

Varenicline

A Review of its Use as an Aid to Smoking Cessation Therapy

Gillian M. Keating and M. Asif A. Siddiqui

Wolters Kluwer Health | Adis, Auckland, New Zealand, an editorial office of Wolters Kluwer Health, Conshohocken, Pennsylvania, USA

Various sections of the manuscript reviewed by:

W.C. Bailey, University of Alabama at Birmingham Lung Health Center, Birmingham, Alabama, USA; *J. Foulds*, Tobacco Dependence Program, School of Public Health, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey, USA; *P. Hajek*, Barts and The London, Queen Mary's School of Medicine and Dentistry, London, England; *D.E. Jorenby*, Center for Tobacco Research and Intervention, University of Wisconsin Medical School, Madison, Wisconsin, USA; *A. McEwen*, Cancer Research UK Health Behaviour Unit, Department of Epidemiology and Public Health, University College London, London, England; *M.L. Muramoto*, University of Arizona College of Medicine, Program for Nicotine and Tobacco Research, Tucson, Arizona, USA; *M.B. Steinberg*, Tobacco Dependence Program, School of Public Health, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey, USA; *S. Tonstad*, Department of Preventive Cardiology, Ullevål University Hospital and University of Oslo, Oslo, Norway.

Data Selection

Sources: Medical literature published in any language since 1980 on 'varenicline', identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE and AdisBase search term was 'varenicline'. EMBASE search terms were 'varenicline' or 'CP-526555'. Searches were last updated 2 Oct 2006.

Selection: Studies of varenicline in smoking cessation. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Varenicline, smoking cessation, pharmacodynamics, pharmacokinetics, therapeutic use, tolerability.

Contents

Summary	946
1. Introduction	947
2. Pharmacological Properties	948
2.1 Mechanism of Action	948
2.2 Pharmacokinetic Profile	948
2.2.1 Special Populations	949
2.2.2 Potential Drugs Interactions	949
3. Therapeutic Efficacy	949
3.1 Phase II Dose-Finding Trials	949
3.2 Phase III Trials	951
3.2.1 Comparisons with Bupropion Sustained-Release	951
3.2.2 Maintenance of Abstinence Trial	953
4. Tolerability	955

5. Dosage and Administration	956
6. Place of Varenicline as an Aid to Smoking Cessation Therapy	956

Summary

Abstract

Varenicline is an orally administered $\alpha 4\beta 2$ nicotinic acetylcholine (ACh) receptor partial agonist. It has been approved by the US FDA (Chantix™) and the European Commission (Champix®) for use as an aid to smoking cessation therapy.

Varenicline is an effective and generally well tolerated treatment for use in smokers who want to quit. In two well designed, phase III trials, 12 weeks' treatment with varenicline was associated with significantly higher continuous abstinence rates at weeks 9–12 than placebo or bupropion sustained-release (SR). In the longer term, continuous abstinence rates for weeks 9 through 52 demonstrated that the odds of remaining abstinent were 2.7 to 3.1 times higher with 12 weeks of varenicline treatment than with placebo; the significant difference between varenicline and bupropion SR was also maintained in the longer term in one trial. Moreover, varenicline appeared to attenuate the urge to smoke, negative affect withdrawal symptoms and the reinforcing effects of smoking. Among those achieving abstinence, an additional 12 weeks of varenicline therapy helped increase the likelihood of long-term abstinence. Thus, varenicline is a valuable new agent for use as an aid to smoking cessation treatment.

Pharmacological Properties

Varenicline has high affinity for $\alpha 4\beta 2$ nicotinic ACh receptors. It demonstrated partial agonist activity, while also antagonising the nicotine response, in both *in vitro* and *in vivo* studies.

Varenicline is almost completely absorbed following oral administration, with high systemic availability. Steady state was reached within 4 days following repeat administration of the drug. Varenicline undergoes minimal metabolism and is primarily excreted renally as unchanged drug, with an elimination half-life of approximately 24 hours. The area under the plasma concentration-time curve for varenicline is increased in patients with moderate or severe renal impairment or end-stage renal disease.

Therapeutic Efficacy

The efficacy of 12 weeks' therapy with oral varenicline 1mg twice daily as an aid to smoking cessation was compared with that of bupropion SR 150mg twice daily and placebo in two randomised, double-blind, multicentre, phase III trials. The carbon monoxide (CO)-confirmed continuous abstinence rates during weeks 9–12 (primary endpoint) and weeks 9–24 were significantly higher in varenicline recipients than in bupropion SR or placebo recipients in both trials. In the longer-term, CO-confirmed continuous abstinence rates for weeks 9 through 52 demonstrated that the odds of remaining abstinent were 2.7 to 3.1 times higher with 12 weeks of varenicline treatment than with placebo. A significant difference favouring varenicline over bupropion SR was seen at this timepoint in one trial, but not in the other trial.

Varenicline ameliorated the urge to smoke and the reinforcing effects of smoking to a significantly greater extent than placebo, although its effect on withdrawal symptoms was less consistent. However, in both trials, varenicline

reduced negative affect withdrawal symptoms to a significantly greater extent than placebo.

In a phase III maintenance of abstinence trial, smokers received open-label varenicline 1mg twice daily for 12 weeks; abstinent participants were then randomised in a double-blind fashion to receive varenicline 1mg twice daily or placebo for an additional 12 weeks. An additional 12 weeks of varenicline was significantly more effective than placebo in maintaining abstinence. The CO-confirmed continuous abstinence rate was significantly higher in varenicline than in placebo recipients for weeks 13–24 (primary endpoint) and weeks 13–52.

Tolerability

Twelve weeks' therapy with varenicline 1mg twice daily was generally well tolerated in the two phase III trials comparing varenicline with bupropion SR and placebo. The most commonly reported adverse events (occurring in more varenicline than placebo recipients) included nausea and abnormal dreams. Among participants who achieved abstinence, mean bodyweight gain between baseline and week 12 (across studies) was 2.37–2.89kg in varenicline recipients, 1.88–2.12kg in bupropion SR recipients and 2.92–3.15kg in placebo recipients. Discontinuation of treatment because of adverse events occurred in 8.6–10.5%, 12.6–15.2% and 7.3–9.0% of participants in the corresponding treatment groups.

1. Introduction

There are over 1.25 billion smokers worldwide.^[1] Smoking is associated with several types of cancer (e.g. lung and bladder cancer), bronchitis, emphysema, cardiovascular disease and increased antenatal and perinatal mortality, and is the leading preventable cause of premature death in developed countries.^[1] Indeed, it is estimated that globally, 4.8 million premature deaths were attributable to smoking in 2000, with 2.4 million deaths occurring in developing countries and 2.4 million deaths occurring in industrialised countries.^[2]

Nicotine, the key addictive component in tobacco, interacts with nicotinic acetylcholine (ACh) receptors.^[3,4] Each receptor comprises five subunits; 17 different types of subunit (α_1 – α_{10} , β_1 – β_4 , γ , δ and ϵ) have been identified to date.^[4,5] Although there are many subtypes of nicotinic ACh receptor, $\alpha_4\beta_2$, $\alpha_3\beta_4$ and α_7 nicotinic ACh receptors predominate in the CNS.^[5]

The dependence-producing effect of nicotine is attributable in part to its agonist activity at the $\alpha_4\beta_2$ nicotinic ACh receptor.^[6–8] Dopamine release in the

nucleus accumbens is increased when nicotine activates this receptor.^[7,9] When a person stops smoking, the absence of nicotine leads to low dopamine levels, which are associated with craving, a key contributor to relapse.^[10,11]

Theoretically, a partial agonist at $\alpha_4\beta_2$ nicotinic ACh receptors would mimic the action of nicotine and increase dopamine levels to some extent, and relieve withdrawal associated with smoking cessation.^[5,12,13] Moreover, competitive binding of a partial agonist to $\alpha_4\beta_2$ nicotinic ACh receptors would prevent nicotine-induced dopaminergic activation in the event that the person smokes, meaning that smoking would not produce reinforcing effects.^[4,5,12,13]

