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Varenicline

A Novel Pharmacotherapy for Smoking Cessation

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Abstract

Varenicline is an orally administered small molecule with partial agonist activity at the $\alpha 4\beta 2$ nicotinic acetylcholine receptor. Varenicline was approved by both the US FDA and the European Medicines Agency of the EU

in 2006 as an aid to smoking cessation. Subsequently, varenicline has been approved in over 80 other countries.

Varenicline is almost entirely absorbed following oral administration, and absorption is unaffected by food, smoking or the time of day. Varenicline undergoes only minimal metabolism and approximately 90% of the drug is excreted in the urine unchanged. Varenicline has a mean elimination half-life after repeated administration of approximately 24 hours in smokers. The area under the plasma concentration-time curve is increased in patients with moderate or severe renal failure. No clinically relevant varenicline-drug interactions have been identified.

In two identical, randomized, double-blind, phase III clinical trials in healthy, motivated-to-quit, mainly Caucasian smokers aged 18–75 years in the US, 12 weeks of treatment with varenicline 1 mg twice daily was associated with significantly higher abstinence rates over weeks 9–12 than sustained-release bupropion 150 mg twice daily or placebo. In a separate phase III trial, an additional 12 weeks of treatment in smokers achieving abstinence in the first 12 weeks was associated with greater abstinence through to week 52 than placebo treatment. Varenicline treatment was also associated with significantly higher rates of abstinence than placebo treatment in randomized, double-blind, clinical trials in smokers in China, Japan, Korea, Singapore, Taiwan and Thailand. In a randomized, open-label, multi-national, phase III trial, varenicline treatment was associated with a significantly higher rate of abstinence than transdermal nicotine-replacement therapy. In these trials, varenicline treatment was associated with lower urge to smoke and satisfaction from smoking in relapsers than placebo or active comparators.

In the two US phase III trials, 12 weeks of treatment with varenicline 1 mg twice daily had an acceptable safety and tolerability profile. Nausea and abnormal dreams were the most common adverse events that occurred in more varenicline than placebo recipients. The incidence and prevalence of nausea were greatest in weeks 1 and 2 of treatment, and declined thereafter. The prevalence of early adverse effects can be reduced by individual dose titration. Adverse events associated with varenicline therapy have been reported in post-marketing surveillance, including neuropsychiatric events such as depressed mood, agitation, changes in behaviour, suicidal ideation and suicide. Currently, it is unclear whether the association of varenicline therapy with these adverse events is causal, coincidental or related to smoking cessation.

Given the greater efficacy of varenicline compared with other pharmacotherapies, and the high risk of morbidity and mortality associated with continued smoking, varenicline is a valuable pharmacological aid to smoking cessation.

Tobacco smoking remains a major global public health burden, with the estimated 5.4 million attributable deaths in 2005 predicted to increase to over 8 million by 2030.[1] Approximately 50% of smokers eventually die of a smoking-attributable disease;[2] not surprisingly, therefore, smoking cessation is associated with substantial decreases in morbidity and mortality,[2] and is also highly cost effective.[3,4] In addition to counselling and behavioural modification strategies, pharmacotherapy plays an important role in aiding smoking cessation. The odds of achieving abstinence from smoking at least 6 months after the beginning of treatment approximately doubles with nicotine replacement therapy (NRT) [risk ratio {RR} 1.58; 95% CI 1.50, 1.66] or sustained-release

bupropion (bupropion SR) [odds ratio {OR} 1.94; 95% CI 1.72, 2.19].[5,6] Varenicline, a structural derivative of a naturally occurring compound, is the most recently approved pharmacological agent for smoking cessation and approximately triples the odds of achieving continuous abstinence from smoking at 12 months after the beginning of treatment.[7] Varenicline was approved as an aid to smoking cessation treatment in the US (as Chantix®) by the US FDA in May 2006, and in EU countries (as Champix®) by the European Medicines Agency in September 2006. Varenicline has subsequently been approved for marketing in over 80 other countries. This review describes the development, clinical pharmacology, efficacy, safety and tolerability, and use in clinical practice of varenicline.

Electronic literature searches were performed with MEDLINE (via PubMed) using the keyword 'varenicline' . The search was conducted for articles indexed up to, and including, 31 October 2008, and an historical date limit was not employed. The bibliographies of selected papers were reviewed for additional relevant studies. Additionally, one congress presentation and two publications from 2009 on the benefit-risk of the drug were included.

1. Rational Design

Tobacco dependence is primarily driven by addiction to nicotine.[8,9] The addictive effect of nicotine, and other drugs of abuse, is at least partly a result of stimulation of dopaminergic neurons in the mesolimbic pathway (see review by Di Chiara[10]), which connects the ventral tegmental area (VTA) of the midbrain to other brain structures, including the nucleus accumbens and the pre-frontal cortex. Nicotine stimulation of dopamine release results from direct activation of nicotinic acetylcholine receptors (nAChRs) in the VTA[11] involving mainly the $\alpha4\beta2$ subtype,[12,13] which was discovered in the late 1980s.[14] The nAChRs are pentameric members of the superfamily of transmembrane ligand-gated ion channels that mediate synaptic neurotransmission.[15] The $\alpha4\beta2$ subtype is a cation-permeable heteromer located in the peripheral and central nervous systems.

It was hypothesized that a partial agonist with higher affinity than nicotine for the $\alpha4\beta2$ nAChR would, by its partial agonist property, moderately stimulate this receptor and antagonize the effect of nicotine, resulting in reduced craving for tobacco and reduced reward from relapse.[16] At the initiation of the discovery and development programme that produced varenicline, only two natural compounds were known to have partial agonist activity at the $\alpha4\beta2$ receptor; one of these was cytisine, an alkaloid produced by certain species of legume.[16,17] Cytisine has been used as an aid to smoking cessation in Central and Eastern Europe for over 40 years. A meta-analysis of three placebo-controlled trials indicated superior efficacy of cytisine over placebo after 3–8 weeks (pooled OR 1.93; 95% CI 1.21, 3.06), which was maintained at 3- to 6-month follow-up in two trials (pooled OR 1.83; 95% CI 1.12, 2.99) and at 2-year follow-up in one trial (OR 1.77; 95% CI 1.29, 2.43).[18] However, the lack of well controlled clinical trials with this compound[17] precludes its recommended use in the modern era of evidence-based medicine. Benzazapine, a related substructure of cytisine, was used as a template to produce a series of substituted analogues with greater potency against the $\alpha4\beta2$ nAChR, of which varenicline possessed the most desirable pharmacological profile. The FDA approval of varenicline marked two decades from the discovery of the $\alpha4\beta2$ receptor to clinical therapy with a drug targeting this receptor – a not atypical period of time for translating basic biomedical research into a pharmacotherapy ('bench to bed').

2. Mechanism of Action

Varenicline binds the $\alpha4\beta2$ subtype nAChR with subnanomolar affinity and high selectivity.[16] In equilibrium binding assays, equilibrium binding affinity (K_i) values were 0.06 nmol/L, 240 nmol/L, 3540 nmol/L and 322 nmol/L for the rat $\alpha4\beta2$, $\alpha3/\beta4$, $\alpha1\beta\gamma\Omega$ and $\alpha7$ nAChR subtypes, respectively. In addition, the affinity of varenicline for the $\alpha4\beta2$ receptor was approximately 3-fold and 16-fold greater than that of cytisine and nicotine (K_i of 0.06 nmol/L, 0.17 nmol/L and 0.95 nmol/L, respectively). Varenicline has moderate affinity for

the serotonin 5-HT_3 receptor (K_i of 350 nmol/L),[19] but negligible affinity for other non-nicotinic receptors (concentration of varenicline producing 50% inhibition [IC_{50}] >1000 nmol/L).[16]

