blind treatment phase (next 12 weeks) and then nontreatment follow-up phase for 28 weeks. Those who successfully abstained from smoking, use of tobacco, NRT for ≥7 days of the treatment period were randomly assigned to varenicline 1 mg BID or placebo.	Varenicline 1 mg BID with an initial dose titration for 12 weeks	Aged 18–75 years, smoked ≥10 cigarettes/d, had <3 months of smoking abstinence in the past year, motivated to quit	Primary end point: exhaled CO-confirmed 4-week CAR for weeks 13–24 Secondary end points: (1) CAR from weeks 13–52; (2) 7-day point prevalence abstinence rates at weeks 12, 24, and 52

Table II (continued).

Trial	Design	Dose	Subjects	Objectives
Tsai et al[38]	Randomized, double-blind, placebo-controlled, 12-week treatment, 12-week follow-up, multicenter clinical trial	Varenicline 1 mg BID with an initial dose titration for 12 weeks Placebo	Cigarette smokers aged 21–73 years, smoked ≥10 cigarettes/d, had <3 months of smoking abstinence in the past year, motivated to quit	Primary end point: exhaled CO-confirmed CAR during the last 4 weeks Secondary end points: (1) CAR from weeks 9–24; (2) 7-day point prevalence abstinence rates at weeks 12–24
Nakamura et al[39]	Randomized, double-blind, placebo-controlled, multicenter clinical trial	Varenicline 0.25 mg BID Varenicline 0.5 mg BID Varenicline 1.0 mg BID with an initial dose titration for 12 weeks Placebo	Cigarette smokers aged 18–75 years, smoked ≥10 cigarettes/d during the previous year, without a period of smoking abstinence >3 months	Primary end point: exhaled CO-confirmed 4-week CAR for weeks 9–12 Secondary end point: CAR weeks 9–24 and weeks 9–52
Aubin et al[40]	52-Week, Phase III, open-label, randomized, multicenter trial	Varenicline 1 mg BID with an initial dose titration for 12 weeks NRT from target quit date 21 mg/d for 6 weeks, 14 mg/d for 2 weeks, then 7 mg/d for 2 weeks	Cigarette smokers aged 18–75 years, weight >45.5 kg, body mass index 15–38 kg/m², smoked ≥15 cigarettes/d, had <3 months of smoking abstinence in the past year, motivated to quit	Primary end point: self-reported and exhaled CO-confirmed 4-week CAR for weeks 9–12 (varenicline) and weeks 8–11 weeks (NRT) Secondary end points: (1) CO-confirmed CAR for the last 4 weeks of treatment through weeks 24–52 (vareni-cline, weeks 9–24 and 9–52; NRT, weeks 8–24 and 8–52); (2) 7-day point prevalence abstinence rates at weeks 24 and 52

SR = sustained release; CO = carbon monoxide; CAR = continuous abstinence rate; CQR = continuous quit rate; MNWS = Minnesota Nicotine With-drawal Scale; mCEQ = Modified Cigarette Evaluation Questionnaire; NRT = nicotine replacement therapy.

urge-to-smoke item of the Minnesota Nicotine Withdrawal Scale (MNWS)[41] and the 10-item Brief Questionnaire of Smoking Urges (QSU-brief).[42] The Modified Cigarette Evaluation Questionnaire (mCEQ) was used to assess the reenforcing effects of smoking.[43] Randomized subjects received 1 of 3 varenicline tartrate dose regimens (0.3 mg QD [n = 126; male, 50.0%; white, 88.1%; mean (SD) age, 41.9 (10.6) years], 1 mg QD [n = 126; male, 43.7%; white, 88.1%; mean (SD) age, 42.9 (10.5) years], or 1 mg BID [n = 125; male, 50.4%; white, 85.6%; mean (SD) age, 41.9 (9.8) years] for 6 weeks plus placebo for 1 week), bupropion hydrochloride SR 150 mg BID (n = 126; male, 45.2%; white, 83.3%; mean [SD] age, 40.5 [10.8] years) for 7 weeks, or matched placebo (n = 123; male, 52.0%; white, 87.8%; mean [SD] age, 41.6 [10.4] years) for 7 weeks. All subjects administered their study medication for 1 week before attempting to quit smoking on day 8 of the study.[35] The 4-week CQRs were significantly higher for varenicline tartrate 1 mg BID (48.0%; $P < 0.001$) and 1 mg QD (37.3%; $P < 0.001$) versus placebo (17.1%) and for bupropion SR (33.3%; $P = 0.002$) versus placebo. The CO-confirmed CQR from week 4 to weeks 12, 24, and 52 for the varenicline tartrate 1-mg BID group were significantly higher than that for the placebo group at each time point. The CQR rate for bupropion SR was significantly higher than that for placebo only at week 12. Craving, as assessed using both the MNWS urge-to-smoke item and the QSU-brief total score, was reduced significantly with varenicline tartrate 1 mg BID compared with placebo at all weekly time points. Bupropion SR reduced craving compared with placebo, although the differences reached statistical significance at week 5 and 7 using the 2 instruments. Discontinuation due to treatment-emergent adverse events (AEs) was 15.9% with bupropion SR, 11.2% to 14.3% with varenicline, and 9.8% with placebo. No dose-related increases occurred in relation to AEs with varenicline (Table II).