Varenicline (Chantix™, Champix®)¹ is an orally administered $\alpha_4\beta_2$ nicotinic ACh receptor partial agonist^[5] and is the first agent in this class to be approved for use in smoking cessation. This article reviews the pharmacological properties of varenicline, as well as its clinical efficacy and tolerability as an aid to smoking cessation treatment.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

2. Pharmacological Properties

2.1 Mechanism of Action

Varenicline (figure 1) had high affinity and selectivity for $\alpha 4\beta 2$ nicotinic ACh receptors in an equilibrium binding assay.^[5] Varenicline had an equilibrium binding affinity (K_i) for rat $\alpha 4\beta 2$ nicotinic ACh receptors of 0.06 nmol/L, with much lower affinity for other nicotinic ACh receptor subtypes (K_i values for $\alpha 3\beta 4$, $\alpha 1\beta \gamma \delta$ and $\alpha 7$ nicotinic ACh receptors of 240, 3540 and 322 nmol/L, respectively).^[5] Thus, varenicline had 4000-, $\approx 60\,000$ - and >5000 -fold greater affinity for $\alpha 4\beta 2$ nicotinic ACh receptors than for $\alpha 3\beta 4$, $\alpha 1\beta \gamma \delta$ and $\alpha 7$ nicotinic ACh receptors. Moreover, varenicline had negligible affinity for non-nicotinic targets.^[5]

A functional electrophysiological assay demonstrated the partial agonist activity of varenicline at $\alpha 4\beta 2$ nicotinic ACh receptors, as well as its antagonism of the nicotine response.^[5] In this assay, in which human $\alpha 4\beta 2$ nicotinic ACh receptors were expressed in *Xenopus* oocytes, varenicline 10 $\mu\text{mol/L}$ was shown to have 68% of the agonist activity of nicotine 10 $\mu\text{mol/L}$.^[5] In addition, varenicline 10 $\mu\text{mol/L}$ exhibited antagonist activity, inhibiting the efficacy of nicotine 10 $\mu\text{mol/L}$ by 34%. Analysis of the full concentration-response curve showed that the concentration of varenicline producing a half-maximal response (EC_{50}) was 2.3 $\mu\text{mol/L}$ and that, relative to nicotine, varenicline had a maximal efficacy of 24%.^[5]

Varenicline also demonstrated partial agonist activity, whilst antagonising the nicotine response, in rats.^[5] In terms of its effect on dopamine turnover in the nucleus accumbens, subcutaneous varenicline 5.6 mg/kg alone had 32% of the effect of subcutaneous nicotine 1 mg/kg, 1 hour post-dose ($p < 0.05$ vs

nicotine alone). In addition, when administered concomitantly, varenicline significantly inhibited the nicotine response by 66% ($p < 0.01$ vs nicotine alone). In microdialysis studies of dopamine release in rat nucleus accumbens, oral varenicline 1 mg/kg had approximately 60% of the maximal nicotine effect on dopamine levels over 6 hours, and reduced the dopamine-enhancing effect of subcutaneous nicotine 0.32 mg/kg to that of varenicline alone.

The functional selectivity of varenicline for $\alpha 4\beta 2$ nicotinic ACh receptors was recently studied in an electrophysiological assay using rat neuronal nicotinic receptors expressed in *Xenopus* oocytes.^[14] Varenicline exhibited an EC_{50} of 2.3 $\mu\text{mol/L}$ for $\alpha 4\beta 2$ receptors, 55 $\mu\text{mol/L}$ for $\alpha 3\beta 4$ receptors and 18 $\mu\text{mol/L}$ for $\alpha 7$ receptors. Thus, the potency of varenicline at $\alpha 3\beta 4$ and $\alpha 7$ receptors was 24- and 8-fold lower than at $\alpha 4\beta 2$ receptors. The difference in selectivity seen between this study^[14] and the earlier study^[5] probably reflects the assays used, in that the equilibrium binding assay used in the earlier study^[5] mainly reflects the affinity of varenicline for the desensitised state of the receptor.^[14]

Relative to the maximum ACh response, varenicline had 13.4% of the efficacy of ACh at $\alpha 4\beta 2$ receptors, 75% at $\alpha 3\beta 4$ receptors, 3.7% at $\alpha 3\beta 2$ receptors, 8.8% at $\alpha 6/\alpha 3\beta 2\beta 3$ receptors and 93% at $\alpha 7$ receptors.^[14] This suggests that as well as being a potent partial agonist at $\alpha 4\beta 2$ receptors, varenicline was a weak partial agonist at $\alpha 3\beta 2$ and $\alpha 6$ -containing receptors, was functionally a full agonist at $\alpha 7$ receptors and had lower potency and greater efficacy at $\alpha 3\beta 4$ receptors than at $\alpha 4\beta 2$ receptors. Whether the activity of varenicline at receptors other than $\alpha 4\beta 2$ contributes to its efficacy as a smoking cessation therapy remains to be determined.

2.2 Pharmacokinetic Profile

Varenicline is almost completely absorbed following oral administration, with high systemic availability.^[15] Following administration of a single dose of varenicline 1mg to healthy adult smokers or nonsmokers, the mean maximum plasma concentration of varenicline was 4.8 and 6.2 ng/mL, reached in a mean 3 hours.^[16] The mean area under the



Fig. 1. Structural formula of varenicline.

plasma concentration-time curve (AUC) from time zero to infinity was 140 ng • h/mL in smokers and 102 ng • h/mL in nonsmokers.^[16]

Varenicline exhibited approximately linear pharmacokinetics with single- or multiple-dose administration over the recommended dosage range.^[15,16] Steady state was reached within 4 days following repeat administration of varenicline.^[15]

The oral bioavailability of varenicline is not affected by food or by the time of day at which it is administered.^[16] The plasma protein binding of varenicline is $\leq 20\%$.^[15]

Varenicline undergoes minimal metabolism, with 92% of the dose excreted as unchanged drug in urine.^[15,17] Small amounts are excreted as the metabolites varenicline *N*-carbamoyl glucuronide and 2-hydroxyvarenicline.^[17] Varenicline did not inhibit the cytochrome P450 (CYP) isozymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5, according to the results of *in vitro* studies.^[15] In addition, varenicline did not induce CYP3A4 and CYP1A2 *in vitro*.^[15]

Following a single dose of radiolabelled varenicline 1mg, 87.1% of the radioactivity was recovered in the urine and 0.9% in the faeces.^[17] *In vitro* studies indicate that the human organic cation transporter OCT2 mediates the active renal secretion of varenicline.^[15]

Varenicline has an elimination half-life of approximately 24 hours.^[15] Following administration of a single dose of varenicline 1mg, its terminal elimination half-life was 20.2 hours in smokers and 13.6 hours in nonsmokers.