Varenicline demonstrated partial agonist activity at the human α4β2 receptor in a functional electrophysiological assay in *Xenopus* oocytes.[16] In this assay, varenicline 10 μmol/L had 68% of the agonist activity at the human α4β2 receptor as the same concentration of nicotine. The concentration of varenicline producing a half-maximal response (EC_{50}) values for varenicline and nicotine were 2.3 μmol/L and 15 μmol/L, respectively. In addition, varenicline antagonized nicotine, reducing its effect by 34%. Varenicline also demonstrated both agonist and antagonist activities *in vivo*.[16] In the nucleus accumbens of male Sprague Dawley rats, mesolimbic dopamine turnover elicited by the maximally effective subcutaneous dose of 5.6 mg/kg was 32% of that induced by the maximally effective subcutaneous dose of nicotine (1 mg/kg). At the same dose, varenicline fully blocked the effect of nicotine (increases in dopamine turnover were the same in the presence or absence of nicotine). In addition, at the maximally effective dose of 1 mg/kg, oral varenicline elicited an increase in extracellular dopamine levels in the rat nucleus accumbens that was approximately 60% of the maximal increase induced by nicotine and, furthermore, reduced the dopamine response to nicotine to that elicited by varenicline alone. In a rat behaviour model, pretreatment with varenicline significantly decreased nicotine self-administration by up to 50%.[20]

In a functional electrophysiological assay employing rat nAChRs expressed in *Xenopus* oocytes, EC_{50} values for varenicline were 2.3 μmol/L, 55 μmol/L and 18 μmol/L for the α4β2, α3β4 and α7 receptors, respectively.[21] In addition, compared with acetylcholine, the response to varenicline was 13.4%, 75%, 3.7%, 8.8% and 93% at the α4β2, α3β4, α3β2, α6/α3β2β3 and α7 receptors, respectively, confirming the partial agonist activity of varenicline at the α4β2 receptor and revealing full agonism at the α7 receptor. In *in vitro* functional patch clamp studies in human embryonic kidney (HEK) cells expressing nAChRs, varenicline elicited 45% of the maximal response to nicotine at the α4β2 receptor.[20] In the same study, varenicline had 40–60% of the effect of nicotine in stimulating dopamine release from rat brain slices *in vitro* and increasing dopamine release from rat nucleus accumbens *in vivo*, and reduced the response to nicotine compared with that elicited by varenicline alone.

On the basis of these data, it is hypothesized that varenicline has a dual mechanism of action in aiding smoking cessation: (a) a partial agonist activity at the α4β2 receptor that reduces the smoking cessation-induced drop in mesolimbic dopamine levels, potentially relieving withdrawal symptoms, and consequent to its agonist activity and high affinity; (b) it antagonizes nicotine's activity at the α4β2 receptor and blocks nicotine-induced dopaminergic activation, potentially reducing reward from smoking relapse.[16,20] It is possible that the activity of varenicline at other nAChRs, for example α7, could play a role in aiding smoking cessation.

3. Absorption and Fate

The absorption, distribution, metabolism and excretion of varenicline have been extensively characterized in humans (table I).[19,22-26] The pharmacokinetic parameters of varenicline do not vary in a clinically meaningful manner with race or sex.[19,26]

3.1 Absorption

Varenicline is almost completely absorbed following oral administration and has high systemic availability.[22] The time to maximum plasma concentration (t_{max}) was approximately 3–4 hours following administration of a single oral dose of 1.0 mg or 3.0 mg in non-smokers or smokers (table I).[27] The mean maximum plasma concentration (C_{max}) was similar in non-smokers and smokers administered 1.0 mg (6.2 ng/mL and 4.8 ng/mL, respectively) or 3.0 mg (10.8 ng/mL and 13.8 ng/mL, respectively) [table I]. The mean area under the concentration-time curve (AUC) from time zero to infinity ($AUC_{0-\infty}$) was also similar in non-smokers

Table I. Varenicline pharmacokinetic parameters, mean (standard deviation)

Study	Number of participants	t_{max} (h)	C_{max} (ng/mL)	AUC (ng • h/mL)	$t_{½}$ (h)	CL_r (mL/min)
Single dose (18–45 y)[a]						
Non-smokers						
0.03 mg	4	2.00 (2.68)	0.135 (0.045)	NC	NC	ND
0.1 mg	4	3.13 (3.42)	0.825 (0.105)	12.6 (0.7)[b]	13.3 (2.0)	ND
0.3 mg	4	1.75 (1.50)	1.90 (0.56)	31.4 (9.6)[b]	12.6 (2.2)	ND
1.0 mg	4	3.00 (2.16)	6.20 (1.10)	102 (14)[b]	13.6 (6.1)	ND
1.0 mg, fed[c]	4	2.63 (1.49)	5.70 (0.57)	97.7 (11.7)[b]	11.1 (2.2)	ND
3.0 mg	4	3.13 (2.25)	10.8 (2.1)	223 (83)[b]	20.5 (10.3)	ND
Smokers						
0.03 mg	4	0.750 (0.289)	0.165 (0.037)	NC	NC	ND
0.1 mg	4	1.50 (0.58)	0.468 (0.071)	9.52 (3.60)[b]	14.8 (6.5)	ND
0.3 mg	4	1.63 (1.11)	2.35 (0.93)	37.9 (9.7)[b]	14.4 (2.9)	ND
1.0 mg	1	3.00	4.8	140[b]	20.2	ND
3.0 mg	4	4.00 (2.83)	13.8 (2.5)	299 (51)[b]	16.6 (4.8)	ND
3.0 mg, fed AM[c]	4	3.75 (0.50)	14.5 (0.58)	273 (52)[b]	18.3 (3.4)	ND
3.0 mg, fed PM[d]	4	4.0 (1.6)	8.50 (1.91)	238 (57.5)[b]	21.6 (6.84)	ND
3.0 mg, RS	4	3.00 (0.82)	14.0 (1.4)	288 (55)[b]	16.5 (7.3)	ND
10.0 mg	4	4.25 (2.36)	13.0 (6.2)	303 (168)[b]	19.5 (5.9)	ND
Multiple dose, smokers (18–45 years)[e]						
1 mg, once daily						
day 1	8	4.00 (1.00–8.00)[f]	4.29 (0.32)	74.7 (8.2)[g]	21.8 (2.6)	88 (23)
day 17	7	4.00 (1.00–8.00)[f]	7.93 (0.90)	144 (24)[g]	23.8 (4.9)	92 (34)
2 mg, once daily						
day 1	7	2.00 (2.00–4.00)[f]	8.67 (1.59)	148 (24)[g]	21.4 (3.4)	121 (29)
day 17	6	2.00 (2.00–4.00)[f]	15.1 (1.8)	280 (33)[g]	24.8 (2.9)	109 (16)
3 mg, once daily						
day 1	8	4.00 (2.00–8.00)[f]	10.8 (3.1)	187 (50)[g]	20.9 (4.1)	155 (60)
day 11[h]	8	4.00 (2.00–8.00)[f]	19.8 (3.8)	352 (87)[g]	25.2 (3.8)	143 (56)
1 mg, twice daily						
day 1	7	4.00 (2.00–8.00)[f]	4.08 (0.82)	39.3 (7.3)[g]	NA	101 (51)
day 14	7	2.00[i] (1.00–4.00)[f]	10.2[i] (1.0)	105 (16)[g]	31.5 (7.7)	125 (54)
Multiple dose, smokers (≥65 years)[j]						
1 mg, once daily						
day 1	8	3.00 (2.00–6.00)[f]	3.86 (0.54)	55.2 (9.8)[g]	NA	130 (45)
day 7	8	2.50 (2.00–6.00)[f]	7.03 (1.21)	126 (32)[g]	27.5 (5.9)[k]	92 (27)
1 mg, twice daily						
day 1	8	2.50 (1.00–6.00)[f]	3.32 (0.61)	30.4 (5.6)[g]	NA	126 (40)
day 7	8	2.00 (1.00–3.00)[f]	8.86 (1.79)	88.4 (19.9)[g]	29.2 (7.9)	130 (28)
Chinese smokers, (18–45 years)[l]						
1 mg, single dose	14	3.00 (0.50–6.00)[f]	4.95 (0.69)	91.36 (21.23)[b]	15.23 (3.38)	115.0 (66.7)
1 mg, twice daily	14	2.50 (1.00–6.00)[f]	9.57 (1.54)	214.85 (59.13)[b]	18.34 (3.61)	100.8 (56.7)

a A double-blind, placebo-controlled, dose-escalation study in 102 healthy male or female smokers and non-smokers aged 18–45 years. Volunteers were randomized to receive a single oral dose of varenicline (0.01, 0.03, 0.1, 0.3, 1.0, 3.0 or 10.0 mg) or placebo.[27]

b $AUC_{0-\infty}$.

c Fed US FDA high-fat breakfast.