In another Phase II multicenter trial, the efficacy and tolerability of 4 varenicline dose regimens—2 with progressive dosing during the first week (titrated) and 2 with a fixed dosing schedule (nontitrated)—were studied.[32] The study was carried out in 2 phases: a 12-week, randomized, double-blind, placebo-controlled study with weekly visits followed by a 40-week assessment after discontinuation of the regimen. The subjects included healthy individuals (aged 18–65 years) who smoked ≥10 cigarettes per day. Subjects were randomly assigned to receive varenicline 0.5 mg BID nontitrated (n = 129; male, 45.0%; white, 85.3%; mean [SD] age, 42.9 [10.1] years), varenicline 0.5 mg BID titrated (n = 130; male, 53.1%; white, 80.8%; mean [SD] age, 43.5 [10.5] years), varenicline 1.0 mg BID nontitrated (n = 129; male, 48.8%; white, 83.7%; mean [SD] age, 43.7 [10.0] years), varenicline 1.0 mg BID titrated (n = 130; male, 48.5%; white, 80.8%; mean [SD] age, 42.2 [10.7] years), or placebo (n = 129; male, 51.9%; white, 72.1%; mean [SD] age, 43.0 [9.4] years) for 12 weeks. Long-term efficacy was assessed during a 40-week follow-up period. The primary efficacy measures were the CO-confirmed 4-week CQR for weeks 4 through 7 and 9 through 12 during treatment and the continuous abstinence rate (CAR) for weeks 9 through 52 for each dose relative to placebo. Secondary efficacy end points during the treatment period included the CO-confirmed 7-day point prevalence abstinence (PPA) (ie, abstaining from smoking during the preceding 7 days) and changes in the

MNWS and the mCEQ by treatment group. The 4-week CQR for weeks 4 through 7 and 9 through 12 were significantly greater in the varenicline treatment groups compared with the placebo group. The CQRs for weeks 4 through 7 were significantly higher for the varenicline 0.5-mg BID nontitrated and titrated groups (37.2% and 35.4%, respectively; both, $P < 0.001$) and for the varenicline 1.0-mg BID nontitrated and titrated groups (38.8% and 40.8%; both, $P < 0.001$) compared with placebo (10.9%). During weeks 9 through 12, CQRs were significantly higher for the varenicline 0.5-mg BID nontitrated and titrated groups (47.3% and 40.8%, respectively; both, $P < 0.001$) and for the varenicline 1.0-mg BID nontitrated and titrated groups (44.2% and 54.6%; both, $P < 0.001$) compared with placebo (11.6%). At week 12, 20.8% to 24.0% of subjects in the varenicline groups were continuously abstinent compared with 7.0% in the placebo group. At weeks 24 and 52, the rates decreased to approximately one third to one half of the rates observed at week 12 but remained significantly higher for the varenicline groups versus placebo[32] (Table II).