2.2.1 Special Populations

Compared with younger smokers, the pharmacokinetics of varenicline were not altered to a clinically significant extent in healthy elderly smokers (mean age 69.4 years) who received varenicline 1mg twice daily for 7 days.^[18] In addition, race and gender did not have a clinically significant effect on the pharmacokinetics of the drug.^[15]

Although the pharmacokinetics of varenicline were not altered in patients with mild renal impairment (creatinine clearance [CLCR] 3.1–4.8 L/h [51–80 mL/min]), 1.5-, 2.1- and 2.7-fold increases

in varenicline AUC occurred when the drug was administered to patients with moderate (CLCR 1.8–3.0 L/h [30–50 mL/min]) or severe (CLCR <1.8 L/h [<30 mL/min]) renal impairment or end-stage renal disease requiring haemodialysis, compared with healthy volunteers.^[15] Thus, varenicline should be used with caution in patients with renal impairment.^[15]

2.2.2 Potential Drugs Interactions

Varenicline did not alter the pharmacokinetics of the smoking cessation therapies bupropion or transdermal nicotine, according to the results of multiple-dose studies.^[15]

In addition, varenicline did not alter the pharmacokinetics of digoxin,^[19] warfarin^[19] or metformin.^[15] Moreover, metformin did not alter the pharmacokinetics of varenicline.^[15] When the OCT2 inhibitor cimetidine (300mg four times daily) was co-administered with a single dose of varenicline 2mg, the systemic exposure of varenicline increased 29%.^[15]

3. Therapeutic Efficacy

3.1 Phase II Dose-Finding Trials

The optimal dosage of oral varenicline for aiding smoking cessation was ascertained in two randomised, double-blind, multicentre, phase II studies.^[20,21]

In one trial, participants (n = 638) were randomised to receive varenicline 0.3mg once daily, 1mg once daily or 1mg twice daily for 6 weeks (followed by placebo for 1 week), bupropion sustained-release (SR) 150mg twice daily for 7 weeks or placebo for 7 weeks.^[20] In the other trial, participants (n = 647) were randomised to receive varenicline 0.5 or 1mg twice daily or placebo for 12 weeks.^[21] Varenicline recipients either received the target dosage from day 1, or were titrated to the target dosage over 1 week.^[21] In both trials, the scheduled quit date was on day 8 of treatment.^[20,21] Following the end of treatment, 75.6%^[20] and 87.5%^[21] of participants entered a non-drug treatment phase, which continued up to week 52. All

Table I. Efficacy of oral varenicline (VAR) in smoking cessation. Results of randomised, double-blind, multicentre, phase II, dose-finding trials in smokers

Study	Treatment (mg) [duration; wk]	No. of participants	CO-confirmed continuous quit rate (% of participants)					
			wk 4–7	wk 4–12	wk 4–24	wk 4–52	wk 9–12	wk 9–52
Nides et al. ^[20]	VAR 0.3 od [6] ^a	126	25.4*	16.7	9.5	7.9		
	VAR 1 od [6] ^a	126	31.0**	15.1	9.5	5.6		
	VAR 1 bid [6] ^a	125	40.8***	28.8**	20.8**	14.4**		
	BUP SR 150 bid [7]	126	28.6**	19.8*	10.3	6.3		
	PL [7]	123	13.8	10.6	7.3	4.9		
Oncken et al. ^[21]	VAR 0.5 bid ^b [12]	259	36.3****				44.0****	18.5****
	VAR 1 bid ^b [12]	259	39.8****				49.4****	22.4****
	PL [12]	129	10.9 ^c				11.6 ^c	3.9 ^c

a Participants received PL in week 7.

b Participants received VAR at the target dosage from day 1 or titrated to the target dosage over 1wk. Results for titrated and non-titrated treatment groups were pooled.

c Primary endpoint.

bid = twice daily; **BUP SR** = bupropion sustained-release; **CO** = carbon monoxide; **od** = once daily; **PL** = placebo; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$ vs PL.

participants received counselling during the studies.^[20,21]

Participants had a mean age of 40.5–43.7 years and had smoked for a mean 23.4–26.0 years; the mean number of cigarettes smoked per day ranged from 18.9 to 21.5.^[20,21] Over 89% of participants had made at least one prior quit attempt.^[20,21] Participants who had received nicotine replacement therapy in the previous 3 months^[20,21] or bupropion in the previous 3 months^[21] or 1 year^[20] were excluded.

Primary endpoints were the 4-week continuous quit rate (defined as complete abstinence for any consecutive 28-day period, as assessed by a daily smoking diary)^[20] and the carbon monoxide (CO)-confirmed continuous quit rate for weeks 4–7, 9–12 and 9–52 (defined as no reported smoking and an exhaled CO level of ≤ 10 ppm).^[21] Secondary endpoints in the former trial were the CO-confirmed continuous quit rates during weeks 4–7, 4–12, 4–24 and 4–52.^[20]

These trials established that the optimal varenicline dosage for promoting smoking cessation was 1mg twice daily.^[20,21]

In the 7-week trial, the 4-week continuous quit rate increased as the dosage of varenicline increased.^[20] Indeed, the 4-week continuous quit rate was significantly higher with varenicline 1mg once daily or 1mg twice daily than with placebo (37.3%

and 48.0% vs 17.1%; both $p < 0.001$). The 4-week continuous quit rate was also significantly higher with bupropion SR (33.3%) than with placebo ($p = 0.002$), although there was no significant difference between recipients of varenicline 0.3mg once daily (28.6%) and placebo recipients.

The CO-confirmed 4-week continuous quit rate during weeks 4–7 was significantly higher with varenicline or bupropion SR than with placebo (table I).^[20] Moreover, the CO-confirmed continuous quit rate remained significantly higher with varenicline 1mg twice daily than with placebo at weeks 4–12, 4–24 and 4–52 (table I). Bupropion SR was associated with a significantly higher CO-confirmed continuous quit rate than placebo at weeks 4–12 (table I); the lack of significant difference between bupropion SR and placebo recipients at subsequent timepoints may reflect the fact that this trial only excluded smokers with relatively recent prior exposure to bupropion (i.e. some participants may have received prior bupropion).^[20]

In the second trial, the CO-confirmed continuous quit rates were significantly higher with varenicline 0.5 or 1mg twice daily than with placebo for weeks 4–7, 9–12 and 9–52 (table I).^[21] For weeks 4–7, odds ratios (ORs) for quitting were 5.0 (95% CI 2.7, 9.2) for varenicline 0.5 mg twice daily versus placebo and 5.9 (95% CI 3.2, 10.9) for varenicline 1mg

twice daily versus placebo. Corresponding ORs for weeks 9–12 were 6.3 (95% CI 3.5, 11.5) and 8.1 (95% CI 4.4, 14.7).

3.2 Phase III Trials

Three well designed phase III trials have examined the effect of oral varenicline 1mg twice daily on smoking cessation.^[22-24] In these trials, the CO-confirmed continuous abstinence rate was defined as the proportion of participants with no reported smoking or use of tobacco or nicotine-containing products, verified by exhaled CO levels of ≤ 10 ppm, over 4 weeks or over a longer period of time as specified. The 7-day point prevalence abstinence rate was defined as the proportion of participants who were abstinent for the preceding 7 days, confirmed by CO measurements.

3.2.1 Comparisons with Bupropion Sustained-Release

Two randomised, double-blind, multicentre trials of identical design ($n = 1025$ ^[22] and 1027 ^[23]) compared varenicline with bupropion SR or placebo. In both trials, participants received varenicline 1mg twice daily, bupropion SR 150mg twice daily or placebo for 12 weeks. Participants randomised to varenicline received varenicline 0.5mg once daily on days 1–3, 0.5mg twice daily on days 4–7 and

1mg twice daily thereafter. Bupropion SR recipients received 150mg once daily on days 1–3, then 150mg twice daily thereafter. The active treatment period was followed by a blinded 40-week follow-up period. The scheduled quit date was on day 8 of treatment and all participants received counselling as recommended by the US Public Health Service guidelines for smoking cessation^[25] during the 52-week study period. Brief (≤ 10 -minute) counselling was provided at weekly clinic visits during the initial 12-week treatment period and at clinic visits at weeks 13, 24, 36, 44 and 52. Telephone visits were conducted 3 days following the quit date and at weeks 16, 20, 28, 32, 40 and 48.^[22,23]

Participants were motivated to quit smoking, had a mean age of 42.0–44.6 years and had smoked for a mean duration of 24.1–27.1 years.^[22,23] In the month prior to starting treatment, participants had smoked a mean 21.0–22.5 cigarettes per day.^[22,23] The majority of participants ($>75\%$) in both studies were White.^[22,23] Over 80% of participants in the study conducted by Gonzales et al.^[22] had made at least one prior quit attempt. Participants with prior exposure to bupropion SR or varenicline were excluded from the studies.^[22,23] Also excluded were participants with certain concomitant disorders, including major depressive disorder requiring treatment in the