Continued next page

Table I. Contd

d Fed standard meal.

e A double-blind, placebo-controlled, dose-escalation study in 44 healthy male or female smokers aged 18–45 years. Volunteers were randomly assigned varenicline or placebo 1 mg, 2 mg or 3 mg once daily, or varenicline 1 mg twice daily, or placebo, for 14 days.[24]

f t_{max} reported as median (range).

g AUC_{0-T}.

h The 3-mg dose group was discontinued on study day 11 because of vomiting.

i t_{max}, C_{max} of the first dose administration interval (0–12 hours post-dose) following 1-mg twice-daily dose administration.

j A randomized, double-blind study in 24 healthy male or female smokers aged ≥65 years. Volunteers were randomized to receive oral varenicline 1 mg once or twice daily for 7 days.[24]

k In 7 participants.

l A non-randomized, open-label study in 14 male or female smokers. Volunteers received single doses of varenicline 1 mg on days 1 and 10, and 1 mg twice daily on days 4–9.[25]

AUC = area under the concentration-time curve from 0 to infinity (∞) or to the end of the dose administration interval (T), where T was the dose administration interval time equal to 12 hours (twice-daily regimen) or equal to 24 hours (once-daily regimen); **CL_r** = renal clearance; **C_{max}** = maximum observed plasma concentration; **NA** = not available; **NC** = not calculated, as all time points were less than the lower limit of quantification; **ND** = not determined; **RS** = restricted smoking; **t_{max}** = time to reach C_{max}; **$t_{½}$** = terminal phase half-life.

and smokers (140 ng • h/mL and 102 ng • h/mL, respectively, in smokers and non-smokers administered 1.0 mg, and approximately 200–300 ng • h/mL in smokers and non-smokers administered 3.0 mg). These pharmacokinetic parameters were unaffected by the time of day the dose was administered or co-administration with food (table I).

After repeat administration of 1–3 mg once daily or 1 mg twice daily in mainly Caucasian smokers aged 18–45 years[24] or >65 years,[24] and Chinese smokers aged 18–45 years,[25] t_{max} ranged from 2 to 4 hours and C_{max} ranged from 7.03 ng/mL to 19.8 ng/mL (table I). The AUC from time zero to the end of the administration interval (AUC_{0-T}; where T was the administration interval time equal to 12 hours for the twice-daily regimen and 24 hours for the once-daily regimen) ranged from 105 ng • h/mL to 352 ng • h/mL (table I). C_{max} and AUC_{0-T} were approximately 2-fold greater after repeat administration than after the initial dose (table I), indicating drug accumulation. Steady-state concentrations of varenicline were achieved by day 4.[24,25]

C_{max} (0.135–10.8 ng/mL) and $AUC_{0-\infty}$ (12.6–223 ng • h/mL) increased in a dose-proportional manner in non-smokers administered a single dose ranging from 0.03 mg to 3.0 mg.[27] In smokers administered 0.03–10.0 mg, C_{max} (0.165–13.0 ng/mL) and $AUC_{0-\infty}$ (9.52–303 ng • h/mL) increased in a dose-proportional manner from 0.03 mg to 3 mg. Similarly, C_{max} and AUC_{0-T} were dose-proportional in smokers administered multiple doses.[23] Together, these data indicate that varenicline has linear pharmacokinetics after single or repeated doses of up to 3 mg/day.

3.2 Distribution

Varenicline distributes into tissues, including the brain.[26] At steady state, the average apparent volume of distribution is 415 litres.[26] Less than 20% of varenicline is bound to plasma protein, and the degree of plasma protein binding is independent of either age or renal function.[26]

3.3 Metabolism

Varenicline undergoes minimal metabolism, with approximately 92% excreted unchanged in the urine and <10% excreted as metabolites.[26] Varenicline *N*-carbamoylglucuronide and hydroxyvarenicline are minor metabolites in the urine. In the circulation, 91% of varenicline-related material is the parent drug and minor metabolites include varenicline *N*-carbamoylglucuronide and *N*-glucosylvarenicline.[26] In a clinical mass-balance study in six healthy male volunteers, four metabolites were detected in the circulation; varenicline *N*-carbamoylglucuronide, *N*-glucosylvarenicline, a putative lactam and *N*-formylvarenicline,

comprising 3.8%, 3.5%, 1.1% and 0.9% of the total administered dose, respectively, with unchanged varenicline accounting for 91%.[22] In the excreta, varenicline, varenicline *N*-carbamoylglucuronide and 2-hydroxyvarenicline comprised 81%, 3.6% and 2.9%, respectively, of the total administered dose. It is currently unclear whether the known metabolites of varenicline are active or inactive.

3.4 Excretion

The plasma elimination half-life ($t_{½}$) of varenicline is approximately 24 hours (table I).[24,26] The large majority of varenicline-related material is excreted in the urine.[22,24] Renal clearance of varenicline is dose-proportional, and is approximately 90 mL/min and 125 mL/min in smokers administered 1 mg once daily or 1 mg twice daily, respectively (table I). Renal elimination of varenicline occurs mainly via glomerular filtration together with active tubular excretion by the human organic cation transporter 2 (hOCT2).[28]

3.5 Hepatic Impairment

As varenicline does not undergo significant hepatic metabolism, its pharmacokinetics should be unaffected in patients with hepatic insufficiency, although no studies on such patients have yet been conducted.[19]

3.6 Renal Impairment

The pharmacokinetics of varenicline have been studied in patients with renal impairment.[19] In patients with mild renal impairment (estimated creatinine clearance >50 mL/min and ≤80 mL/min), pharmacokinetics were unchanged compared with subjects with normal renal function (estimated creatinine clearance >80 mL/min). However, in patients with moderate renal impairment (estimated creatinine clearance ≥30 mL/min and ≤50 mL/min), varenicline exposure (as assessed by AUC curves) was increased 1.5-fold. Similarly, varenicline exposure was increased 2.1-fold in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). In patients with end-stage renal disease requiring dialysis, varenicline exposure was increased by 2.7-fold following treatment with 0.5 mg once daily for 12 days. Plasma C_{max} and AUC were similar to healthy individuals receiving approximately 1 mg twice daily. Therefore, caution is warranted with the use of varenicline in individuals with renal impairment.

4. Drug-Drug Interactions

In *in vitro* studies, varenicline did not inhibit human cytochrome P450 (CYP) enzymes in pooled liver microsomes (IC_{50} >6400 ng/mL for 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5) and did not induce 1A2 or 3A4 in human hepatocytes.[19] In addition, <10% of the clearance of varenicline is through metabolism.[19] Therefore, there is very limited potential for interactions between varenicline and drugs metabolized by CYP enzymes.

In a study of 12 smokers, co-administration of cimetidine 1200 mg/day, an efficient inhibitor of hOCT2, reduced the renal clearance of varenicline, resulting in a 29.0% increase in systemic exposure.[28] In separate studies in smokers, varenicline 1 mg twice daily did not alter the steady-state pharmacokinetics of warfarin,[29] digoxin 0.2 mg once daily,[30] metformin 500 mg twice daily (a substrate of hOCT2)[19] or bupropion SR 150 mg twice daily.[19] In a study of 39 smokers, co-administration of varenicline 1 mg twice daily and transdermal nicotine 21 mg/day for up to 12 days did not alter the pharmacokinetics of nicotine.[19] However, premature discontinuation due to adverse events (nausea, headache, vomiting, dizziness, dyspepsia and fatigue) occurred at a greater frequency in the group receiving combination therapy compared with those receiving nicotine alone.