In a Phase III, randomized, double-blind, placebo- and active-treatment controlled, parallel-group, multicenter clinical trial, 1025 healthy individuals who smoked were enrolled for a treatment phase of 12 weeks with a 40-week nondrug follow-up period.[36] Participants received the titrated active drugs as either varenicline 1 mg BID (n = 352; male, 50.0%; white, 79.5%; mean [SD] age, 42.5 [11.1] years), bupropion SR 150 mg BID (n = 329; male, 58.4%; white, 80.2%; mean [SD] age, 42.0 [11.7] years) or placebo (n = 344; male, 54.1%; white, 76.2%; mean [SD] age, 42.6 [11.8] years) through week 12.[36] The primary end point was exhaled CO-confirmed 4-week CAR for weeks 9 through 12 (defined as the proportion of participants who reported no smoking [not even a puff] or use of any nicotine-containing products, confirmed by an exhaled CO measurement of ≤10 ppm). The secondary end points were CAR from weeks 9 through 24 and from weeks 9 through 52. Other secondary end points were 7-day PPA rates at weeks 12, 24, and 52. The MNWS, QSU-brief, and mCEQ were used to assess the outcomes related to craving, withdrawal, and the reinforcing effects of smoking. The hierarchy of comparisons was varenicline versus placebo followed by varenicline versus bupropion SR. The CO-confirmed 4-week CAR for weeks 9 through 12 was significantly higher for varenicline versus placebo (44.0% vs 17.7%; $P < 0.001$) and versus bupropion SR (29.5%; $P < 0.001$). Bupropion SR was also significantly higher compared with placebo (17.7%; $P < 0.001$). The CAR for weeks 9 through 24 was significantly higher for varenicline versus placebo (29.5% vs 10.5%; $P < 0.001$) and versus bupropion SR (20.7%; $P = 0.007$). The CAR for weeks 9 through 52 was significantly greater for varenicline than for placebo (21.9% vs 8.4%; $P < 0.001$), but the difference was not significant as compared with bupropion SR (16.1%). The 7-day PPA at week 12 was significantly higher for varenicline versus placebo (50.3% vs 21.2%; $P < 0.001$) and versus bupropion SR (35.9%; $P < 0.001$). At week 24, 33.5% of the varenicline group were abstinent versus 14.5% of the placebo group ($P < 0.001$) and 24.9% of the bupropion SR group ($P = 0.01$). At week 52, the 7-day PPA rate was 28.1% in the varenicline group versus 14.0% in the placebo group ($P < 0.001$) and 22.8% in the bupropion SR group ($P = 0.13$). Both varenicline and bupropion SR were associated with a significant reduction in the urge to smoke

and negative effects compared with placebo (both, $P < 0.001$). The 52-week study completion rates were 60.5% for varenicline, 56.0% for bupropion SR, and 54.0% for placebo. Participants who withdrew prematurely from the study were assumed to have not been able to quit smoking. The most common reason for discontinuation for both treatment and nondrug follow-up was loss to follow-up (Table II and III).

A Phase III, randomized, double-blind, placebo-controlled, multicenter trial was conducted to determine the efficacy and tolerability of varenicline for smoking cessation compared with placebo or bupropion SR.[4] The study consisted of a 12-week treatment period with follow-up to 52 weeks. A total of 1027 participants were randomly assigned to varenicline titrated to 1 mg BID, bupropion SR titrated to 150 mg BID, or placebo for 12 weeks, plus weekly smoking cessation counseling. The primary end point was the 4-week CAR for the last 4 weeks of study drug treatment (weeks 9–12). CARs from weeks 9 through 24 and weeks 9 through 52 were evaluated as secondary end points. Statistical significance was declared within each end point by comparing varenicline with placebo and varenicline with bupropion SR. During the last 4 weeks of treatment (weeks 9–12), 43.9% of participants in the varenicline group were continuously abstinent from smoking compared with 17.6% in the placebo group ($P < 0.001$) and 29.8% in the bupropion SR group ($P < 0.001$). For weeks 9 through 24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group ($P < 0.001$) and 20.2% in the bupropion SR group ($P = 0.003$). For weeks 9 through 52, 23.0% of participants in the varenicline group were continuously abstinent compared with 10.3% in the placebo group ($P < 0.001$) and 14.6% in the bupropion SR group ($P = 0.004$). The odds ratio

Table III. Results of varenicline clinical trials.

Trial	Primary End Point (CAR weeks 9–12)	Secondary End Points	
		CAR weeks 9–24	CAR weeks 9–52
Jorenby et al[4]	Varenicline 43.9%	Varenicline 29.7%	Varenicline 23.0%
	Bupropion SR 29.8%	Bupropion SR 20.2%	Bupropion SR 14.6%
	Placebo 17.6%	Placebo 13.2%	Placebo 10.3%
Gonzales et al[36]	Varenicline 44.0%	Varenicline 29.5%	Varenicline 21.9%
	Bupropion SR 29.5%	Bupropion SR 20.7%	Bupropion SR 16.1%
	Placebo 17.7%	Placebo 10.5%	Placebo 8.4%
Tonstad et al[37]*	Varenicline 49.6%		Varenicline 43.6%
	Placebo 36.9%		Placebo 36.9%
Tsai et al[38]	Varenicline 32.3%	Varenicline 46.8%	
	Placebo 70.5%	Placebo 21.8%	
Aubin et al[40]	Varenicline 55.9%	Varenicline 32.4%	Varenicline 26.1%
	NRT 43.2%	NRT 27.3%	NRT 20.3%