Table II. Efficacy of oral varenicline (VAR) in smoking cessation. Results of pivotal phase III trials in smokers

Study [design details]	Treatment (mg) [duration; wk]	No. of participants	CO-confirmed continuous abstinence rate (% of participants)				
			wk 9–12 ^a	wk 9–24	wk 9–52	wk 13–24 ^a	wk 13–52
Comparisons with BUP SR							
Gonzales et al. ^[22]	VAR 1 bid [12]	352	44.0***††	29.5***†	21.9***		
[r, db, mc]	BUP SR 150 bid [12]	329	29.5***	20.7***	16.1***		
	PL [12]	344	17.7	10.5	8.4		
Jorenby et al. ^[23]	VAR 1 bid [12]	344	43.9***††	29.7***†	23.0***†		
[r, db, mc]	BUP SR 150 bid [12]	342	29.8***	20.2**	14.6		
	PL [12]	341	17.6	13.2	10.3		
Maintenance of abstinence trial							
Tonstad et al. ^[24]	VAR 1 bid [24]	603				70.5***	43.6*
[ol→r, db] ^b	VAR 1 bid [12] → PL [12]	607				49.6	36.9

a Primary endpoint.

b The 12wk double-blind phase of this multicentre trial was preceded by an open-label 12wk period during which all participants ($n = 1927$) received VAR 1mg bid. Only participants who were abstinent entered the double-blind phase of the trial.

bid = twice daily; **BUP SR** = bupropion sustained-release; **CO** = carbon monoxide; **db** = double-blind; **mc** = multicentre; **ol** = open-label; **PL** = placebo; **r** = randomised; * $p < 0.05$, ** $p = 0.01$, *** $p \leq 0.001$ vs PL; † $p < 0.01$, †† $p < 0.001$ vs BUP SR.

previous 12 months, panic disorder, psychosis or bipolar disorder.^[22,23]

The primary efficacy endpoint was the CO-confirmed 4-week continuous abstinence rate for weeks 9–12.^[22,23] Secondary efficacy endpoints included the continuous abstinence rates for weeks 9–24 and 9–52, and 7-day point prevalence abstinence rates. The effect of varenicline on craving, withdrawal and the reinforcing effects of smoking was also assessed in these trials.^[22,23] Craving and withdrawal were assessed using the 9-item Minnesota Nicotine Withdrawal Scale (MNWS) and the 10-item Brief Questionnaire of Smoking Urges (QSU-Brief). Reinforcing effects were evaluated using the 12-item modified Cigarette Evaluation Questionnaire (mCEQ), which was completed by all participants at baseline and during the first week of treatment, and by those who had smoked between weeks 1 and 7.

Intent-to-treat analyses were conducted in these studies.^[22,23] The study completion rates at week 52 were 60.5%^[22] and 70%^[23] for varenicline, 56%^[22] and 65%^[23] for bupropion SR, and 54%^[22] and 60%^[23] for placebo.

Effect on Abstinence Rates

Varenicline recipients achieved significantly higher CO-confirmed continuous abstinence rates during the last 4 weeks of treatment (i.e. weeks 9–12) than bupropion SR or placebo recipients in both trials (table II).^[22,23] ORs were 1.9 (95% CI 1.4, 2.7) [$p < 0.001$]^[22] and 1.9 (95% CI 1.4, 2.6) [$p < 0.001$]^[23] for varenicline versus bupropion SR, and 3.9 (95% CI 2.7, 5.5) [$p < 0.001$]^[22] and 3.9 (95% CI 2.7, 5.5) [$p < 0.001$]^[23] for varenicline versus placebo. Bupropion SR was also superior to placebo (table II), with ORs of 2.0 (95% CI 1.4, 2.9) [$p < 0.001$]^[22] and 2.0 (95% CI 1.4, 2.9) [$p = 0.001$].^[23]

In addition, the CO-confirmed continuous abstinence rate between weeks 9 and 24 was significantly higher with varenicline than with bupropion SR (OR 1.6; 95% CI 1.1, 2.3; $p = 0.007$ ^[22] and OR 1.7; 95% CI 1.2, 2.4; $p = 0.003$ ^[23]) or placebo (OR 3.7; 95% CI 2.4, 5.6; $p < 0.001$ ^[22] and OR 2.8; 95% CI 1.9, 4.2; $p < 0.001$ ^[23]) in both trials (table II).

Between weeks 9 and 52, the CO-confirmed continuous abstinence rate was significantly higher with varenicline than with bupropion SR in the study conducted by Jorenby et al.^[23] (OR 1.8; 95% CI 1.2, 2.6; $p = 0.004$), but not in the study conducted by Gonzales et al.^[22] (OR 1.5; 95% CI 1.0, 2.2; $p = 0.057$) [table II]. Varenicline was superior to placebo in both trials (OR 3.1; 95% CI 2.0, 4.9; $p < 0.001$ ^[22] and OR 2.7; 95% CI 1.7, 4.1; $p < 0.001$ ^[23]) [table II].

In both trials, significantly higher 7-day point prevalence abstinence rates were achieved with varenicline than with bupropion SR or placebo at week 12 (50.3% vs 35.9% and 21.2%; both $p < 0.001$ ^[22] and 50.3% vs 36.3% and 20.8%; both $p < 0.001$ ^[23]) and week 24 (33.5% vs 24.9% and

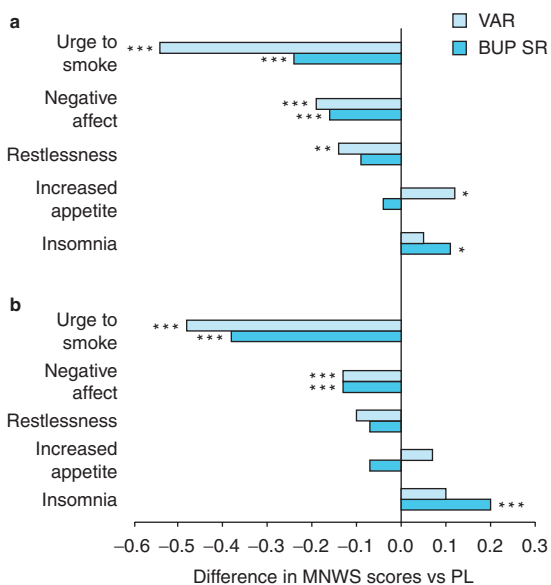


Fig. 2. Effect of oral varenicline (VAR) on craving and withdrawal symptoms during smoking cessation. In two double-blind, multicentre trials (study 1^[22] [a] and study 2^[23] [b]), participants were randomised to receive VAR 1mg bid, bupropion sustained-release (BUP SR) 150mg bid or placebo (PL) for 12wk. Minnesota Nicotine Withdrawal Scale (MNWS) scores were averaged over weeks 1–7; shown are the differences between VAR and PL and between BUP SR and PL. Each item on the 9-item MNWS is scored from 0 (not at all) to 4 (extreme) [negative affect and insomnia are composites of more than one item]. The number of evaluable participants in study 1^[22] was 340–341 for VAR, 317–318 for BUP SR and 336–337 for PL, and in study 2^[23] was 331 for VAR and 327–328 for BUP SR (not specified for PL). **bid** = twice daily; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs PL.