5. Dose-Finding Trials

A variety of methods have been proposed to measure abstinence from tobacco smoking in clinical studies of treatments for smoking cessation.[31] A widely employed measure is the carbon monoxide (CO)-confirmed continuous abstinence

Table II. Abstinence rates in phase II studies of varenicline

Study (duration)	Treatment	Number of participants	CAR (%)[a]	OR (95% CI) vs placebo	p-Value
Nides et al.[32] (7 wk)	Varenicline 1 mg bid	127	48.0[b]	4.71 (2.60, 8.53)	<0.001
	Varenicline 1 mg od	128	37.3[b]	2.97 (1.63, 5.40)	<0.001
	Varenicline 0.3 mg od	128	28.6[b]	1.97 (1.07, 3.65)	0.03[c]
	Bupropion SR 150 mg bid	128	33.3[b]	2.53 (1.38, 4.63)	0.002
	Placebo	127	17.1[b]		
Oncken et al.[33] (12 wk)	Varenicline 1.0 mg bid titrated	130	54.6	NR	<0.001
	Varenicline 1.0 mg bid non-titrated	129	44.2	NR	<0.001
	Varenicline 1.0 mg bid (pooled data)	259	49.4	8.07 (4.42, 14.70)	<0.001
	Varenicline 0.5 mg bid titrated	130	40.8	NR	<0.001
	Varenicline 0.5 mg bid non-titrated	129	47.3	NR	<0.001
	Varenicline 0.5 mg bid (pooled data)	259	44.0	6.32 (3.47, 11.50)	<0.001
	Placebo	129	11.6		
Niaura et al.[34] (12 wk, flexible administration)	Varenicline 0.5–2.0 mg/day	157	40.1	5.66 (3.08, 10.40)	<0.001
	Placebo	155	11.6		
Nakamura et al.[35] (12 wk)	1 mg bid	130	65.4	2.98 (1.78, 4.99)	<0.001
	0.5 mg bid	128	55.5	1.94 (1.17, 3.22)	0.01
	0.25 mg bid	128	54.7	1.88 (1.14, 3.12)	0.013
	Placebo	129	39.5		

a Weeks 9–12 unless otherwise stated.

b Any 4 weeks during the study.

c The Dunnett adjustment for four contrasts vs control requires $p < 0.015$ for significance at $\alpha = 0.05$.[32]

bid = twice daily; **CAR** = continuous abstinence rate; **NR** = not reported; **od** = once daily; **OR** = odds ratio; **SR** = sustained release.

rate (CAR) for a specified period of time; this is defined as a self-report of no smoking during that time period (not even a puff) that is verified by an expired-air CO concentration of ≤10 parts per million.

At dosages of 1 mg twice daily or 1 mg once daily, varenicline was associated with significantly higher CARs than placebo in a 7-week, dose-ranging phase II study (table II).[32] In this double-blind, multicentre study, healthy smokers aged 18–65 years (n = 638) were randomized to 6 weeks of treatment with varenicline 0.3 mg once daily (n = 128), 1.0 mg once daily (n = 128) or 1.0 mg twice daily (n = 127) followed by 1 week of placebo, bupropion SR 150 mg twice daily (n = 128) or placebo (n = 127) for 7 weeks. CARs for any 4 weeks during treatment were 48% ($p < 0.001$ vs placebo), 37.3% ($p < 0.001$ vs placebo), 33.3% ($p = 0.002$ vs placebo) and 17.1%, for varenicline 1 mg twice daily, varenicline 1 mg once daily, bupropion SR and placebo, respectively.

The efficacy of varenicline 0.5 mg and 1.0 mg titrated and non-titrated dose regimens was investigated in a randomized, double-blind, multicentre, 12-week phase II study in 647 healthy smokers aged 18–65 years (table II).[33] Individuals who received 0.5 mg titrated doses received a once-daily dose for 7 days followed by twice-daily doses thereafter; those who received 1.0 mg titrated doses received 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, then 1.0 mg twice daily thereafter. In the primary efficacy measure, the 4-week CAR for weeks 9–12 was 54.6% and 44.2% in the 1.0 mg twice-daily titrated and non-titrated groups, respectively; 40.8% and 47.3% in the 0.5 mg twice-daily titrated and non-titrated groups, respectively; and 11.6% in the placebo group ($p < 0.001$ for each varenicline group vs placebo). On the basis of the phase II trials, it was determined that 1 mg twice daily for 12 weeks, with titration, is the optimal dosage of varenicline for aiding smoking cessation.

6. Efficacy for Smoking Cessation

As an aid to smoking cessation therapy, varenicline 1 mg twice daily has demonstrated greater efficacy than placebo, bupropion SR 150 mg twice daily or transdermal NRT in motivated-to-quit smokers aged 18–75 years with no recent history of serious or unstable disease (including psychiatric disorders) [table III].[35-41]

6.1 Versus Sustained-Release Bupropion or Placebo for 12 Weeks

In two separate but identically designed double-blind, phase III, clinical trials in the US, smokers were randomized to varenicline 1 mg twice daily, bupropion SR 150 mg twice daily or placebo for 12 weeks.[36,37] Individuals randomized to varenicline received 0.5 mg once daily on days 1–3, 0.5 mg twice daily on days 4–7 and 1 mg twice daily thereafter; those randomized to bupropion SR received 150 mg once daily on days 1–3 and 150 mg twice daily thereafter. The target quit date (TQD) was day 8 of treatment. Brief counselling sessions were provided during weekly clinic visits to all participants, in accordance with recommendations in the *US Public Health Service Clinical Practice Guidelines: Treating Tobacco Use and Dependence*.[42] The majority (>75%) of patients in each study were Caucasian. Participants had no prior exposure to varenicline or bupropion SR.

The primary endpoint of the studies was the CAR for weeks 9–12 ($CAR_{9–12}$). In the study of 1025 smokers from 19 centres, $CAR_{9–12}$ was 44% in the varenicline group (OR 3.85; 95% CI 2.70, 5.50; $p < 0.001$ vs placebo and OR 1.93; 95% CI 1.40, 2.68; $p < 0.001$ vs bupropion SR), 29.5% in the bupropion SR group (OR 2.00; 95% CI 1.38, 2.89; $p < 0.001$ vs placebo) and 17.7% in the placebo group (table III).[36] Analyses by treatment group interactions revealed no significant differences in the efficacy of varenicline between groups with different baseline characteristics such as sex, ethnic origin and smoking history.[36] Very similar results were obtained in the separate trial of 1027 smokers from 14 centres (table III).[37]

6.2 Versus Transdermal Nicotine Replacement Therapy (NRT)

Varenicline and transdermal NRT were compared in an open-label phase III trial conducted in Belgium, France, the Netherlands, the UK and

Table III. Phase III efficacy data of varenicline in smoking cessation. All studies were for 12-weeks

Study	Treatment	Number of participants	$CAR_{9–12}$ (%)	OR (95% CI)	p-Value
Gonzales et al.[36]	Varenicline 1 mg bid	352	44.0	1.93 (1.40, 2.68) vs bupropion	<0.001
				3.85 (2.70, 5.50) vs placebo	<0.001
	Bupropion SR 150 mg bid	329	29.5	2.00 (1.38, 2.89) vs placebo	<0.001
	Placebo	344	17.7		
Jorenby et al.[37]	Varenicline 1 mg bid	344	43.9	1.90 (1.38, 2.62) vs bupropion	<0.001
				3.85 (2.69, 5.50) vs placebo	<0.001
	Bupropion SR 150 mg bid	342	29.8	2.02 (1.40, 2.92) vs placebo	0.001
	Placebo	341	17.6		
Tsai et al.[40]	Varenicline 1 mg bid	126	59.5	3.22 (1.89, 5.47) vs placebo	<0.001
	Placebo	124	32.3		
Wang et al.[41]	Varenicline 1 mg bid	165	50.3	2.31 (1.45, 3.67) vs placebo	<0.001
	Placebo	168	31.6		
Aubin et al.[39]	Varenicline 1 mg bid	376	55.9	1.70 (1.26, 2.28) vs NRT	<0.001
	NRT 21 mg/day	370	43.2[a]		

a CAR for weeks 8–11.

bid = twice daily; **$CAR_{9–12}$** = continuous abstinence rate from weeks 9 to 12; **NRT** = nicotine-replacement therapy; **OR** = odds ratio; **SR** = sustained release.

the US.[39] In this study, smokers were randomized to varenicline twice daily titrated to 1 mg for 12 weeks (n = 376) or transdermal NRT 21 mg/day reducing to 7 mg/day for 10 weeks (n = 370). The TQD occurred at the week 1 visit in both treatment groups; in accordance with the manufacturer's recommendations, varenicline treatment was initiated 1 week before the TQD (the day following the baseline visit), whereas NRT treatment began on the TQD. The primary endpoint was CAR during the last 4 weeks of each treatment, in participants who had received at least one dose of the study drug. CAR was 55.9% and 43.2% in the varenicline and NRT groups, respectively ($p < 0.001$) [table III]. CAR from the end of drug treatment to week 52 was 26.1% for varenicline and 20.3% for NRT ($p = 0.056$).