CAR = continuous abstinence rate; SR = sustained release; NRT = nicotine replacement therapy.
*Primary end point = CAR weeks 13–24; secondary end point = CAR weeks 13–52.

comparing bupropion SR with placebo at the end of the study was not statistically significant. During weeks 1 through 7, subjects in the varenicline group reported significantly less urge to smoke ($P < 0.001$) and had significantly fewer AEs ($P = 0.001$) than those in the placebo group, as assessed using the MNWS. Bupropion SR was associated with comparable relief from the urge to smoke and tolerability profile (compared with placebo) but was associated with significantly increased ratings of insomnia ($P < 0.001$). In the varenicline, bupropion SR, and placebo groups, 10.5%, 12.6%, and 7.3%, respectively, of participants discontinued the treatment due to AEs. Overall study completion rates at week 52 were 70% in the varenicline group, 65% in the bupropion SR group, and 60% in the placebo group. At week 52, only those who met all criteria were classified as abstinent (Tables II and III).

A 52-week multicenter trial was conducted to determine whether subjects who quit smoking after 12 weeks of treatment with varenicline maintained greater abstinence rates than placebo controls during an additional 12 weeks of treatment and until 52 weeks after treatment initiation.[37] During the first 12 weeks of open-label treatment, subjects were given varenicline 1 mg BID (n = 1927; male, 48.8%; white, 96.2%; mean [SD] age, 44.2 [10.7] years). Then the patients who had successfully abstained from smoking and other uses of tobacco and NRT for at least the last 7 days of the treatment period were randomly assigned to receive either varenicline 1 mg BID (n = 603; male, 50.2%; white, 96.7%; mean [SD] age, 45.4 [10.4] years) or placebo (n = 607; male, 48.3%; white, 97.0%; mean [SD] age, 45.3 [10.4] years) and continued into a 12-week, double-blind treatment phase. Thereafter, the subjects continued into a nontreatment follow-up phase for an additional 28 weeks (for a total of 52 weeks in the study). The primary efficacy end point was CO-confirmed CAR from weeks 13 through 24. The secondary efficacy end points were the CAR from weeks 13 through 52. The MNWS was used to assess the experience of craving and withdrawal after the end of treatment with varenicline. During the last week (week 12) of treatment, 64.1% of the subjects who had been cigarette smokers were abstinent from smoking, other uses of tobacco, or use of NRT. The CAR for weeks 13 through 24 was significantly higher for subjects randomized to varenicline than to placebo (70.5% vs 49.6%; $P < 0.001$). The CAR for weeks 13 through 52 was also significantly higher for the varenicline group than for the placebo group (43.6% vs 36.9%; $P = 0.02$). The 7-day point prevalence of abstinence at week 24 ($P < 0.001$) and at week 52 ($P = 0.01$) was significantly higher for subjects who received varenicline than for those who received placebo. The median time to the first lapse/smoke (postrandomization to double-blind treatment) was significantly longer for subjects receiving varenicline than for those receiving placebo (198 vs 87 days, respectively; log-rank $P < 0.001$). During the open-label phase, 11.9% experienced AEs that led to treatment discontinuation. During the double-blind treatment phase, the incidence of AEs was similar for the varenicline and placebo groups (46% and 45%, respectively). In this randomized clinical trial, smokers who successfully quit after taking open-label varenicline for an initial 12 weeks experienced a significantly reduced relapse rate when taking an additional 12 weeks of varenicline 1 mg BID compared with placebo (Tables II and III).