14.5%; $p = 0.01$ and $p < 0.001$ ^[22] and 35.2% vs 26.3% and 17.9%; $p = 0.009$ and $p < 0.001$ ^[23]). At week 52, the 7-day point prevalence abstinence rate was significantly higher with varenicline than with placebo (28.1% vs 14%; $p < 0.001$ ^[22] and 30.5% vs 17.3%; $p < 0.001$ ^[23]); 7-day point prevalence abstinence rates with bupropion SR were 22.8% (not significant vs varenicline)^[22] and 23.4% ($p = 0.05$ vs varenicline).^[23] Bupropion SR was superior ($p < 0.05$) to placebo at all timepoints in the study by Jorenby et al.^[23] (not specified in Gonzales et al.^[22]).

Effects on Craving, Withdrawal and the Reinforcing Effects of Smoking

Varenicline ameliorated the urge to smoke to a significantly greater extent than placebo, although its effect on withdrawal symptoms was less consistent.^[22,23]

In terms of craving, the difference between varenicline or bupropion SR recipients and placebo recipients in the mean MNWS urge to smoke score significantly favoured the active treatments in both trials (figure 2).^[22,23] In addition, the QSU-Brief total craving score significantly favoured varenicline and bupropion SR versus placebo in both trials (figure 3).^[22,23] Similarly, scores for QSU-Brief Factor 1 (assessing pleasure) and QSU-Brief Factor 2 (assessing relief of negative affect) significantly favoured varenicline and bupropion SR versus placebo in the study by Jorenby et al.^[23] (figure 3).

In terms of withdrawal symptoms, the MNWS negative affect score significantly favoured varenicline and bupropion SR recipients, compared with placebo recipients, in both trials (figure 2).^[22,23] Only varenicline recipients in the study by Gonzales et al.^[22] had a significantly lower MNWS restlessness score than placebo recipients (figure 2). With regard to the MNWS insomnia score, there was no significant difference between varenicline and placebo recipients in either study; however, in both studies, bupropion SR recipients had significantly higher MNWS insomnia scores than placebo recipients (figure 2). A significantly higher MNWS score for increased appetite was seen with varenicline

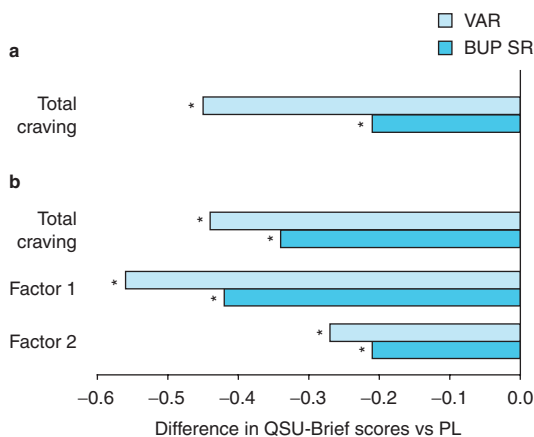


Fig. 3. Effect of oral varenicline (VAR) on craving symptoms during smoking cessation. In two double-blind, multicentre trials (study 1^[22] [a] and study 2^[23] [b]), participants were randomised to receive VAR 1mg bid, bupropion sustained-release (BUP SR) 150mg bid or placebo (PL) for 12wk. Brief Questionnaire of Smoking Urges (QSU-Brief) scores were averaged over weeks 1–7; shown are the differences between VAR and PL and between BUP SR and PL. Each item on the 10-item QSU-Brief is scored from 1 (strongly disagree) to 7 (strongly agree). The total craving score is the sum of all 10 items. Factor 1 is the sum of five items assessing pleasure and factor 2 is the sum of three items assessing negative affect relief. The number of evaluable participants in study 1^[22] was 341 for VAR, 318 for BUP SR and 337 for PL, and in study 2^[23] was 330 for VAR and 328 for BUP SR (not specified for PL). **bid** = twice daily; * $p \leq 0.001$ vs PL.

versus placebo recipients in the study by Gonzales et al.^[22] (figure 2).

Varenicline reduced the reinforcing effects of smoking to a significantly greater extent than placebo.^[22,23] In both trials, mCEQ scores for smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving reduction significantly favoured varenicline versus placebo (figure 4).^[22,23] There was no significant difference between varenicline and placebo recipients in the aversion score. Significant differences between bupropion SR and placebo recipients were seen for smoking satisfaction in the study by Jorenby et al.^[23] and in both trials for psychological reward^[22,23] (figure 4).

3.2.2 Maintenance of Abstinence Trial

The effect of an additional 12 weeks' treatment with varenicline was examined in a maintenance of abstinence trial.^[24] This multicentre study included

1927 smokers who received open-label varenicline for 12 weeks (varenicline was titrated to the target dosage of 1mg twice daily as described in the other phase III trials^[22,23] [see section 3.2.1]). It was recommended that participants take varenicline for 1 week before attempting to quit smoking. 1210 participants who had abstained from smoking and not used tobacco or nicotine replacement therapy for at least the last 7 days of the open-label period and who had a CO level of ≤ 10 ppm were then randomised in a double-blind manner to receive varenicline 1mg twice daily or placebo for an additional 12 weeks. Participants were then followed up for a further 28 weeks (during which blinding was maintained). Participants received brief (≤ 10 -minute) counselling sessions throughout the trial; clinic visits occurred at baseline, weekly through weeks 1–8 and at weeks 10, 12, 13, 14, 16, 20, 24, 25, 28, 36, 44 and 52, with phone visits at weeks 26, 32, 40 and 48.

Trial participants had a mean age of approximately 45 years and had smoked for a mean duration of approximately 28 years; participants had smoked a mean of approximately 21 cigarettes per day in the month prior to treatment.^[24] Over 80% of trial participants had made at least one serious prior attempt to quit smoking and over 95% of participants were White. Participants were excluded from the study if they had received a smoking cessation aid (e.g. nicotine replacement therapy, bupropion, clonidine or nortriptyline) in the previous month or if they had certain concomitant disorders, including depression requiring treatment in the previous 12 months, panic disorder, psychosis or bipolar disorder.^[24]

The primary endpoint was the CO-confirmed continuous abstinence rate for weeks 13–24.^[24] The key secondary endpoint was the continuous abstinence rate for weeks 13–52. Additional efficacy endpoints included the 7-day point prevalence abstinence rate and the time to first lapse.

An additional 12 weeks of varenicline was significantly more effective than placebo in maintaining abstinence.^[24] The CO-confirmed continuous abstinence rate was significantly higher in varenicline than in placebo recipients for weeks 13–24 (table II), with an OR of 2.48 (95% CI 1.95, 3.16) [$p < 0.001$].

Similarly, the CO-confirmed continuous abstinence rate was significantly higher with varenicline than with placebo for weeks 13–52 (table II), with an OR of 1.34 (95% CI 1.06, 1.69) [$p = 0.02$].

The 7-day point prevalence abstinence rate was significantly higher in varenicline recipients than in placebo recipients at week 24 (OR 2.82; 95% CI 2.18, 3.64; $p < 0.001$) and week 52 (OR 1.33; 95% CI 1.06, 1.67; $p = 0.01$).^[24] During the double-blind phase of the trial, the median time to first lapse was