6.3 Pooled Analyses of Phase III Data

A pooled analysis of the data from the two US phase III trials confirmed the differences in $CAR_{9–12}$ between varenicline (44.0%; $p < 0.0001$ vs both bupropion SR and placebo), bupropion SR (29.7%; $p < 0.001$ vs placebo) and placebo (17.7%).[43] A Cochrane Collaboration meta-analysis of five clinical trials of varenicline with a bupropion SR and/or placebo control arm(s) calculated that the pooled OR for continuous abstinence up to 12 months with varenicline was 3.22 (95% CI 2.43, 4.27) versus placebo and 1.66 (95% CI 1.28, 2.16) versus bupropion SR.[7]

An important issue for the clinician is whether there are any factors that predict the likelihood of successful smoking cessation. The pooled analysis of the US phase III studies[43] indicated that varenicline is effective regardless of baseline nicotine dependence (figure 1), age, sex, baseline daily cigarette consumption or time to first cigarette of the day. Although the absolute efficacy of varenicline (as well as that of bupropion and placebo) tended to decline with increased nicotine dependence, the efficacy of varenicline relative to placebo did not.

6.4 Asian Populations

Varenicline 1 mg twice daily has also demonstrated efficacy as a smoking cessation aid in 12-week, randomized, double-blind, placebo-controlled studies of smokers in Taiwan and Korea (table III),[40] Japan (table II),[35] and China, Thailand and Singapore (table III).[41]

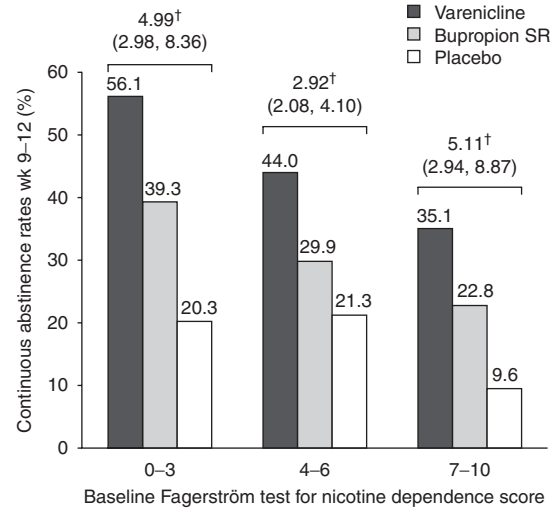

Fig. 1. Efficacy of varenicline in phase III studies by Fagerström Test for nicotine dependence score (data from Nides et al.[43]). p-Value for treatment by subgroup interaction is 0.2558. † Odds ratio versus placebo (95% confidence interval). **SR** = sustained release.

6.5 Extended Treatment

An additional 12 weeks of varenicline therapy increased the CAR in a phase III study in smokers in seven countries (n = 1210), most of whom (>95%) were Caucasian.[38] Participants who were abstinent for at least the final 7 days of 12 weeks of open-label treatment with varenicline 1 mg twice daily were randomized to double-blind treatment with varenicline or placebo for an additional 12 weeks. CAR for weeks 13–24 and weeks 13–52 were significantly higher in the varenicline group than in the placebo group (70.5% and 49.6%, and 43.6% and 36.9%, respectively).

6.6 Self-Regulated Flexible Dosing

In a recently published phase II study, a 12-week, self-regulated, flexible administration regimen of varenicline was also efficacious for aiding smoking cessation.[34] In this randomized, double-blind, placebo-controlled study, 320

smokers received varenicline or placebo in fixed doses (week 1: titrated from 0.5 mg/day to 1.0 mg/day) followed by a self-regulated flexible schedule (weeks 2–12: 0.5–2.0 mg/day). The primary outcome of CAR favoured varenicline over placebo for weeks 4 through 7 (38.2% vs 11.6%), weeks 9 through 12 (40.1% vs 11.6% [table II]), weeks 9 through 24 (28.0% vs 9.0%) and weeks 9 through 52 (22.3% vs 7.7%) [all $p < 0.001$].

7. Reduction of Withdrawal and Urge to Smoke

In the phase II and III clinical trials, varenicline reduced the urge to smoke, cravings and satisfaction from smoking (in relapsers) [table IV] – symptoms usually considered as surrogates for smoking abstinence. These patient-reported outcomes were assessed using the Minnesota Nicotine Withdrawal Scale (MNWS),[44] the brief Questionnaire of Smoking Urges (QSU-brief)[45] and the modified Cigarette Evaluation Questionnaire (mCEQ).[46]

7.1 Comparison With Placebo

In the phase III study of 1025 healthy smokers from 19 centres, MNWS urge to smoke and negative affect were significantly less in participants receiving varenicline or bupropion SR than in those receiving placebo (figure 2, table IV).[36] These data were not adjusted for abstinence. For urge to smoke, the effect size (least square mean difference divided by pooled SD at baseline) versus placebo in the varenicline group was approximately twice that in the bupropion SR group (–0.67 vs –0.30). For negative affect, the effect size versus placebo was approximately the same in the varenicline and bupropion SR groups (–0.30 and –0.25). Although restlessness and increased appetite were lower and higher, respectively, in the varenicline group compared with placebo, the effect sizes were small (–0.16 and 0.15, respectively). Total craving score by the QSU-brief was significantly less than with placebo in both the varenicline and bupropion SR groups (effect size –0.33 [$p < 0.001$] and –0.15 [$p = 0.001$], respectively). Relapsers in the varenicline group had moderate but significant reductions in smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving relief compared with placebo relapsers, as measured with the mCEQ. In contrast, the only subscale to be significantly reduced in the bupropion SR group was psychological reward. Similar results were observed in other studies (table IV).[35,37,40]

A pooled analysis of the US phase III trials investigated urge to smoke, withdrawal and reward from relapse in the week following TQD, when withdrawal symptoms were expected to be the most severe.[47] In abstinent and non-abstinent participants combined, MNWS urge to smoke was lower with varenicline (1.32; $p < 0.05$ vs placebo, $p < 0.05$ vs bupropion) than with bupropion SR (1.47; $p < 0.05$ vs placebo) or placebo (1.76). Among abstinent participants, MNWS negative affect was lower in the varenicline (0.60; $p < 0.05$) and bupropion (0.52; $p < 0.05$) groups than in the placebo group (0.81). In comparison with placebo, neither varenicline nor bupropion SR significantly reduced restlessness, insomnia or appetite. Ratings of satisfaction and psychological reward from the first cigarette smoked after TQD were significantly lower with varenicline (2.60 and 2.20, respectively; both $p < 0.05$ vs bupropion and placebo) than with bupropion SR (3.01 and 2.43; both $p < 0.05$ vs placebo) or placebo (3.18 and 2.61, respectively).

In a double-blind, crossover, placebo-controlled study in a laboratory setting, varenicline improved mood and cognition during abstinence from smoking.[48] In this study, 67 motivated-to-quit smokers aged ≥18 years without serious or unstable disease (including psychiatric disorders) completed two 21-day treatment phases, each comprising run-in with varenicline or placebo (days 1–10), mandatory smoking abstinence (days 11–13), scheduled smoking lapse (day 14) and observation (days 15–21). Symptoms of abstinence were assessed from days 10–14 using a 19-item checklist for withdrawal symptoms, QSU-brief for craving, and the Positive and Negative Affect Schedule for positive and negative affect. Cognitive function was assessed at baseline and day 13. The Cigarette Evaluation Scale

Table IV. Effect of varenicline (VAR) on nicotine withdrawal, urge to smoke and reinforcing effects of smoking: least-squares mean, difference (95% CI) vs comparator[a]