The results of 2 randomized, double-blind, placebo-controlled trials conducted in an Asian population were consistent with the results observed in the Phase III trials. In a randomized, double-blind, placebo-controlled trial in Korea and Taiwan with a 12-week treatment period and a 12-week follow-up period, subjects were administered varenicline 1 mg BID (titrated during the first week) (n = 126; male, 84.9%; mean age, 39.7 years) and placebo (n = 124; male, 92.7%; mean age, 40.9 years). The smoking cessation rates were significantly higher in the varenicline group than in the placebo group at the end of treatment (59.5% vs 32.3%; P < 0.001). Posttreatment CAR (weeks 9–24) was significantly greater in the varenicline group than the placebo group (46.8% vs 21.8%; P < 0.001). The 7-day PPA was 67.5% with varenicline versus 36.3% with placebo at week 12 and 57.1% versus 29.0% with placebo at week 24 (both, P < 0.001).[38] Nakamura et al[39] conducted a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in which the subjects (n = 515; male, 74.8%; mean age range, 39.0–40.2 years) were randomized to receive varenicline 0.25 mg BID, 0.5 mg BID, 1.0 mg BID, or placebo for 12 weeks followed by a 40-week nontreatment follow-up phase. The CAR achieved with varenicline 1 mg BID was 65.4% (highest among all doses) compared with 39.5% with placebo (P < 0.001). The CAR for weeks 9 through 52 was significantly greater for varenicline 1 mg BID than placebo (34.6% vs 23.3%; P = 0.036). The CARs for weeks 9 through 24 of treatment with varenicline 0.25, 0.5, and 1.0 mg BID were 33.6%, 35.2%, and 37.7%, respectively, while the CARs for weeks 9 through 52 at 0.25 and 0.5 mg BID were 27.3% and 28.9% but failed to reach significance versus placebo (29.5% for weeks 9–24 and 23.3% for weeks 9–52) (Tables II and III).

Varenicline was compared to transdermal NRT in a Phase III, randomized, open-label, multicenter trial.[40] Participants were aged 18 to 75 years and smoked at least 15 cigarettes per day with a period of abstinence <3 months in the previous year. Participants were randomly allocated to receive either titrated varenicline 1 mg BID (n = 376; male, 48.4%; white, 92.6%; mean [SD] age, 42.9 [10.5] years) for 12 weeks or NRT transdermal patches (n = 370; male, 50.0%; white, 93.5%; mean [SD] age, 42.9 [12.0] years) for 10 weeks. The primary end point was CO-confirmed CAR during the last 4 weeks of treatment (varenicline, weeks 9–12; NRT, weeks 8–11). Secondary efficacy end points included CO-confirmed CAR for the last 4 weeks of treatment for weeks 24 through 52. The CAR for the last 4 weeks of treatment was significantly greater for varenicline than for NRT (55.9% vs 43.2%; P < 0.001). The CARs for weeks 24 through 52 were not significantly higher for varenicline than NRT. For weeks 1 through 7, the scores on the urge-to-smoke scale were significantly lower with varenicline than with NRT (P < 0.001). With varenicline, participants reported significantly lower smoking satisfaction (P < 0.001), psychological reward (P = 0.001), and craving reduction (P < 0.001) (Tables II and III).

VARENICLINE SAFETY PROFILE AND TOLERABILITY

The safety profile of varenicline was reported in 6 clinical trials.[4,36–40] Gonzales et al[36] reported study drug discontinuations due to AEs were 8.6% for varenicline, 15.2% for bupropion SR, and 9.0% for placebo. Nausea, the most common AE with vareni-

cline (28.1%), was mostly mild to moderate, diminished over time, and resulted in few treatment discontinuations (2.6%). Insomnia was the most common AE with bupropion SR (21.9%). Jorenby et al[4] reported that nausea was the most common AE with varenicline (29.4%). Other common symptoms in the varenicline group were insomnia (14.3%) and abnormal dreams (13.1%). Insomnia was the most common AE associated with bupropion SR (21.2%), followed by headache (7.9%) and dry mouth (7.6%). Tonstad et al[37] reported that the AEs that contributed most frequently to treatment discontinuation were nausea (3.2%), headache (1.0%), insomnia (0.9%), depression (0.8%), and fatigue (0.6%). Vomiting was reported in 2.9% of subjects. Tsai et al[38] reported that nausea (varenicline 43.7% and placebo 11.3%), insomnia (15.1% and 13.7%, respectively), increased appetite (7.9% and 6.5%), constipation (7.1% and 6.5%), anxiety (5.6% and 2.4%), and abnormal dreams (5.6% and 0.8%) were the most common AEs. Nakamura et al[39] reported that the most prevalent AEs with varenicline 1 mg BID were nasopharyngitis (35.9%), nausea (24.4%), and headache (10.3%). Nausea was dose related (7.2% at 0.25 mg BID, 9.7% at 0.5 mg BID, and 24.4% at 1 mg BID) versus placebo (7.8%). Aubin et al[40] reported that the most frequent AEs in both treatment groups were nausea (varenicline group 37.2%, NRT group 9.7%), insomnia (21.3% and 19.2%, respectively), headache (19.1% and 9.7%), and abnormal dreams (11.7% and 8.4%).