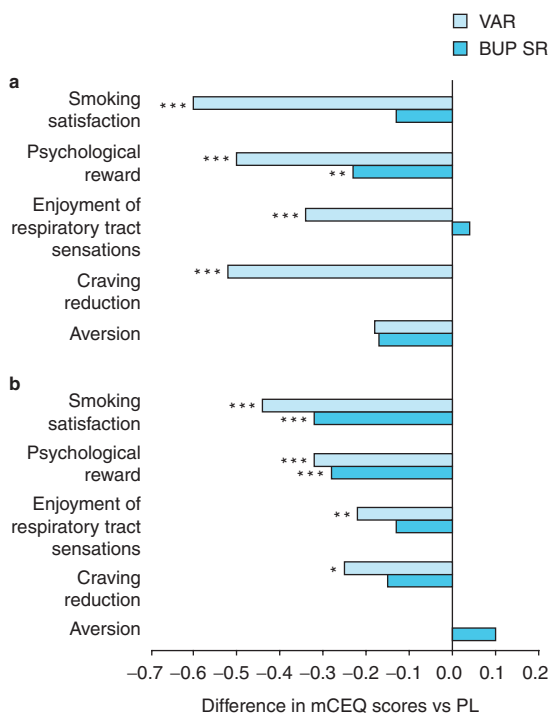


Fig. 4. Effect of oral varenicline (VAR) on reinforcing effects during smoking cessation. In two double-blind, multicentre trials (study 1^[22] [a] and study 2^[23] [b]), participants were randomised to receive VAR 1mg bid, bupropion sustained-release (BUP SR) 150mg bid or placebo (PL) for 12wk. The modified Cigarette Evaluation Questionnaire (mCEQ) was completed by all participants at baseline and during the first week of treatment and by those who had smoked from weeks 1 to 7, and scores were averaged over weeks 1–7. Shown are the differences between VAR and PL and between BUP SR and PL. Each item on the 12-item mCEQ is scored from 1 (not at all) to 7 (extremely) [the depicted symptoms are generally composites of more than one item]. The number of evaluable participants was 296–298 for VAR, 288–290 for BUP SR and 319 for PL in study 1,^[22] and 298–300 for VAR and 302–304 for BUP SR in study 2^[23] (not specified for PL). **bid** = twice daily; * $p < 0.05$, ** $p \leq 0.01$, *** $p < 0.001$ vs PL.

significantly longer with varenicline than with placebo (198 vs 87 days; $p < 0.001$).

4. Tolerability

Tolerability data were obtained from one of the dose-finding trials^[21] and the three phase III trials^[22-24] discussed in section 3. Only descriptive analyses were reported in most of these trials.^[22-24]

The dose-finding trial^[21] revealed that the incidence of nausea was 34.9% in varenicline recipients in whom the drug was titrated to the target dosage of 1mg twice daily over 1 week, compared with 41.9% in varenicline recipients who started treatment at the target dosage. The finding that titration apparently reduced the incidence of nausea formed the basis for the 1-week titration period used in subsequent trials.

Varenicline was generally well tolerated in the two phase III trials comparing varenicline with bupropion SR.^[22,23] Discontinuation of treatment because of adverse events occurred in 8.6%^[22] and 10.5%^[23] of varenicline 1mg twice daily recipients, in 15.2%^[22] and 12.6%^[23] of bupropion SR 150mg twice daily recipients and in 9.0%^[22] and 7.3%^[23] of placebo recipients.

Nausea was the most commonly occurring treatment-emergent adverse event in varenicline recipients (figure 5); however, it was of mild to moderate severity in the majority of participants^[22,23] and diminished over time.^[22] Discontinuation of treatment because of nausea occurred in 2.6% of varenicline recipients, 1.8% of bupropion SR recipients and 0.3% of placebo recipients.^[22] Other adverse events reported in varenicline recipients are shown in figure 5.^[22,23] The most commonly reported adverse event in recipients of bupropion SR was insomnia.^[22,23]

In each trial, two serious adverse events were attributed to study drug treatment: an episode of atrial fibrillation in a varenicline recipient and a grand mal seizure in a bupropion SR recipient in the study by Gonzales et al.;^[22] and worsening vertigo, elevated blood pressure and chest pain in a varenicline recipient and angioedema in a bupropion SR recipient in the study by Jorenby et al.^[23] No deaths occurred during active treatment in either trial.^[22,23]

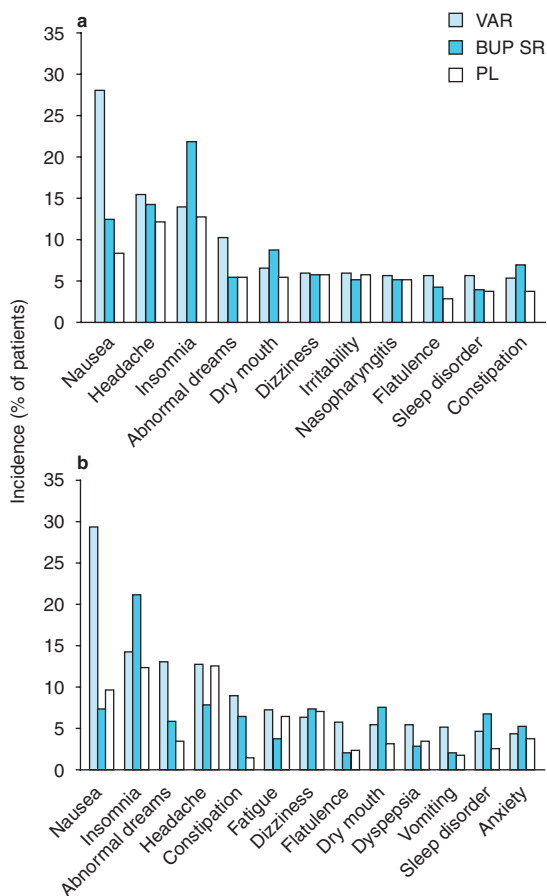


Fig. 5. Tolerability of oral varenicline (VAR) in smoking cessation. Incidence of treatment-emergent adverse events in two randomised, double-blind, multicentre studies in which participants received VAR 1mg bid, bupropion sustained-release (BUP SR) 150mg bid or placebo (PL) for 12wk.^[22,23] Study 1^[22] (a) included 349 VAR recipients, 329 BUP SR recipients and 344 PL recipients and study 2^[23] (b) included 343 VAR recipients, 340 BUP SR recipients and 340 PL recipients. In study 1,^[22] reported adverse events occurred in $\geq 5\%$ of VAR recipients and in more VAR than PL recipients, and in study 2,^[23] reported adverse events occurred in $\geq 5\%$ of VAR or BUP SR recipients compared with PL recipients. **bid** = twice daily.

The tolerability profile of varenicline in the phase III maintenance of abstinence trial^[24] was similar to that seen in the other phase III trials.^[22,23] During open-label treatment with varenicline, the most commonly reported adverse events included nausea (33.5% of participants), insomnia (19.6%) and headache (15.8%); discontinuation of treatment because of adverse events occurred in 11.9% of participants.

During the double-blind phase of the trial, nasopharyngitis occurred in 4.8% of varenicline recipients versus 5.3% of placebo recipients, headache in 2.8% versus 2.0%, irritability in 2.7% versus 4.5%, insomnia in 2.7% versus 2.8%, fatigue in 1.5% versus 1.8%, dyspepsia in 1.5% versus 1.0%, and nausea in 1.2% versus 0.7%. Discontinuation of treatment because of adverse events occurred in 1.7% of varenicline recipients and 1.3% of placebo recipients. Three trial participants died, although none of the deaths were considered to be related to treatment.

Two of the phase III trials examined bodyweight change among participants who were abstinent during weeks 9–12.^[22,23] Between baseline and week 12, varenicline recipients gained a mean 2.37^[22] and 2.89kg,^[23] bupropion SR recipients gained a mean 2.12^[22] and 1.88kg^[23] and placebo recipients gained a mean 2.92^[22] and 3.15kg.^[23]

No clinically significant differences were seen between varenicline and placebo recipients in terms of vital signs, ECG recordings or laboratory parameters in the dose-finding trial.^[21]

5. Dosage and Administration

Oral varenicline has been approved by the US FDA and the European Commission for use as an aid to smoking cessation therapy.^[15,26]

In the US, the recommended varenicline dosage is 1mg twice daily.^[15] Treatment should start 1 week before the person's scheduled quit date. Varenicline should be titrated to the target dosage over a 1-week period, with varenicline 0.5mg once daily administered on days 1–3 and 0.5mg twice daily administered on days 4–7; treatment with 1mg twice daily should start on day 8. Varenicline should be taken after eating. The recommended duration of treatment is 12 weeks; those who have successfully quit smoking at the end of 12 weeks may receive varenicline for an additional 12 weeks to further increase the likelihood of maintaining long-term abstinence.^[15]

Local prescribing information should be consulted for precautions and dosage recommendations in special populations.