Effect	Versus placebo								Versus NRT 21 mg/day
	Gonzales et al.[36]		Jorenby et al.[37]		Tsai et al.[40]	Nakamura et al.[35]			Aubin et al.[39]
	VAR 1 mg bid	BUP SR 150 mg bid	VAR 1 mg bid	BUP SR 150 mg bid	VAR[b] 1 mg bid	VAR 1 mg bid	VAR 0.5 mg bid	VAR 0.25 mg bid	VAR 1 mg bid
MNWS									
Urge to smoke	−0.54	−0.24	−0.48	−0.38	−0.40	−0.51	−0.46	−0.26	−0.32
	(−0.66, −0.42)	(−0.36, −0.12)	(−0.59, −0.37)	(−0.49, −0.27)	(−0.57, −0.23)	(−0.71, −0.32)	(−0.66, −0.26)	(−0.45, −0.06)	(−0.44, −0.21)
Negative affect	−0.19	−0.16	−0.13	−0.13	NR	−0.28	−0.24	−0.13	−0.16
	(−0.27, −0.11)	(−0.25, −0.08)	(−0.21, −0.05)	(−0.21, −0.05)		(−0.41, −0.15)	(−0.37, −0.12)	(−0.25, 0.00)	(−0.24, −0.07)
Restlessness	−0.14	−0.09	−0.10	−0.07	NR	−0.38	−0.28	−0.19	−0.20
	(−0.24, −0.03)	(−0.20, 0.01)	(−0.20, 0.00)	(−0.17, 0.03)		(−0.54, −0.22)	(−0.44, −0.12)	(−0.35, −0.03)	(−0.31, −0.10)
Increased appetite	0.12	−0.04	0.07	−0.07	NR	−0.09	0.12	0.14	0.09
	(0.00, 0.24)	(−0.16, 0.08)	(−0.04, 0.19)	(−0.19, 0.05)		(−0.32, 0.15)	(−0.12, 0.36)	(−0.09, 0.38)	(−0.02, 0.21)
Insomnia	0.05	0.11	0.10	0.20	NR	0.07	0.05	0.04	−0.07
	(−0.05, 0.15)	(0.00, 0.21)	(−0.01, 0.20)	(0.09, 0.30)		(−0.09, 0.22)	(−0.10, 0.21)	(−0.12, 0.19)	(−0.17, 0.04)
QSU-brief									
Total craving score	−0.45	−0.21	−0.44	−0.34	−0.39	−0.51	−0.51	−0.30	NR
	(−0.57, −0.32)	(−0.34, −0.08)	(−0.57, −0.31)	(−0.47, −0.21)	(−0.60, −0.17)	(−0.74, −0.28)	(−0.74, −0.28)	(−0.53, −0.07)	
Factor 1 (pleasure)	NR	NR	−0.56	−0.42	NR	−0.60	−0.60	−0.37	NR
			(−0.71, −0.40)	(−0.58, −0.27)		(−0.86, −0.34)	(−0.86, −0.34)	(−0.63, −0.11)	
Factor 2 (negative affect relief)	NR	NR	−0.27	−0.21	NR	−0.38	−0.38	−0.22	NR
			(−0.38, −0.16)	(−0.32, −0.10)		(−0.56, −0.19)	(−0.56, −0.20)	(−0.40, −0.04)	
mCEQ									
Smoking satisfaction	−0.60	−0.13	−0.44	−0.32	−0.39	−0.74	−0.67	−0.29	−0.54
	(−0.80, −0.41)	(−0.32, 0.06)	(−0.61, −0.25)	(−0.50, −0.15)	(−0.67, −0.10)	(−1.07, −0.41)	(−0.99, −0.35)	(−0.61, 0.02)	(−0.77, −0.31)
Psychological reward	−0.50	−0.23	−0.32	−0.28	NR	−0.53	−0.42	−0.24	−0.32
	(−0.65, −0.34)	(−0.38, −0.07)	(−0.47, −0.16)	(−0.43, −0.13)		(−0.76, −0.30)	(−0.64, −0.19)	(−0.46, −0.02)	(−0.51, −0.13)
Enjoyment of respiratory tract symptoms	−0.34	0.04	−0.22	−0.13	NR	−1.00	−0.57	−0.47	−0.39
	(−0.52, −0.16)	(−0.14, 0.22)	(−0.39, −0.05)	(−0.30, 0.04)		(−1.33, −0.66)	(−0.90, −0.25)	(−0.78, −0.15)	(−0.60, −0.17)
Craving reduction	−0.52	0.00	−0.25	−0.15	NR	−0.45	−0.40	−0.27	−0.52
	(−0.77, −0.27)	(−0.25, 0.24)	(−0.49, −0.02)	(−0.38, 0.08)		(−0.87, −0.03)	(−0.80, 0.01)	(−0.66, 0.13)	(−0.79, −0.24)
Aversion	−0.18	−0.17	0.00	0.10	NR	−0.38	−0.60	−0.50	−0.07
	(−0.36, 0.00)	(−0.35, 0.00)	(−0.15, 0.16)	(−0.05, 0.25)		(−0.65, −0.10)	(−0.86, −0.33)	(−0.76, −0.24)	(−0.25, 0.11)

a Repeated measures analysis of data for weeks 1–7, except where indicated. A negative score indicates a reduction in the parameter vs the comparator (MNWS range of possible scores, 0–4; QSU-brief range of possible scores, 1–7; mCEQ range of possible scores, 1–7).

b Repeated measures analysis for weeks 1–6.

bid = twice daily; **BUP** = bupropion; **mCEQ** = Modified Cigarette Evaluation Questionnaire; **MNWS** = Minnesota Nicotine Withdrawal Scale; **NR** = not reported; **NRT** = nicotine-replacement therapy; **QSU-brief** = brief Questionnaire of Smoking Urges; **SR** = sustained release.

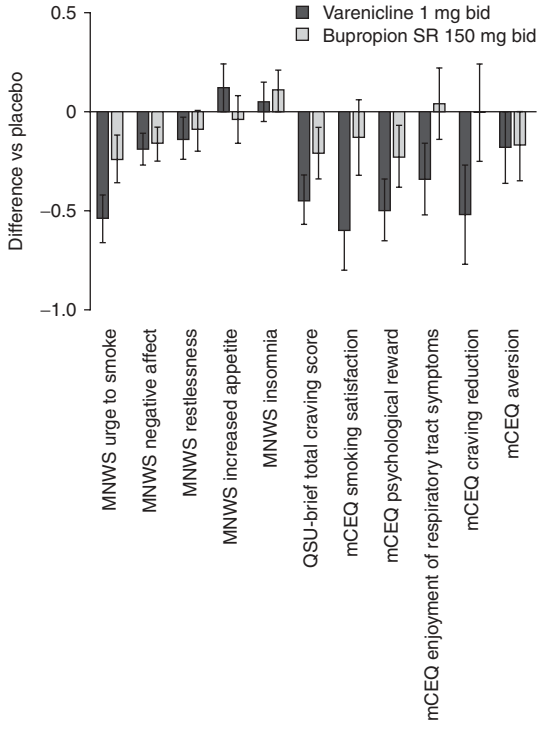

Fig. 2. Effect of varenicline and sustained-release (SR) bupropion on participant-reported outcomes: least squares means, differences (95% CI) versus placebo. Data from the US phase III study in 1025 smokers (Gonzales et al.[36]). **bid** = twice daily; **mCEQ** = modified Cigarette Evaluation Questionnaire; **MNWS** = Minnesota Nicotine Withdrawal Scale; **QSU-brief** = brief Questionnaire of Smoking Urges.

and the Sensory Questionnaire were administered immediately following the lapse cigarette on day 14 to assess the rewarding effects of lapse. During abstinence, withdrawal symptoms ($p = 0.04$), urge to smoke ($p < 0.001$) and negative affect ($p = 0.01$) were lower in the varenicline phase than in the placebo phase, whereas levels of positive affect ($p = 0.046$), sustained attention ($p = 0.018$) and working memory ($p = 0.001$) were greater. During the lapse, rewarding effects of smoking were significantly lower during the varenicline phase compared with placebo.

7.2 Comparison with NRT

In the randomized, open-label, phase III trial,[39] MNWS urge to smoke, negative affect and restlessness were lower in the varenicline group than in the NRT group. Between-group differences in MNWS increased appetite or insomnia scores were not significant (table IV). It is unclear why a partial agonist of $\alpha 4\beta 2$ receptors (varenicline) would be more effective in alleviating nicotine-withdrawal symptoms than nicotine itself, a full agonist. Relapsers in the varenicline group experienced lower smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving reduction than relapsers on NRT. Aversion scores were not significantly different between the groups (table IV).

8. Safety and Tolerability

Varenicline exhibited an acceptable safety and tolerability profile in clinical trials, with nausea, abnormal dreams and insomnia being the most frequent adverse events (table V) [see also additional table, Supplementary Digital Content 1, http://links.adisonline.com/DGZ/A3].

8.1 Overall Tolerability

Treatment-emergent adverse events and discontinuations due to adverse events generally occurred at similar frequencies amongst smokers treated with varenicline, placebo or bupropion (table V).

8.2 Common Adverse Events

The most frequent adverse events associated with varenicline treatment were nausea, abnormal dreams and insomnia (supplementary digital content). In the varenicline, bupropion and placebo groups, in the US phase III studies, the incidence of nausea was 28.1–29.4%, 7.4–12.5% and 8.4–9.7%, the incidence of abnormal dreams was 10.3–13.1%, 5.5–5.9% and 3.5–5.5%, and the incidence of insomnia was 14.0–14.3%, 21.2–21.9% and 12.4–12.8%, respectively.[36,37] In a pooled analysis of the US phase III studies, the onset of nausea occurred mainly in the first week of treatment, with approximately 16% of participants experiencing nausea at this time. The prevalence of nausea was highest in week 2 (18%) and declined thereafter.[43] The pattern of adverse

Table V. Treatment-emergent adverse events and discontinuations due to adverse events in phase II and III studies of varenicline

Study (duration)	Treatment	Number of participants	Treatment-emergent adverse events [n (%)]	Discontinuations due to adverse events [n (%)]
Gonzales et al.[36]	Varenicline 1 mg bid	349	275 (78.8)	30 (8.6)
	Bupropion SR 150 mg bid	329	258 (78.4)	50 (15.2)
	Placebo	344	257 (74.7)	31 (9.0)
Jorenby et al.[37]	Varenicline 1 mg bid	344	NR (NR)	NR (10.5)
	Bupropion SR 150 mg bid	342	NR (NR)	NR (12.6)
	Placebo	341	NR (NR)	NR (7.3)
Aubin et al.[39]	Varenicline 1 mg bid	376	319 (84.8)	30 (8.0)
	NRT 21 mg/day	370	260 (70.3)	16 (4.3)
Tonstad et al.[38]	Initial 12 week, open-label			
	varenicline 1 mg bid	1927	NR (NR)	229 (11.9)
	12-week extended treatment, randomized			
	varenicline 1 mg bid	602	NR (46)	10 (1.7)
	placebo	604	NR (45)	8 (1.3)
Tsai et al.[40]	Varenicline 1 mg bid	126	109 (86.5)	8 (6.3)
	Placebo	124	98 (79.0)	1 (0.8)
Wang et al.[41]	Varenicline 1 mg bid	165	127 (77.0)	3 (1.8)
	Placebo	168	108 (64.3)	3 (1.8)
Nakamura et al.[35]	1 mg bid	156	125 (80.1)	5 (3.2)
	0.5 mg bid	155	125 (80.6)	4 (2.6)
	0.25 mg bid	153	121 (79.1)	3 (2.0)
	Placebo	154	110 (71.4)	3 (1.9)
Williams et al.[49] (52 wk)	Varenicline 1 mg bid	251	NR (96.4)	71 (28.3)
	Placebo	126	NR (82.5)	13 (10.3)
Niaura et al.,[34] flexible dosing	Varenicline 0.5–2.0 mg/day	157	121 (77.1)	11 (7.0)
	Placebo	155	102 (65.8)	7 (4.5)
Oncken et al.[33]	Varenicline 1.0 mg bid titrated	129	NR (79.3)	NR (21.7)
	Varenicline 1.0 mg bid non-titrated	124	NR (85.3)	NR (13.7)
	Varenicline 0.5 mg bid titrated	129	NR (90.3)	NR (14.0)
	Varenicline 0.5 mg bid non-titrated	124	NR (81.4)	NR (7.3)
	Placebo	121	NR (86.3)	NR (17.4)
Nides et al.[32] (7 wk)	Varenicline 1 mg bid	125	NR (92.0)	NR (11.2)
	Varenicline 1 mg od	126	NR (88.1)	NR (12.7)
	Varenicline 0.3 mg od	126	NR (90.5)	NR (14.3)
	Bupropion SR 150 mg bid	126	NR (89.7)	NR (15.9)
	Placebo	123	NR (87.8)	NR (9.8)

bid = twice daily; **NR** = not reported; **NRT** = nicotine-replacement therapy; **od** = once daily; **SR** = sustained release.

events was similar in the open-label, phase III study,[39] although the varenicline-associated incidence of nausea (37.2% vs 9.7% with NRT) and insomnia (21.3% vs 19.2% with NRT) was greater than in the US studies (supplementary digital content).

Adverse events observed in Asian smokers were reasonably consistent with those seen in Western populations (table V and supplementary digital content). However, in the study conducted in Japan, nasopharyngitis was the most common adverse event in all treatment groups.[35]

In the phase II study with a self-regulated, flexible administration regimen,[34] the most frequent adverse event with varenicline was insomnia (21.7% vs 11.0% in the placebo group), followed by headache (15.9% and 12.9%), respiratory tract infection (15.9% and 9.7%) and nausea (13.4% and 5.2%) [supplementary digital content]. Although the incidence of nausea in varenicline-treated individuals was lower than in other studies, the same was true in the placebo group. It is possible that a flexible-administration strategy, which is closer to everyday clinical practice, may lead to less frequent nausea and other adverse effects, and a lower likelihood of discontinuation for adverse effects than a fixed dose schedule.[34]

In a randomized, double-blind study in healthy smokers aged 18–75 years, the safety profile of varenicline over 52 weeks of treatment was similar to that observed in the 12-week studies (table V and supplementary digital content).[49] The most common adverse events in the varenicline group were nausea (40.2% vs 7.9% in the placebo group), abnormal dreams (22.7% vs 7.1%) and insomnia (19.1% vs 9.5%).

One commonly reported adverse effect of smoking cessation is weight gain. A recent Cochrane review reported that varenicline may reduce weight gain during treatment.[50] However, the authors found no evidence that varenicline significantly reduced weight gain at the end of treatment and there are no follow-up data currently available.

8.3 Psychiatric Adverse Events

Recent post-marketing reports have raised concerns about neuropsychiatric symptoms in some patients taking varenicline.[51] The Cochrane Tobacco Addiction Group recently authored a preliminary benefit-risk assessment of varenicline, to review its efficacy as an aid to smoking cessation and to weigh the potential benefits against possible risks including neuropsychiatric safety.[52] The article describes the FDA public health advisory and that the labelling of varenicline in the US and Europe has been changed accordingly to include a warning to both physicians and patients. In the US, the FDA communicates its advice through a Medication Guide that specifically advises varenicline patients about such events: ''If either you, your family or caregiver notice agitation, depressed mood, or changes in behaviour that are not typical for you, or if you have suicidal thoughts or actions, stop taking Chantix and call your doctor right away''.[53]

Because of methodological considerations (reduced variance, increased power), as highlighted in the review by Cahill et al.,[52] it is usual practice for phase II and III smoking cessation trials to exclude smokers who are ''perceived to be at increased risk of adverse events or unpredictable outcomes''. Varenicline phase II and III clinical trials excluded smokers requiring treatment for depression currently or within the past 12 months, past or present history of panic disorder, psychosis or bipolar disorder; or history of drug (except nicotine) or alcohol abuse or dependence within the past 12 months.[32-34,36,37,40,41] Additionally, adolescents, elderly, pregnant or nursing women, and patients with serious or unstable disease were excluded. Therefore, varenicline phase II and III safety data in patients with a history of mental illness are not available. In-depth *post hoc* inferential analyses have been conducted using data from all completed, randomized, placebo-controlled, clinical trials to examine psychiatric adverse events in subjects from the clinical programme (congress communication from 10th Annual Conference of Society for Research on Nicotine and Tobacco Europe, Rome, Italy, September 23-26, 2008).[54,55]

However, other recently published reports of varenicline for smoking cessation have included patients with a history of mental illness. These articles are of interest since clinical experience in this population is currently lacking; however, because of the limitations in the study designs, none of these articles can provide conclusive evidence of a causal link, or lack of, between varenicline and psychiatric adverse events in smokers.

In a non-randomized study, Stapleton et al.[56] evaluated varenicline compared with NRT in 412 smokers in a community clinic, of whom 111 (27%)

were being treated for a mental illness (primary diagnosis: depression, 64; bipolar disorder, 14; psychosis, 7; psychosis and depression, 24; eating disorder, 2). The study found no evidence that varenicline exacerbated mental illness; however, the small sample size and varying clinical diagnoses of participants precluded any firm conclusions.

In a second study, participants with a probable history of depression were more likely to report neuropsychiatric adverse effects (including tension/agitation, irritability, slightly worse confusion, nausea and trouble sleeping) at early varenicline treatment (21 days) than those without a history of depression; however, depression and stress scores declined in all participants and the proportions reporting new/worsening depressive symptoms were equal in both groups.[57] However, since there was no placebo group in this trial, it was not clear which symptoms were due to varenicline and which were due to nicotine withdrawal.

A third report involved a case series of 19 smokers with schizophrenia who were stable outpatients on antipsychotic medications and who requested varenicline treatment. Four patients discontinued (one temporarily) due to nausea/vomiting. Thirteen quit smoking within 3 weeks of initiating treatment and maintained abstinence for at least 12 weeks, and all 13 patients continued varenicline treatment beyond the 24-week regimen to prevent relapse. The authors report that ''patients in this series have remained clinically stable with no clinical evidence of psychotic relapse or significant worsening of psychiatric symptoms or side effects of antipsychotic medications. None of the 19 patients had a psychiatric hospitalization within 24 weeks of starting varenicline''.[58]

The Cochrane preliminary benefit-risk assessment of varenicline was based on a total of 11 published varenicline studies, including the study by Stapleton et al.[56] In conclusion, the authors state that ''In view of the potential, if unproven, risk that varenicline may be associated with serious neuropsychiatric adverse outcomes, patients attempting to quit smoking with varenicline, and their families and caregivers, should be alerted about the need to monitor for neuropsychiatric symptoms, including changes in behaviour, agitation, depressed mood, suicidal ideation and suicidal behaviour, and to report such symptoms immediately to the patient's healthcare provider''.[52]

Other clinical trials in patients with psychiatric disorders are in progress (clinicaltrials.gov identifier numbers NCT00644969, NCT00727103, NCT00702793, NCT00621777, NCT00548470, NCT00802919 and NCT00554840) and should provide a clearer picture of the safety of varenicline in smokers with mental illnesses.

8.4 Abuse Potential

As a partial agonist of the $\alpha4\beta2$ nAChR with a longer $t_{½}$ than nicotine, varenicline would be expected to have a low potential for abuse. Consistent with this hypothesis, a study found that the abuse liability profile of varenicline is similar to placebo and much less than amphetamine.[59] In this double-blind, double-dummy, crossover study in smokers (n = 23) and non-smokers (n = 22), each participant received amphetamine 15 mg or 30 mg, varenicline 1 mg or 3 mg and placebo in 1 of 10 possible randomly assigned sequences. Because of the expected adverse effects of nausea and vomiting, varenicline doses >3 mg were not tested. In both smokers and non-smokers, the positive effects of varenicline 3 mg or 1 mg, measured primarily by visual analogue scale (VAS) drug high, mean Multiple Choice Subjective Price Monetary Value Procedure, VAS drug liking, and Addiction Research Center Inventory Abuse Potential, were significantly lower than those of amphetamine 15 mg and 30 mg and similar to those of placebo, except for VAS drug high in non-smokers, who rated both doses higher than placebo. In smokers, for example, mean (95% CI) peak rating for VAS drug high was 17.2 (5.9, 28.5), 26.6 (15.0, 38.1), 21.9 (10.2, 33.6) 55.2 (43.6, 66.7) and 70.2 (59.0, 81.5) for placebo, varenicline 1 mg, varenicline 3 mg, amphetamine 15 mg and amphetamine 30 mg, respectively. Both groups reported unpleasant effects from varenicline 3 mg, measured by the VAS bad effects and VAS nausea subscales. However, with varenicline 1 mg, while smokers

had scores on these subscales similar to placebo scores, non-smokers had higher scores, suggesting that the latter may be more sensitive to these negative effects of varenicline.

9. Varenicline in Clinical Practice

There have been case reports of exacerbation of existing psychiatric disorders in patients taking varenicline for smoking cessation.[60-64] However, in a case series of schizophrenic stable outpatients treated with varenicline, there was no deterioration in psychotic symptoms.[58]

9.1 Post-Marketing Surveillance

In the US, the FDA has received reports of the following adverse events occurring in patients treated with varenicline in clinical practice: depressed mood, agitation, changes in behaviour, suicidal ideation and suicide.[51] These reports originated from members of the public and healthcare professionals, and in most cases detailed information is lacking. Therefore, it is unclear whether there are chronological or dosage relationships between varenicline intake and symptoms. In addition, the event rates are unclear, as the reports were voluntary and the patient population size is not known with certainty. Importantly, it is not known whether there is a causal relationship between these neuropsychiatric events and exposure to varenicline.

The European prescribing information was updated in January 2008 to note that depressed mood may be a symptom of nicotine withdrawal, and that depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. It was also noted that these symptoms have been reported in individuals attempting to quit smoking while using varenicline.[26] The US prescribing information was updated in January 2008 to note the occurrence of neuropsychiatric events in smokers treated with varenicline and to recommend that individuals receiving treatment should be observed for such events.[19] It was also noted that patients with pre-existing psychiatric disorders did not participate in the pre-marketing clinical trials of varenicline.

In May 2008, the US-based Institute for Safe Medication Practices (ISMP), a private agency that is not a governmental or regulatory authority, issued a report analysing varenicline-associated post-marketing adverse events.[65] This report recommended caution with the use of varenicline in certain settings such as individuals operating machinery or electronic equipment (as a result of reported cases of lapse in alertness or motor control), and that patients and doctors exercise caution in the use of varenicline and consider the use of alternative approaches to smoking cessation. However, the report did not establish causality between varenicline and the post-marketing adverse events, and did not consider the frequency of use of varenicline when comparing the frequency of varenicline-associated adverse events with other drugs.

It should also be noted that the ISMP report was based on crude reporting frequencies. Subsequent disproportionality analysis that aimed to contextualize these same frequency data established that the majority of adverse event reports associated with varenicline were not exceptional when considered alongside reports for other drugs or relative to chance expectations.[66] Consequently, any interpretation of crude reporting frequencies should be considered with caution and in context.

Currently, the event rates for neuropsychiatric symptoms in smokers treated with varenicline in clinical practice, and whether the association is coincidental, causal or a consequence of smoking cessation itself, remain to be elucidated. According to the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition – Text Revision,* the following adverse psychological symptoms may result from nicotine withdrawal: dysphoric or depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating and restlessness.[67]

9.2 Observational Study

In an observational study in the UK, varenicline appeared to be more effective than NRT

in achieving smoking cessation.[56] In this study, 412 smokers attempting to quit received seven group support sessions over 6 weeks as well as pharmacotherapy with either NRT (n = 204) or varenicline (n = 208). The group receiving varenicline had a higher CAR over the last 2 weeks of treatment (4 weeks following the TQD) than the NRT group (OR 1.70; 95% CI 1.09, 2.67). However, the limitations of the study design preclude any firm conclusions on the relative efficacy of these pharmacotherapies. Varenicline appeared equally effective in those with (n = 111) and without (n = 301) mental illness, and no exacerbation of symptoms was observed in those with mental illness. The varenicline group experienced less severe craving than the NRT group, although there was no difference in adverse mood between the groups. The adverse event rate was higher in the varenicline group than in the NRT group, although most individuals found varenicline to be tolerable.

As previously discussed in section 7.1, treatment with varenicline improved mood and cognition in a well controlled study in a laboratory setting.[48]

10. Conclusion

Tobacco smoking is the leading preventable cause of morbidity and mortality worldwide. Only a very small proportion of smokers succeed in quitting unaided. Varenicline, a natural-product derivative produced by rational design, seems to be currently the most effective pharmacological aid to smoking cessation. The most common adverse effects of varenicline therapy in clinical trials were nausea and abnormal dreams. In post-marketing surveillance, psychiatric adverse events in individuals prescribed varenicline for smoking cessation have been reported. Currently it is unclear whether there is a causal link between varenicline therapy and psychiatric adverse events, and they may result from smoking cessation rather than varenicline therapy itself. Until new data investigating this issue become available, caution may be warranted with the use of varenicline in certain patients. However, potential use of varenicline therapy should be considered with a benefit-risk approach rather than risk aversion, given that half of individuals who continue to smoke will die prematurely of a smoking-attributable disease.

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