The most commonly reported AEs were gastrointestinal disorders (nausea [usually mild to moderate and transient], vomiting, flatulence, constipation, dyspepsia, and abdominal pain), psychiatric disorders (insomnia, abnormal dreams, and irritability), headache, nasopharyngitis, and fatigue.[4,36,40] Postmarketing surveillance raised further tolerability issues. The US Food and Drug Administration (FDA) issued a public health advisory reporting an association between varenicline and an increased risk of behavioral change, agitation, depressed mood, and suicidal ideation and behavior.[44] The safety profile review of varenicline by the FDA is ongoing.

Use in Pregnant Women

In preclinical trials, oral administration of varenicline succinate 30 mg/kg · d^{-1} to pregnant rabbits was associated with reduced fetal weight; this reduction was not evident at 10 mg/kg · d^{-1}. In an experimental rat study, varenicline succinate 15 mg/kg · d^{-1} orally was associated with decreased fertility and increased auditory startle response in the offspring.[8] There are no adequate, well-controlled studies in pregnant women, so varenicline cannot be recommended for smoking cessation during pregnancy.[45]

DISCUSSION

With its unique mechanism of action, varenicline may be an asset in the smoking cessation armamentarium. In Phase III trials,[4,36] the CARs for weeks 9 through 52 were significantly higher with varenicline than with placebo. All the clinical trials reviewed for this study reported significantly better results with varenicline than with placebo with regard to the MNWS, QSU-brief, and mCEQ scales. Varenicline was also more efficacious than bupropion SR through 24 weeks. Extended use of varenicline helps recent ex-smokers maintain their abstinence and prevents relapse.[37] How-

ever, the results of certain trials[4,36] have also raised several issues. In the Phase III trials, generally healthy smokers were included, which may not represent the smokers who are most likely to seek treatment.[36] Patients with serious medical illness or current or recent depression were excluded from the trial.[4] It is not clear whether varenicline can help maintain abstinence beyond 52 weeks, especially since it had a relatively small margin of improvement over placebo (43.6% vs 36.9% abstinent at 52 weeks).[37] The trials involved more intensive in-person and telephone counseling than could be done in the community and in general practice.

The studies did not address the effects of varenicline on smokers with a history of bupropion use. Some smokers might have taken bupropion for smoking cessation or for treatment of depression; therefore, the results might be different in the broader population. The CAR at week 52 for those assigned to receive bupropion SR was somewhat lower[36] than that reported in prior bupropion SR studies reporting 52-week CAR (CAR from week 4 through 7 was 46% and at 12 months was 21%).[8,46] It is important to note the 43.6% CAR achieved at week 52 in the study by Tonstad et al[37] reflected only participants who were abstinent for ≥1 week at the end of the first 12 weeks of treatment. There was a significant difference in validated CAR rates at the end of treatment and a smaller but still significant difference 6 months later.[37] The 12-week point prevalence rate of abstinence was unusually high (64.1%) and surpassed the rates of ~50% that were observed in the other 2 smoking cessation studies of 12 weeks of treatment with varenicline versus bupropion or placebo.[4,36] This difference might be due to the open-label design of the first phase of this study compared with the double-blind design of the other studies. As of the writing of this manuscript, there were no data regarding the efficacy of the combination of varenicline and NRT. In addition, postmarketing surveillance is needed to detect any rare but serious complications. While awaiting the answers to these questions, a prudent course would be to view varenicline as a valuable addition to the pharmacotherapy available to help individuals who smoke achieve smoking cessation. Varenicline might prove to be particularly appropriate for those in whom other treatments have failed. Appropriate use of varenicline may decrease the incidence of smoking, which is the leading preventable risk to human health. Community-based trials of varenicline are needed to test its efficacy and safety in individuals who smoke with varying comorbidities and risk patterns.

CONCLUSIONS

Varenicline is the first smoking cessation treatment that was associated with a significant long-term relapse prevention effect (up to 52 weeks). Varenicline, with its unique profile of agonist and antagonist properties, increased smoking cessation rates (both short and long term) compared with both placebo and bupropion SR.

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