6. Place of Varenicline as an Aid to Smoking Cessation Therapy

Quitting smoking is associated with major health benefits.^[27] However, the majority of people who initially stop smoking following a quit attempt will resume smoking and many will require several quit attempts before achieving long-term cessation.^[28] Treatment increases the likelihood of a smoker achieving long-term abstinence.^[28]

Smoking cessation treatment involves both non-pharmacological and pharmacological approaches; indeed, quit rates are optimised when smoking cessation programmes integrate both these components.^[4,25] Helping the smoker establish a quit plan and providing practical counselling and support are important elements of treatment.^[25] In terms of pharmacological therapy, agents approved to aid smoking cessation in the US include varenicline, bupropion SR and nicotine replacement therapy (i.e. nicotine gum, inhalers, lozenges, nasal spray and patches). US Public Health Service guidelines for smoking cessation recommend the use of pharmacological therapy in all smokers who are trying to quit, except in special circumstances (special consideration is needed in adolescent smokers and pregnant or breastfeeding women, for example).^[25] The guidelines were issued prior to the availability of varenicline and recommend nicotine replacement therapy and bupropion SR as first-line treatments.^[25] Clonidine and nortriptyline are recommended as second-line therapies, although neither of these agents is approved in the US for use in smoking cessation.^[25]

Nicotine replacement therapy reduces the severity of nicotine craving and withdrawal symptoms.^[4] It has been shown to approximately double long-term abstinence rates compared with placebo (table III).^[29] The adverse event profile differs depending on the route of nicotine administration (table III).^[25]

The antidepressant bupropion SR is a non-nicotine treatment for smoking cessation; its mechanism of action in smoking cessation is not completely understood, although is presumably mediated by noradrenergic and/or dopaminergic mechanisms.^[32] It has also been suggested that bupropion may act as a noncompetitive antagonist at the nicotinic recep-

Table III. Features of pharmacological smoking cessation therapies^[4,25,27,29-31]

Drug	Mechanism of action	Long-term abstinence rate ^a		OR (95% CI) for long-term abstinence rate vs placebo ^b	Most commonly reported adverse events
		active drug	placebo		
Varenicline	$\alpha 4\beta 2$ Nicotinic acetylcholine receptor partial agonist; also blocks the action of nicotine	21.9 ^[22] and 23.0 ^[23]	8.4 ^[22] and 10.3 ^[23]	3.1 (2.0, 4.9) ^[22] and 2.7 (1.7, 4.1) ^[23]	Nausea, abnormal dreams
Bupropion SR	Probably mediated by noradrenergic and/or dopaminergic mechanisms; may also act as a noncompetitive antagonist at the nicotinic receptor	20.0	10.2	2.1 (1.8, 2.4)	Insomnia, dry mouth
Nicotine replacement therapy	Reduces the severity of nicotine craving and withdrawal symptoms	19.5	11.5	1.7 (1.5, 1.8)	Sore mouth, dyspepsia, hiccups, jaw ache
gum					
inhaler					
lozenge/tablet					
nasal spray					
patch	14.6	8.6	1.8 (1.6, 2.0)	Local skin reactions, insomnia	
Clonidine	α -Noradrenergic agonist; suppresses sympathetic activity	24.9	14.4	1.9 (1.3, 2.7)	Dry mouth, drowsiness, dizziness, sedation, constipation
Nortriptyline	Tricyclic antidepressant; noradrenergic activity and some dopaminergic activity	17.2	7.0	2.8 (1.7, 4.6)	Sedation, dry mouth, blurred vision, urinary retention, lightheadedness, shaky hands

a Abstinence rate at 9–52wk for varenicline (results of two pivotal clinical trials).^[22,23] Trial participants were followed for ≥ 12 wk after the end of treatment for clonidine^[30] and for ≥ 6 mo for other agents^[29,31] (results of meta-analyses).

b Result obtained with monotherapy.

OR = odds ratio; SR = sustained release.

tor.^[3,4] Bupropion SR approximately doubles long-term abstinence rates compared with placebo (table III).^[31] The most commonly reported adverse events in bupropion SR recipients include insomnia and dry mouth.^[32]

The main features of clonidine and nortriptyline are also summarised in table III.^[29,30]

Varenicline is the first in a new class of agents, the $\alpha 4\beta 2$ nicotinic ACh receptor partial agonists. Thus, it provides clinicians and smokers with an entirely new pharmacological option.^[33] In preclinical studies, the partial agonist activity of varenicline resulted in moderate stimulation of dopamine (section 2.1), which theoretically may reduce symptoms of craving and withdrawal. Varenicline also blocked

the nicotine response (section 2.1), which theoretically may blunt the reinforcing effects of smoking. Varenicline was also shown to be a full agonist at $\alpha 7$ nicotinic ACh receptors (section 2.1); whether this activity contributes to the efficacy of the drug remains to be seen, although it has been suggested that $\alpha 7$ nicotinic ACh receptors play a role in nicotine addiction.^[4]

Well designed phase III trials indicate that 12 weeks' therapy with varenicline is associated with 9- to 12-week continuous abstinence rates that are significantly higher than those achieved with bupropion SR or placebo (section 3.2). Moreover, the odds of achieving longer-term abstinence (weeks 9–52) were 2.7 to 3.1 times higher with varenicline

than with placebo, as well as being significantly higher with varenicline than with bupropion SR in one trial (section 3.2). It should be noted that these phase III trials did not include smokers with prior bupropion use, although the phase II trials only excluded those with relatively recent use of bupropion (section 3.1). The maintenance of abstinence trial demonstrated that varenicline had a relapse prevention effect. In this trial, varenicline recipients who successfully quit smoking were significantly more likely to maintain abstinence if they received an additional 12 weeks of treatment (section 3.2). It should be noted that the long-term abstinence rates achieved in this study may be higher than those achieved in the 'real world' setting, given that participants who did not quit in the open-label phase of the study were eliminated from the subsequent double-blind phase.^[33]

Varenicline appeared to attenuate both the urge to smoke and the reinforcing effects of smoking (section 3.2). Effects on withdrawal symptoms were less consistent, with significantly lower scores seen in varenicline recipients for some withdrawal symptoms (e.g. negative affect, restlessness in one study) but not others (insomnia, increased appetite) [section 3.2].

Varenicline was generally well tolerated in these trials; the most commonly reported adverse event was mild to moderate nausea (section 4), which tended to resolve over time. The observation in one of the dose-finding trials^[21] that gradually titrating varenicline to a dosage of 1mg twice daily was associated with a numerically lower incidence of nausea than starting treatment at this dosage led to the recommendation that the drug be titrated to the target dosage over the period of 1 week (section 4).

Most smokers who quit will experience weight gain.^[25] Both nicotine replacement therapy (especially nicotine gum) and bupropion SR appear to delay weight gain after smokers have quit, although weight gain occurs when the treatment is stopped.^[25] Clinical trial participants who were abstinent and receiving 12 weeks' therapy with varenicline gained a mean 2.4 and 2.9kg, compared with approximately 3kg in abstinent placebo recipients and approxi-

mately 2kg in abstinent bupropion SR recipients (section 4). These results suggest that the weight gain is a consequence of quitting smoking, rather than being linked to varenicline per se.

Guidelines suggest that combination therapy may improve long-term abstinence rates.^[25] Trial data are limited, although it does appear that combining different nicotine replacement therapies^[4] and using nicotine replacement therapy in combination with bupropion SR^[3,4] improves abstinence rates. No clinically relevant pharmacokinetic interactions were observed when varenicline was co-administered with bupropion SR or transdermal nicotine (section 2.2.2). However, in a small study (n = 39), discontinuation because of adverse events occurred in 36% of participants receiving combination therapy with varenicline and transdermal nicotine, compared with 6% of participants receiving transdermal nicotine alone, suggesting that combination therapy was less well tolerated.^[15] Thus, it would be useful to have more data on the tolerability of combination therapy with varenicline and other smoking cessation treatments, before examining the efficacy of such treatment. It may be that the mechanism of action of varenicline (i.e. its antagonism of the nicotine response) means that combination therapy with nicotine replacement therapy would yield no additional benefit.

Smoking cessation treatment is generally acknowledged to be a cost-effective intervention.^[25,34] There are currently no pharmacoeconomic data specifically pertaining to the use of varenicline as an aid to smoking cessation treatment. It would also be of interest to examine the use of varenicline in special populations (such as pregnant smokers, smokers with concomitant psychiatric disorders and populations of greater ethnic diversity) and its longer-term use in smokers.

In conclusion, the $\alpha\beta 2$ nicotinic ACh receptor partial agonist varenicline is an effective and generally well tolerated treatment for use in smokers who want to quit. In two well designed, phase III trials, 12 weeks' treatment with varenicline was associated with significantly higher continuous abstinence rates at weeks 9–12 than placebo or bupropion SR.

In the longer term (weeks 9–52), the odds of remaining abstinent were 2.7 to 3.1 times higher with varenicline than with placebo; the significant difference between varenicline and bupropion SR was also maintained in the longer term in one trial. Moreover, varenicline appeared to attenuate the urge to smoke, negative affect withdrawal symptoms and the reinforcing effects of smoking. Among those achieving abstinence, an additional 12 weeks of varenicline therapy helped prevent relapse by increasing the likelihood of long-term abstinence. Thus, varenicline is a valuable new agent for use as an aid to smoking cessation treatment.

Disclosure

During the peer review process, the manufacturer of the agent under review was offered an opportunity to comment on this article; changes based on any comments received were made on the basis of scientific and editorial merit.

References

- Taylor AL, Bettcher DW. WHO framework convention on tobacco control: a global "good" for public health. *Bull World Health Organ* 2000 Jul; 78 (7): 920-9
- Ezzati M, Lopez AD. Estimates of global mortality attributable to smoking in 2000. *Lancet* 2003 Sep 13; 362: 847-52
- Frishman WH, Mittle W, Kupersmith A, et al. Nicotine and non-nicotine smoking cessation pharmacotherapies. *Cardiol Rev* 2006 Mar/Apr; 14 (2): 57-73
- Foulds J, Steinberg MB, Williams JM, et al. Developments in pharmacotherapy for tobacco dependence: past, present and future. *Drug Alcohol Rev* 2006 Jan; 25 (1): 59-71
- Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an $\alpha 4\beta 2$ nicotinic receptor partial agonist for smoking cessation. *J Med Chem* 2005 May 19; 48 (10): 3474-7
- Tapner AR, McKinney SL, Nashmi R, et al. Nicotine activation of $\alpha 4^*$ receptors: sufficient for reward, tolerance, and sensitization. *Science* 2004 Nov 5; 306: 1029-32
- Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacol Biochem Behav* 2001; 70: 439-46
- Maskos U, Molles BE, Pons S, et al. Nicotine reinforcement and cognition restored by targeted expression of nicotinic receptors. *Nature* 2005 Jul 7; 436 (7): 103-7
- Di Chiara G. Role of dopamine in the behavioural actions of nicotine related to addiction. *Eur J Pharmacol* 2000; 393: 295-314
- Malin DH. Nicotine dependence: studies with a laboratory model. *Pharmacol Biochem Behav* 2001; 70 (551-559)
- Hughes JR, Higgins ST, Bickel WK. Nicotine withdrawal versus other drug withdrawal syndromes: similarities and dissimilarities. *Addiction* 1994; 89: 1461-70
- Coe JW, Vetelino MG, Bashore CG, et al. In pursuit of $\alpha 4\beta 2$ nicotinic receptor partial agonists for smoking cessation: carbon analogs of (-)-cytisine. *Bioorg Med Chem Lett* 2005 Jun 15; 15 (12): 2974-9
- Coe JW, Brooks PR, Wirtz MC, et al. 3,5-Bicyclic aryl piperidines: a novel class of potent $\alpha 4\beta 2$ selective neuronal nicotinic acetylcholine receptor partial agonists for smoking cessation. *Bioorg Med Chem Lett* 2005 Nov 15; 15 (22): 4889-97
- Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at $\alpha 4\beta 2$ and a full agonist at $\alpha 7$ neuronal nicotinic receptors. *Mol Pharmacol* 2006 Sep; 70 (3): 801-5
- Pfizer Inc. Chantix™ (varenicline) tablets: prescribing information [online]. Available from URL: <http://www.chantix.com> [Accessed 2006 Jun 28]
- Faessel HM, Smith BJ, Gibbs MA, et al. Single-dose pharmacokinetics of varenicline, a selective nicotinic receptor partial agonist, in healthy smokers and nonsmokers. *J Clin Pharmacol* 2006 Sep; 46 (9): 991-8
- Obach RS, Reed-Hagen AE, Krueger SS, et al. Metabolism and disposition of varenicline, a selective $\alpha 4\beta 2$ acetylcholine receptor partial agonist, in vivo and in vitro. *Drug Metab Dispos* 2006 Jan; 34 (1): 121-30
- Burstein A, Fullerton T, Clark D, et al. Safety, tolerability, and multiple-dose pharmacokinetics of varenicline in elderly smokers [abstract]. 11th Annual Meeting and 7th European Conference of the Society for Research on Nicotine and Tobacco; 2005 Mar 16-20; Prague
- Faessel H, Burstein A, O'Gorman M, et al. Safety, tolerability, and pharmacokinetic evaluation of concomitant administration of varenicline and digoxin or warfarin [abstract]. 11th Annual Meeting and 7th European Conference of the Society for Research on Nicotine and Tobacco; 2005 Mar 16-20; Prague
- Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective $\alpha 4\beta 2$ nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med* 2006 Aug 14/28; 166: 1561-8
- Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med* 2006 Aug 14/28; 166: 1571-7
- Gonzales D, Rennard SI, Nides M, et al. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296 (1): 47-55
- Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296 (1): 56-63
- Tonstad S, Tønnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA* 2006 Jul 5; 296 (1): 64-71
- Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence: clinical practice guideline. Rockville (MD): US Department of Health and Human Services, Public Health Service, 2000 Jun
- Pfizer Inc. Pfizer's anti-smoking pill Champix® approved in Europe [media release]. Available from URL: <http://mediaroom.pfizer.com> [Accessed 2006 Oct 3]
- Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract* 2006 May; 60 (5): 571-6
- Henningfield JE, Fant RV, Buchhalter AR, et al. Pharmacotherapy for nicotine dependence. *CA Cancer J Clin* 2005 Sep/Oct; 55 (5): 281-99

29. Silagy C, Lancaster T, Stead L, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2004; 3: CD000146
30. Gourlay SG, Stead LF, Benowitz NL. Clonidine for smoking cessation. *Cochrane Database Syst Rev* 2004; 3: CD000058
31. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2004; 4: CD000031
32. GlaxoSmithKline. Zyban® (bupropion hydrochloride) sustained-release tablets: prescribing information [online]. Available from URL: <http://us.gsk.com> [Accessed 2006 Jul 3]
33. Kleges RC, Johnson KC, Somes G. Varenicline for smoking cessation: definite promise, but no panacea. *JAMA* 2006 Jul 5; 296 (1): 94-5
34. Cromwell J, Bartosch WJ, Fiore MC, et al. Cost-effectiveness of the clinical practice recommendations in the AHCPR guideline for smoking cessation. *JAMA* 1997 Dec 3; 278 (21): 1759-66

Correspondence: Gillian M. Keating, Wolters Kluwer Health | Adis, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz