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A Preliminary Benefit-Risk Assessment of Varenicline in Smoking Cessation

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Abstract

Varenicline is a recently developed medication for smoking cessation, which has been available on prescription since 2006. It is a selective nicotinic acetylcholine receptor partial agonist, and is designed to reduce withdrawal symptoms and to lessen the rewards of continued smoking. Our objective in this article is to assess the efficacy of varenicline as an aid to smoking cessation and to weigh the potential benefits against the possible risks. We identified ten randomized controlled trials and one cohort study with historical controls. In total there were 7999 participants, 5112 of whom received varenicline. Eight of the trials compared varenicline with placebo for cessation, two compared it with nicotine replacement therapy and one tested extended use for relapse prevention. Three of the varenicline/placebo trials also included a bupropion arm. The recommended dosage of varenicline 1 mg twice daily more than doubled the chances of quitting at 6 months or longer, with a relative risk (RR) compared with placebo of 2.38 (95% CI 2.00, 2.84). It also outperformed bupropion (RR 1.52 [95% CI 1.22, 1.88]) and nicotine replacement (RR 1.31 [95% CI 1.01, 1.71]). A reduced dosage regimen of 1 mg daily also increased cessation (RR 1.88 [95% CI 1.35, 2.60]). In the trials,

varenicline significantly reduced craving and other withdrawal symptoms. The most frequent adverse event was nausea, occurring in 30–40% of varenicline users. However, this was generally reported at mild to moderate levels, diminished over time and was associated with attributable discontinuation rates of between 0.6% and 7.6%. Other commonly occurring adverse events included insomnia, abnormal dreams and headache. Serious adverse events were rare, with no treatment-related deaths during the treatment or follow-up phases.

Postmarketing surveillance has raised new questions about the safety of varenicline. In February 2008, the US FDA issued a public health advisory note, reporting a possible association between varenicline and an increased risk of behaviour change, agitation, depressed mood, and suicidal ideation and behaviour. They have required the manufacturers to revise the labelling of varenicline and the Summary of Product Characteristics, and to issue a medication guide. It is arguable that much of the reported behavioural and mood changes may be associated with nicotine withdrawal, although some effects occurred in people who continued to smoke while taking the medication. 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.

Smoking increases the risk of heart disease, stroke, cancers, respiratory disorders and complications of pregnancy. About half of all continuing smokers in the US and UK will die prematurely of tobacco-related diseases.[1,2] By 2030, it is predicted that tobacco will be the single biggest cause of death, with an estimated 10 million smokers worldwide dying of tobacco-related illnesses.[3] Smoking prevalence in the developed world is estimated to be at approximately 35% for men and 22% for women, and in the developing world 50% for men and 9% for women.[4] Smoking prevalence remains stable in the US at approximately 21%, despite the national health objective of reducing it to 12% by 2010.[5] This is comparable to the 2006 UK prevalence of 22%.[6]

Approximately 70% of smokers report that they would like to give up smoking, with nearly 90% of those citing concerns about their health as the main reason. Just under half of all US smokers report making a quit attempt in any given year. These efforts are largely unassisted and unsuccessful, with a probable long-term success rate of approximately 2–3%.[7,8] Even for long-term smokers, there are substantial health benefits in giving up smoking. Smokers who quit before the age of 50 halve their risk of dying in the next 15 years compared with continuing smokers.[9] After 10 years of abstinence, the risk of lung cancer drops to approximately half that of a continuing smoker; the risk of heart attack is halved after 1 year of abstinence, and after 15 years reverts to that of someone who has never smoked.

Nicotine meets all the US Surgeon General's primary criteria for drug addiction, which state that the drug must promote compulsive use, must have psychoactive effects and must reinforce its own use (USSG).[10] Nicotine dependency is classified as a substance use disorder[11] and is ranked higher on the scale of dependency than alcohol, amphetamines, cannabis or solvents,

with only heroin and cocaine estimated to be more addictive.[12] Typically, those smokers who do manage to quit have made at least four attempts to do so before succeeding. The aim of our review is to assess the efficacy of varenicline as an aid to smoking cessation, and to weigh the potential benefits against the possible associated harms of using this drug.[13]

1. What is Varenicline?

Varenicline was developed by Pfizer Inc. in 1997,[14] and is described as a selective nicotinic acetylcholine receptor (nAChR) partial agonist. The drug is structurally related to the naturally occurring alkaloid compound cytisine, which has been shown to be an effective partial agonist for α4β2 nAChRs.[15,16] Cytisine was developed as a treatment for tobacco dependence in Eastern Europe in the 1960s, and is still commercially available in some Eastern and Central European countries and through internet sales, under the trade name of Tabex®.[17] Its manufacturers, Sopharma Pharmaceuticals, developed their phytoproduct from the plant *Cytisus Laburnum L.* (Golden Rain). A multicentre trial of cytisine for smoking cessation is currently underway,[18] and its efficacy in earlier trials has been systematically reviewed.[19]

Varenicline was approved as a prescription-only aid to smoking cessation in August 2006 by the US FDA and since then it has been used by an estimated 5.5 million smokers in the US. In December 2006 it was approved by the European Medicines Evaluation Agency, and in July 2007 by the National Institute for Health and Clinical Excellence for prescribing by the UK National Heath Service (NHS).[20,21] This makes it only the third pharmacotherapy to be licensed for smoking cessation, after nicotine replacement therapy (NRT) and bupropion.

Varenicline is marketed under the name of Chantix® in the US, and as Champix® elsewhere in the world. The recommended regimen is 1 mg twice daily for 12 weeks, with the option of an additional 12-week course if needed. The drug is available as 0.5 mg and 1 mg tablets, with the lower dose recommended for titration during the first week to minimize the risk of adverse effects. People taking the drug may remain on the lower dose if they find they cannot tolerate the 1 mg dose regimen.[22]

The main addictive agent in tobacco is nicotine. It is mediated through nAChRs, which are cholinergic receptors that form ligand-gated ion channels in cellular plasma membranes, and are selectively distributed throughout the peripheral and central nervous systems. The α4β2 receptor subtype is predominant in the human brain and is thought to be the main receptor mediating nicotine dependence.[23]

Varenicline was designed to selectively activate the α4β2 nAChRs, mimic the action of nicotine and cause a moderate and sustained release of mesolimbic dopamine.[24] This, it was suggested, should counteract withdrawal symptoms associated with reduced dopamine release during smoking cessation attempts. Because varenicline is a partial agonist at the receptor sites, it elicits some dopamine overflow but not the substantial increases evoked by nicotine (a full agonist). It is estimated that it stimulates between 30% and 60% of the dopamine flow produced by nicotine. In tandem with the agonist mechanism, its antagonist properties mean that it also blocks the reinforcing effects of a subsequent nicotine challenge on dopamine release from the mesolimbic neurones thought pivotal to the development of nicotine dependence. Therefore, any tobacco smoked by someone taking varenicline will be less rewarding.[14,23]

2. Literature Search

We searched the Cochrane Tobacco Addiction Review Group specialized register for trials, using the terms 'varenicline' or 'nicotine receptor partial agonist' and 'smoking' appearing in the title or abstract, or as keywords. This register of trials of tobacco use interventions has been developed and is regularly updated from highly sensitive electronic searching of MEDLINE, EMBASE, PsycINFO and Web of Science, together with hand searching of specialist journals, conference proceedings, and reference lists of previous trials and overviews. We also performed

additional searches of MEDLINE, EMBASE, CINAHL and PsycINFO, using the major MESH terms 'nicotinic-agonists' and 'receptors, nicotinic'. We also searched UK and US web-based clinical trial registers for ongoing and recently completed trials. We contacted the authors of ongoing studies where necessary. The primary searches were conducted in March 2008 and updated in July 2008.

2.1 Methodology

The summary effects reported here are taken from meta-analyses conducted in our Cochrane systematic review of varenicline.[25] In our assessment of the quality and findings of the trials, we have adhered where possible to the proposed Russell Standard, which defines optimal methodology for smoking cessation trials.[26] We have, therefore, used the information from trial reports to conduct intention-to-treat analyses, taking as the denominator the total number of smokers randomized to each condition, and counting those who dropped out or were lost to follow-up as continuing smokers. We preferred the most rigorous definition of abstinence (continuous or prolonged in preference to point prevalence), and we favoured biochemically verified smoking status over self-report. We also took the long-term outcome (6 months continuous abstinence rate [CAR] or longer) to be more clinically informative than the end-of-treatment findings, since this is a stronger predictor of permanent cessation and is likely to deliver the greatest health benefits.[27] However, in this review we have also sought to address the key findings reported by the trials.

All the trial reports have presented their findings as odds ratios, i.e. [intervention group quitters/intervention group non-quitters]/[control group quitters/control group non-quitters]. We have converted these findings into relative risks (RRs), i.e. [intervention group quitters/all intervention participants]/[control group quitters/all control group participants]. RRs are always slightly lower than odds ratios, because of the higher denominators, but statistical significance and relative measures of efficacy are preserved.

3. Benefits

3.1 Smoking Cessation

We identified ten randomized controlled trials (RCTs) of varenicline, all supported and managed by Pfizer Inc. We also found one cohort study with historical controls that compared varenicline with NRT. Table I describes the characteristics of these studies, and table II describes their results.

Eight randomized, double-blinded, placebo-controlled trials evaluated varenicline for smoking cessation.[29-34,37,38] Three of these[29,30,33] also included a bupropion arm. One randomized open-label trial[28] compared varenicline with NRT but without a placebo arm. One trial[36] evaluated varenicline as an aid to relapse prevention.

Nakamura et al.,[31] Nides et al.[33] and Oncken et al.[34] were all phase II dose-ranging trials, Niaura et al.[32] was a phase II flexible administration trial, and the remaining studies were phase III intervention trials. All of the trials were multicentre studies; Gonzales et al.,[29] Jorenby et al.,[30] Niaura et al.,[32] Nides et al.[33] and Oncken et al.[34] were all set wholly in the US, Williams et al.[38] in the US and Australia, Nakamura et al.[31] in Japan, and Tsai et al.[37] in Taiwan and South Korea. Tonstad et al.[36] was set in the US, Canada and Europe, and Aubin et al.[28] in the US and in four European countries. The RCTs included 7587 participants, 4904 of whom took varenicline.

The treatment phase lasted for 6 weeks,[33] 12 weeks[29-32,34,37] or 52+ weeks.[38] The relapse prevention trial[36] used a 12-week regimen in the open-label phase but then randomized successful quitters to an additional 12-week maintenance phase of varenicline or placebo. All the trials apart from Niaura et al.[32] used a regimen of varenicline 1 mg tablets or bupropion 150 mg tablets taken twice daily. The four phase II trials also tested different permutations of dose and titration: Nakamura et al.[31] compared twice-daily dosages of 0.25 mg, 0.5 mg and 1 mg with placebo, and also stratified participants on their degree of nicotine dependence. Niaura et al.[32] allowed participants to regulate their own dose

Table I. Summary of study design for the trials included in this review

Study	Country/setting	Participants	Interventions	Outcomes
Aubin et al.[28]	24 research centres in Belgium, France, the Netherlands, UK, US Trial design: randomized, open-label, clinical trial	757 healthy adult volunteers; varenicline arm 378, NRT arm 379. No participation in a varenicline trial for previous year or use of NRT in previous 6 mo	1. Varenicline 1 mg × 2/d for 12 wk, titrated first wk 2. Nicotine patch (21 mg wk 2–6, 14 mg wk 7–9, 7 mg wk 10–11). No placebo control group[a]	1. CO-confirmed CAR for last 4 wk treatment (varenicline wk 9–12, NRT wk 8–11) 2. CO-confirmed CAR at wk 9–24 and wk 9–52 (varenicline) and wk 8–24 and wk 8–52 (NRT) 3. 7-d PP abstinence at EoT and at wk 24 and 52
Gonzales et al.[29]	19 research centres, US Trial design: RCT	1025 healthy adult volunteers, allocated to varenicline (352), bupropion (329) or placebo (344). No previous use of bupropion	1. Varenicline 1 mg 2/d 2. Bupropion 150 mg 2/d 3. Placebo inactive tablets. Treatment period was 12 wk[a]	1. Continuous validated abstinence at wk 9–12 2. Continuous abstinence at wk 9–24 and 9–52 3. 7-d PP abstinence at wk 12, 24 and 52
Jorenby et al.[30]	14 research centres, US Trial design: RCT	1027 healthy adult volunteers, allocated to varenicline (344), bupropion (342) or placebo (341). No previous use of bupropion	1. Varenicline 1 mg 2/d 2. Bupropion 150 mg 2/d 3. Placebo inactive tablets. Treatment period was 12 wk[b]	1. Continuous validated abstinence at wk 9–12 2. Continuous abstinence at wk 9–24 and wk 9–52 3. 7-d PP abstinence at wk 12, 24 and 52
Nakamura et al.[31]	19 study sites, Japan Trial design: RCT (phase II)	619 healthy adult volunteers; 515 classified as nicotine dependent. Allocated to varenicline 0.25 mg (153), 0.5 mg (156), 1 mg (156) or placebo (154)	1. Varenicline 0.25 mg 2/d 2. Varenicline 0.50 mg 2/d 3. Varenicline 1 mg 2/d 4. Placebo tablet 2/d[a]	1. Continuous validated abstinence at wk 9–12 2. Continuous abstinence at wk 9–24 and 9–52 3. 7-d PP abstinence at wk 2, 12, 24 and 52
Niaura et al.[32]	5 study sites, US Trial design: RCT (phase II)	320 healthy adult volunteers, allocated to varenicline (160) or placebo (160)	1. Varenicline 0.5 mg ad lib (minimum 0.5; maximum 2 mg/d) 2. Placebo tablets ad lib (minimum 1, maximum 4/d) Treatment period was 12 wk[a]	1. Continuous validated abstinence at wk 4–7 and 9–12 3. Continuous abstinence at wk 9–24 and 9–52 3. 7-d PP abstinence at wk 12, 24 and 52
Nides et al.[33]	7 research centres, US Trial design: RCT (phase II)	638 healthy adult volunteers, allocated to varenicline (group 1 [128], group 2 [128], group 3 [127]), bupropion (128), placebo (127). No use of NRT in previous 3 mo, or bupropion in previous 12 mo	1. Varenicline 0.3 mg 1/d for 6 wk + 1 wk placebo 2. Varenicline 1 mg 1/d for 6 wk + 1 wk placebo 3. Varenicline 1 mg 2/d for 6 wk + 1 wk placebo 4. Bupropion 150 mg 2/d for 7 wk 5. Placebo tablets 2/d for 7 wk	1. Continuous verified 4-wk abstinence for any part of treatment period 2. CQR wk 4–7; CQR from wk 4 to wk 12, 24 and 52

Continued next page

Table I. Contd

Study	Country/setting	Participants	Interventions	Outcomes
Oncken et al.[34]	10 research centres, US Trial design: RCT (phase II)	647 healthy adult volunteers, allocated to varenicline (group 1 [129], group 2 [130], group 3 [129], group 4 [130]) or placebo (129)	1. Varenicline 0.5 mg non-titrated (2/d for 12 wk) 2. Varenicline 0.5 mg titrated (wk 1 1/d, wk 2–12 2/d) 3. Varenicline 1 mg non-titrated (2/d for 12 wk) 4. Varenicline 1 mg titrated (0.5 mg 1/d for 3 d, 0.5 mg 2/d for 4 d, 1 mg 2/d wk 2–12) 5. Placebo tablets 2/d 12 wk[a]	1. Continuous verified 4-wk abstinence at wk 4–7 and 9–12 2. Continuous verified abstinence at wk 2–12 and 9–52. 3. 7-d PP abstinence throughout treatment phase and at wk 12, 24 and 52
Stapleton et al.[35]	Tobacco dependence clinic, London, UK Trial design: cohort study with historical controls	204 NRT users (May–November 2006), 208 varenicline users (January–April 2007). 28% of NRT group and 25% of varenicline group had concurrent mental illness	1. NRT group selected their preferred type and dose 2. Varenicline dose not stated, but presumably recommended dosage of 1 mg twice daily Both treatments 12 wk with seven weekly group sessions for support, dispensing and assessment	1. CO-verified prolonged abstinence (2 wk) at wk 4 post-quit date 2. Self-reported abstinence at wk 4 post-quit date
Tonstad et al.[36]	24 research centres, (6 in US, 18 in Canada, Czech Republic, Denmark, Norway, Sweden, UK) Trial design: RCT	1210 successful quitters (62.8% of initial cohort) following a 12-wk open-label course of varenicline for smoking cessation, randomized to varenicline (603) or placebo (607) for a further 12 wk	1. Varenicline 1 mg 2/d for 11 wk after 1-wk titrated dose 2. Placebo tablets[b]	1. Relapse prevention: maintenance of continuous validated abstinence at wk 24 2. Continuous validated abstinence at wk 52 3. 7-d PP abstinence at wk 24 and 52
Tsai et al.[37]	10 research centres, (5 in Taiwan, 5 in South Korea) Trial design: RCT	250 healthy adult volunteers, allocated to varenicline (126) or placebo (124)	1. Varenicline 1 mg 2/d 2. Placebo tablet × 2/d[a]	1. Continuous validated abstinence at wk 9–12 2. Continuous abstinence at wk 9–24 3. 7-d PP abstinence at wk 12 and 24
Williams et al.[38]	9 research centres (8 in US, 1 in Australia) Trial design: RCT	377 healthy adult volunteers, allocated to varenicline (251) or placebo (126)	1. Varenicline 1 mg 2/d, titrated for the first wk 2. Placebo inactive tablets. Treatment for 52 wk	1. Safety of smokers treated continuously with varenicline over 52 wk, measured at wk 53 by level and tolerability of adverse events and incidence of SAEs 2. 7-d CO-verified PP abstinence at all visits

a All received a self-help booklet and brief counselling at each visit. Regular face-to-face and clinic support.

b All received brief counselling at each visit. Regular face-to-face and clinic support.

Ad lib = as much as needed, when needed (*ad libitum*); **CAR** = continuous abstinence rate; **CO** = carbon monoxide; **CQR** = continuous quit rate; **EoT** = end of treatment; **NRT** = nicotine replacement therapy; **PP** = point prevalence; **RCT** = randomized controlled trial; **SAE** = serious adverse events.

after titration during the first week but required them to take a minimum of one and a maximum of four tablets daily (0.5 mg per tablet in the intervention group). Nides et al.[33] tested daily dosages of 0.3 mg, 1 mg and 2×1 mg against bupropion and placebo, while Oncken et al.[34] compared twice-daily 0.5 mg with twice-daily 1 mg, in both titrated and non-titrated regimens. Aubin et al.[28] compared the standard 12-week regimen of varenicline with 10 weeks of nicotine patch use.

All the trials provided moderately intensive behavioural support to all participants throughout the treatment and follow-up phases. This consisted of self-help materials and brief (≤10 minutes) individual counselling at clinic visits or by phone, in accordance with the Public Health Service Clinical Practice Guideline.[27]

Of the ten randomized trials, all except Williams et al.[38] reported randomization procedures in sufficient detail to be assessed as at minimal risk in their attempts to control selection bias. Aubin et al.[28] was an unblinded, open-label trial, which may have led to the differential drop-out rates after randomization, with nine participants assigned to nicotine patch declining to take part compared with two in the varenicline group. None of the trials reported any assessment of the integrity of the double-blinding procedure. For the relapse prevention trial,[36] the integrity of the

Table II. Results (quit rates) of trials included in this review. All rates are calculated as intention-to-treat measures (i.e. denominator includes all randomized, with those dropping out assumed to be continuing smokers)

Study	EoT quit rate (%)		9–24 wk (%)		9–52 wk (%)	
	varenicline	placebo	varenicline	placebo	varenicline	placebo
Aubin et al.[28][a]	55.9***	43.2	32.2	26.6	25.9*	19.8
Gonzales et al.[29]	44.0***	17.7	29.5***	10.5	21.9***	8.4
Jorenby et al.[30]	43.9***	17.6	29.7***	13.2	23.0***	10.3
Nakamura et al.[31] (1 mg)	66.7***	39.0	40.4*	28.6	35.9*	22.7
Niaura et al.[32] (ad lib 1–4 tablets daily; each tablet 0.5 mg or placebo)	39.4***	11.3	27.5***	8.8	21.9***	7.5
Nides et al.[33][b]						
0.3 mg daily	25.4*		9.5		7.9	
1.0 mg daily	31.0**	13.8	9.5	7.3	5.6	4.9
1.0 mg×2 daily	40.8***		20.8**		14.4**	
Oncken et al.[34]						
0.5 mg×2 daily	44.0***	11.6	23.6***	5.4	18.5***	3.9
1.0 mg×2 daily	49.4***		29.0***		22.4***	
Stapleton et al.[35][c]	72.1*	61.3	No assessment beyond 4 wk after quit date			
Tonstad et al.[36][d]			70.5***	49.6	43.6	36.9
Tsai et al.[37]	59.5***	32.3	46.8***	21.8	No 52-wk assessment	
Williams et al.[38] 7-d point prevalence abstinence	Interim rates not reported in detail				36.7	7.9

a Comparator was NRT, without a placebo group.

b Timepoints are wk 4–7, wk 4–24 and wk 4–52.

c Timepoint was 4 wk, with NRT the comparator and no placebo group.

d Double-blind phase only.

Ad lib = as much as needed, when needed (*ad libitum*); **EoT** = end of treatment; **NRT** = nicotine replacement therapy; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

double-blind phase may be questionable, since all randomized participants were accustomed to varenicline from the open-label phase.

All the varenicline trials, except Williams et al.,[38] defined their abstinence outcome as 'continuous' and all the trial outcomes were biochemically verified by expired carbon monoxide (CO) levels ≤10 parts per million. The primary outcome for Nides et al.[33] was the continuous quit rate (CQR), which was defined as any 4-week period of abstinence during the treatment period. Both Niaura et al.[32] and Oncken et al.[34] defined their primary outcome as the CQR for weeks 4–7 and weeks 9–12. In the remaining trials, the CAR was measured at weeks 9–12 and 9–24, and also at weeks 9–52 in all trials except Tsai et al.[37] 'Continuous abstinence', as defined in these trials, excludes the first 8 weeks of treatment, and could more accurately be termed 'prolonged abstinence'.[39] All of the trials (apart from Tonstad et al.,[36] whose participants were all, by definition, quitters at 12 weeks, and Tsai et al.,[37] who followed participants for 24 weeks only) also reported CO-verified 7-day point prevalence abstinence at the same three time-points (end of treatment, 24 and 52 weeks).

3.1.1 Varenicline versus Placebo

All eight trials that compared varenicline with placebo for smoking cessation found statistically significant results in favour of the intervention at all of the selected endpoints. The Nides et al.[33] and Nakamura et al.[31] trial comparisons chosen for our primary meta-analysis were between the 1 mg twice-daily group and the placebo group, since this matched the regimen eventually recommended for clinical practice. We included the Niaura et al.[32] trial in our meta-analyses since the mean daily modal dose was comparable to the other trial regimens (varenicline 1.35 mg and placebo 1.63 mg). For the Oncken et al.[34] trial we combined the 1 mg titrated and non-titrated groups for the meta-analysis, since titration did not affect cessation rates. We excluded the Williams et al.[38] trial from the meta-analysis since the methods of randomization and allocation concealment were not reported, participants had continued receiving treatment or placebo up to and beyond the 52-week assessment, and they were assessed for point prevalence rather than continuous abstinence. Analyses that included the Williams et al.[38] data also demonstrated significantly increased heterogeneity.

The pooled RR for validated continuous abstinence 6 months or more from the start of the intervention (longest follow-up), based on seven cessation trials of varenicline versus placebo,[29-34,37] was 2.38 (95% CI 2.00, 2.84).[25] This was almost identical to the RRs for continuous abstinence at the 9- to 12-week end-of-treatment assessment (2.43; 95% CI 2.16, 2.74) and at 24 weeks (2.40; 95% CI 2.06, 2.81),[25] indicating no important difference in relapse rates between treatment and control groups once the treatment phase was complete.

Quit rates at the longest follow-up (24+ weeks) for the 1 mg twice-daily dose ranged from 14.4% to 46.8% in the varenicline groups, compared with 3.9% to 22.7% in the placebo groups (see table II). The two Asian trials[31,37] reported higher quit rates across the board than the American- and European-based trials. This may in part be attributable to the relatively high proportion of participants making their first ever quit attempt in these trials, i.e. 36% in the Japanese trial and 51% in the South Korean/Taiwanese trial, compared with approximately 10% in the non-Asian trials.

We also assessed the efficacy of the lower dose regimen, pooling the 9–52 week CARs for the Nakamura et al.,[31] Nides et al.[33] and Oncken et al.[34] trials, all of which tested the effects of administering 1 mg daily (2×0.5 mg[31,34] or 1×1 mg[33]). The RR for this regimen was 1.88 (95% CI 1.35, 2.60),[25] indicating a more modest but still beneficial effect of the lower dose treatment. This level of efficacy is comparable to the RRs of quitting with NRT[36] (RR 1.58; 95% CI 1.50, 1.66) or with bupropion[38] (RR 1.75; 95% CI 1.58, 1.94). This finding offers a valid alternative for users of varenicline who have difficulty in tolerating the adverse effects of the medication at full dose.

The long-term safety trial[38] found a 53-week follow-up RR for 7-day point prevalence abstinence of 4.91 (95% CI 2.56, 9.42).[25]

3.1.2 Varenicline versus Bupropion

Bupropion is licensed for use as a smoking cessation therapy in the UK (Zyban®) and US (Welbutrin®), where it is also used as an antidepressant. It is a prescription-only treatment, and carries a 1 : 1000 risk of causing seizures. The RR of quitting with bupropion compared with placebo is 1.75 (95% CI 1.58, 1.94), based on a meta-analysis of 31 trials (9940 people).[40]

As well as the varenicline/placebo comparison, three trials[29,30,33] also compared varenicline with bupropion. The pooled RR for varenicline versus bupropion for continuous abstinence at 52 weeks (longest follow-up) was 1.52 (95% CI 1.22, 1.88).[25] While the Gonzales et al.[29] and Jorenby et al.[30] trials excluded any former users of bupropion, the Nides et al.[33] trial only excluded those participants who had used it during the previous 12 months. This yielded a rate of previous usage across the five groups in the Nides et al.[33] trial of between 13% and 20.6%. Although the results of this trial showed bupropion doubling the chances of quitting compared with placebo at 12 weeks, at later endpoints (24 and 52 weeks) it failed to demonstrate significant separation from placebo. We conducted a sensitivity analysis to test the effect of excluding the Nides et al.[33] trial from the varenicline/bupropion meta-analysis, but the RR remained statistically significant at 1.46 (95% CI 1.17, 1.83).

3.1.3 Varenicline versus Nicotine Replacement Therapy

Nicotine replacement is the most widely used pharmacotherapy for smoking cessation, with its efficacy and safety well established in clinical trials. It comes in a variety of formulations (chewing gum, skin patch, nasal spray, inhalator, lozenge and microtab) and can be bought over the counter in many countries. The RR of quitting with NRT compared with placebo is 1.58 (95% CI 1.50, 1.66), based on a meta-analysis of 110 trials (43 040 people).[41]

The randomized open-label trial[28] comparing varenicline with nicotine patch found a RR for varenicline compared with NRT at week 52 of 1.31 (95% CI 1.01, 1.71).

A recent cohort evaluation study,[35] using historical controls, compared varenicline with NRT in a London smoking cessation clinic. This pragmatic study of a clinic population included smokers with concurrent mental illness (111/412), which is a group usually excluded from clinical trials. Because the final assessment was at 4 weeks after the quit date, we did not include this study in our meta-analyses. However, the results for those receiving psychiatric treatment were reassuring, with no evidence of harm from the use of varenicline and with similar 5-week abstinence rates to the rest of the cohort (71.7% vs 72.1%). The study demonstrated a benefit of varenicline over single NRT therapy at 4 weeks (RR 1.25; 95% CI 1.05, 1.48). A comparison between varenicline and combination NRT therapy at 4 weeks in this trial failed to detect a benefit of varenicline (RR 1.09; 95% CI 0.91, 1.30).

3.1.4 Varenicline for Relapse Prevention

Tonstad et al.[36] conducted a two-phase study of relapse prevention, with an open-label phase of 12 weeks of varenicline, followed by a randomized, double-blind phase in which successful quitters were assigned either to a further 12 weeks of varenicline or to placebo for relapse prevention. The RR at the end of the double-blind treatment phase (24 weeks) was 1.42 (95% CI 1.29, 1.56) in favour of the varenicline group. This effect declined over time but remained statistically significant to the end of the follow-up period, with a RR at 52 weeks of 1.18 (95% CI 1.03, 1.36). A relapse prevention trial with follow-up beyond 12 months may be needed to test whether the apparent convergence of intervention and placebo groups continues to the point of no significant effect.

3.2 Craving and Withdrawal

Smokers who attempt to quit are likely to experience withdrawal symptoms, including depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty in concentrating, restlessness or impatience, decreased heart rate and increased appetite or weight gain.[11] Varenicline's properties as a partial agonist, causing moderate activation of the $\alpha4\beta2$ nAChRs, would

be expected to mitigate craving and withdrawal symptoms, while its antagonist properties in blocking nicotine binding could be expected to lead to reduced smoking satisfaction and psychological reward in those who continue to smoke while taking the drug. The varenicline trials that tested craving, withdrawal and the reinforcing effects of smoking used the Minnesota Nicotine Withdrawal Scale (MNWS) to assess craving and symptoms of withdrawal; craving, as measured on the Brief Questionnaire of Smoking Urges (QSU-B) and enjoyment of concurrent smoking, as measured on the modified Cigarette Evaluation Questionnaire (mCEQ).

All the trials that measured craving and withdrawal symptoms reported significant reductions in craving ('desire or craving to smoke' on the MNWS and total craving score on the QSU-B) among participants using varenicline compared with those receiving placebo. Four trials that contributed data to a meta-analysis[29-31,37] yielded a RR reduction of 0.61 (95% CI 0.57, 0.66) in the scored measure of craving (range of scores 0–4) in favour of varenicline. The three phase II trials[31,33,34] that compared different doses of varenicline against placebo all confirmed a dose-response relationship for the reduction of craving. Lower doses of varenicline (0.25 mg and 0.5 mg in the study by Nakamura et al.,[31] 0.5 mg in the study by Oncken et al.,[34] and 0.3 mg and 1 mg once daily in the study by Nides et al.[33]) all conferred a significant benefit in the reduction of craving, but not as great a reduction as the 1 mg twice-daily optimal dose. The Niaura et al.[32] trial, which allowed participants to regulate their own dose, demonstrated a consistent benefit of varenicline over placebo in reducing withdrawal symptoms and the urge to smoke. Those who continued to smoke while receiving varenicline reported significantly less satisfaction and enjoyment than did those receiving placebo.

4. Risks

4.1 Study Populations

At this stage in the development of varenicline, most of the data on adverse outcomes comes from controlled clinical trials conducted by the manufacturers of the drug. In accordance with usual practice, the trial protocols excluded those smokers perceived to be at increased risk of adverse events or unpredictable outcomes. Therefore, the current findings may not be generalizable beyond this atypically 'healthy' population of trial participants. The exclusion criteria routinely ruled out adolescents and the elderly, the very underweight or overweight, pregnant and nursing women, those at risk of conceiving, people with serious or unstable disease (e.g. cardiovascular disease, chronic respiratory impairment, cancer, renal or hepatic disease, uncontrolled hypertension) and people with depression, psychosis, bipolar disorder, drug or alcohol dependence, or eating disorders. Anyone who had recently used NRT, clonidine or nortriptyline was also excluded.

Any consideration of the safety of varenicline must allow for the fact that we currently lack extensive evidence from pragmatic community-based studies. Stapleton et al.[35] is the only study reported so far that has included and assessed smokers attempting to quit with varenicline while diagnosed with mental illness. Trials are currently planned or underway to test the safety, tolerability and efficacy of varenicline in various subgroups and populations, including patients with co-morbidities (cardiovascular disease, cancer, chronic obstructive pulmonary disease, Alzheimer's disease, schizophrenia, depression, substance abuse), pregnant women and adolescents, and to assess treatment in combination with telephone or internet counselling, and in combination with bupropion, nicotine patch, naltrexone or mecamylamine, to treat smokeless tobacco use and as an aid to relapse prevention.[42]

4.2 Adverse Events

In the trials, adverse events were monitored weekly during treatment for the first 7 weeks,[29,30,33,34] from weeks 1 to 7 and at week 12,[32] or weekly throughout treatment.[28,31,37] Tonstad et al.[36] monitored at week 13 (end of the open-label phase) and at week 25 (end of the double-blind phase) and Williams et al.[38] monitored weekly from weeks 1 to 8 and then

monthly to week 52. The trials reported only those adverse events occurring in at least 5% of the varenicline groups and at higher rates than in the placebo groups.

The main reported adverse effect of varenicline was nausea. The proportion of participants reporting nausea associated with varenicline use was reported at approximately 29% in the Gonzales et al.[29] and Jorenby et al.[30] trials, 37% in the Aubin et al.[28] trial and 40% in the Williams et al.[38] trial, with attributable discontinuation rates from 0.6% to 7.6%. The exception to this pattern was Niaura et al.,[32] who reported nausea in only 13% of the varenicline group, making it the fourth most commonly occurring adverse event in that trial after disturbed sleep, headache and respiratory tract infections. The authors attributed this reduced incidence to lower dose administration (mean daily dosage 1.35 mg) but commented that the placebo group also experienced reduced levels of nausea compared with similar groups in other trials. The evidence from the Asian trials was inconclusive, with the Japanese varenicline group[31] reporting lower rates of nausea than their American counterparts (24.4% vs 29%), while the South Korean/Taiwanese group[37] reported higher rates (43.7%).

The three phase II trials that used a range of dosage regimens found a dose-response relationship for the incidence of nausea: rates ranged from 17.5% (0.3 mg daily) to 52% (1 mg twice daily) in the Nides et al.[33] trial. In the Oncken et al.[34] trial, rates of nausea were significantly higher in the 1 mg twice-daily non-titrated group (41.9%) and in the titrated group (34.9%) than with placebo (14.9%; $p < 0.001$ for both). In the 0.5 mg twice-daily non-titrated group the incidence of nausea was 22.6% ($p = 0.12$ compared with placebo), while in the 0.5 mg titrated group the rate was comparable to the placebo group at 16.3%. The Japanese trial,[31] reporting only on the highly nicotine-dependent group (515/619), similarly identified a dose-response association between the occurrence of nausea and the level of medication, with an incidence of 7.2% in the 0.25 mg group, rising to 9.7% in the 0.5 mg group and 24.4% in the 1 mg group, compared with a placebo group rate of 7.8%.

In the relapse prevention study,[36] nausea was reported in 33.5% of varenicline users during the open-label phase; once the successful quitters were randomized to varenicline or placebo, rates of nausea fell to 1.2% in the varenicline group and 0.7% in the placebo group. This virtual elimination of nausea as an adverse event may suggest that habituation over 12 weeks of treatment had resolved the condition. However, it is also plausible that those who suffered most with adverse events during the open-label phase may not have successfully completed treatment or, having quit, were less likely to accept the invitation to take part during the double-blind phase.

In the two phase III bupropion trials,[29,30] an average of 9.5% of patients in the varenicline groups discontinued treatment but remained in the trial for follow-up, compared with an average of 14% in the bupropion groups and 8% in the placebo groups. Discontinuation rates for any adverse event were highest in the Williams et al.[38] long-term safety trial, at 28.3% in the varenicline group and 10.3% in the control group.

Meta-analyses of the four main adverse events in the varenicline versus placebo groups yielded RRs of 3.21 (95% CI 2.71, 3.80) for nausea, 1.50 (95% CI 1.26, 1.79) for insomnia, 2.79 (95% CI 2.09, 3.72) for abnormal dreams and 1.20 (95% CI 1.00, 1.45) for headache.[25]

4.3 Serious Adverse Events

There were no treatment-related deaths in any of the intervention groups during treatment or follow-up phases. Non-fatal serious adverse events (SAEs) occurred in all ten trials and in the cohort study. The details of each study by study arm are given in table III.

Aubin et al.[28] reported ten SAEs during treatment phase (two in the varenicline group and eight in the nicotine patch group) and three during the follow-up phase (two in the varenicline group); two were attributed to treatment. Gonzales et al.[29] reported 14 (four in the varenicline group, one of which may have been attributable to study medication). Jorenby et al.[30] reported 12 in the treatment and five in the follow-up phases for the intervention groups (one event in the varenicline

Table III. Serious adverse events (SAEs) by study and study arm

Study	Placebo	Varenicline	Bupropion	NRT
Aubin et al.[28]		Depression[a] Constipation		Bile duct cancer + sepsis; Gastrointestinal bleeding 2 × myocardial infarcts Salivary gland tumour 2 × chest pain Aggravation of knee trauma
Gonzales et al.[29]	Lung cancer Acute myocardial infarct Schizophrenia (acute exacerbation) Chest pain Urinary tract infection Atrial fibrillation Under-arm chest pain	Abdominal pain Atrial fibrillation[a] Pneumonia Possible stroke	Cholecystitis and septic shock Headache *Grand mal* seizure[a]	
Jorenby et al.[30]	Five SAEs, no further details	Cancer (lung or brain) Acute coronary syndrome Chest pain Dehydration + periorbital cellulites Acute psychosis, emotional lability Vertigo, ↑ BP, chest pain[a]	Ectopic pregnancy Angiodoema[a] Gunshot wound Post-op bleeding Lower leg pain Breast cancer	
Nakamura et al.[31]	Three SAEs, no further details	Cholecystitis[a] Angina pectoris[a] Eight SAEs, no further details		
Niaura et al.[32]	None	None during treatment In 30 d post-treatment Myocardial infarct Ventricular fibrillation Spontaneous abortion		
Nides et al.[33]		Transient ischaemic attacks[a]	Bloody diarrhoea Syncope[a] Two convulsions[a]	
Oncken et al.[34]	Syncope Suicide attempt	0.5 × 2 nt: syncope 0.5 × 2 t: duodenal ulcer, cholesteatoma, unstable angina, post-road traffic accident seizure 1.0 mg × 2: paroxysmal supraventricular tachycardia, aseptic meningitis, multiple sclerosis, carcinoid colon cancer		

Continued next page

Table III. Contd

Study	Placebo	Varenicline	Bupropion	NRT
Stapleton et al.[35]		Headaches, blurred vision (eye surgery) Severe psychological reaction		
Tonstad et al.[36]	Five SAEs in D-B phase	Three deaths: one suicide 27 d after D-B phase; one lung cancer 19 d after D-B phase; one rectal sarcoma 197 d after last dose 20 SAEs during or after open-label phase; 10 SAEs in D-B phase		
Tsai et al.[37]	Three traffic accidents	Peritonitis/acute appendicitis Acute pyelonephritis Unstable angina[a]		
Williams et al.[38]	Three SAEs, no further details	15 SAEs, including bilateral subcapsular cataracts[a]		

a Possibly or probably attributable to study medication.

BP = blood pressure; **D-B** = double-blinded; **NRT** = nicotine replacement therapy; **nt** = non-titrated group; **post-op** = post-operative; **t** = titrated group; ↑ indicates increased.

group attributed to study medication). Nakamura et al.[31] reported ten SAEs across the three varenicline groups (two of them possibly treatment related), compared with three in the placebo group. Niaura et al.[32] reported no SAEs in either group during the treatment phase and three events during the follow-up phase in the varenicline group that were not considered to be associated with the medication. Nides et al.[33] noted one SAE in the varenicline group that may have been linked to study medication. Oncken et al.[34] reported nine SAEs in the varenicline group during the treatment phase and two in the follow-up phase. Stapleton et al.[35] recorded two SAEs in the varenicline group, both of which had been referred to the Medicines and Healthcare products Regulatory Agency (MHRA) monitoring system. Tonstad et al.[36] reported 20 non-fatal SAEs during the open-label phase, followed by ten in the double-blind varenicline group and five in the double-blind placebo group. Tsai et al.[37] reported three SAEs in each of the groups, one of which was deemed possibly treatment-related. Williams et al.[38] reported 18 SAEs (15 in the varenicline group and 3 in the control group, with 4 consequent discontinuations), one of which was attributed to the study medication by the investigator. Events that were probably or possibly related to varenicline usage included atrial fibrillation, angina pectoris, transient ischaemic attacks, depression, cholecystitis and bilateral subcapsular cataracts. However, the incidence of suchevents was extremely low and did not compromise the decision to license the drug for general use.

4.4 Postmarketing Surveillance Events

Postmarketing surveillance has recently raised further safety concerns. In February 2008, the FDA issued a public health advisory note[43] that reported that an association between varenicline and an increased risk of behaviour change, agitation, depressed mood, suicidal ideation and behaviour ''appears increasingly likely''. The FDA also confirmed that the labelling of varenicline had been changed accordingly and that the

Summary of Product Characteristics had also been revised[22] to include the following warning:

''Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. These symptoms have also been reported while attempting to quit smoking with Champix. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly.''

The FDA revised its online advice[44] in May 2008 to read as follows:

''The issues described in this communication have been addressed in the product labeling and FDA has approved the Medication Guide. If either you, your family or caregiver notice agitation, depressed mood, or changes in behavior that are not typical for you, or if you have suicidal thoughts or actions, stop taking Chantix and call your doctor right away.''[45]

Also in May 2008, the US Institute for Safe Medication Practices[46] (a non-profit and non-governmental organization) issued strong warnings to people taking varenicline while operating aircraft, heavy vehicles and other machinery, or in any situation where a lapse in alertness or motor control could lead to massive, serious injury. The advice was based on their analysis of FDA post-marketing surveillance data, but may have been a flawed assessment as it failed to establish causality or the relationship between rates of varenicline use and the incidence of the reported events. Pfizer Inc.[47] is currently examining the same data, using a disproportionate analysis approach.

In December 2008, the Australian National Prescribing Service Limited,[48] while acknowledging varenicline's efficacy for smoking cessation, also recommended caution in the use of the drug, particularly for users with a history of psychiatric illness or seizure disorders.

Although much of the reported behavioural and mood changes may be associated with nicotine withdrawal, some effects occurred in people who continued to smoke while taking the medication. However, it is difficult to quantify the risk of such events from these reports. Smokers are known to be at increased risk of suicide compared with non-smokers, and heavy smokers to be at higher risk than light smokers. However, a recent study points out that controlling for mental disorders, including substance dependency, reduced the association between smoking and suicidal thoughts and behaviours to the point where it was no longer statistically significant. The study was not able to determine whether the link was based on common cause (i.e. both smoking and suicidal behaviours are consequences of mental and substance use disorders) or on a mediation mechanism (i.e. smoking has a causal effect on suicidal behaviours that is mediated by mental disorders).[49] Foulds[50] observes that, given the rates of attempted suicides each year in the US (approximately 1/200 non-smokers and 1/100 smokers), the number of US smokers (45 million), the proportion who make a quit attempt each year (between one-third and one-half) and the number of smokers who use varenicline to try and quit each year (2 million), we might expect in any given year that many thousands of smokers will use the drug and will also make a concurrent suicide attempt without there necessarily being a causal connection between the two.

A summary of the current research agenda of the Chantix® medical team, regarding the safety profile of varenicline, was recently posted on the Society for Research on Nicotine and Tobacco discussion list. Their projects include an in depth analysis of neuropsychiatric adverse events in all nine completed, placebo-controlled clinical trials, which involved approximately 2700 patients treated with Chantix®; the inclusion of the Columbia Suicide Severity Rating Scale in current and future trials of varenicline; systematic epidemiological and intervention trials to better distinguish between adverse events associated with nicotine withdrawal and those associated with drug treatments; and the funding of independent investigator-initiated research into the safety and efficacy of varenicline in different subpopulations, such as depression, alcohol and schizophrenia (Flammer M, Senior Medical Director, Pfizer, personal communication).

In the UK, the MHRA, which co-ordinates the yellow card system for reports of adverse drug reactions, has recorded (to June 2008) 7384

reports for varenicline, including 2286 psychiatric disorders, 1587 gastric disorders and 1029 nervous system disorders. Twenty-one fatalities among varenicline users have been reported through this system, including eight suicides. There were also 14 suicide attempts and 187 reports of suicidal ideation.[51] These figures should be considered in the context of a prescribing pattern in England during 2007 (the year in which it was approved for NHS use in the UK) of >450 000 prescriptions dispensed for varenicline.[52] The MHRA points out that the data must be viewed with caution, since "healthcare professionals are asked to report even if they only have a suspicion that the medicine may have caused the adverse drug reaction. The fact that a report has been submitted does not necessarily mean that the medicine has been proven to cause a reaction."[53]

5. Conclusions

In randomized trials, varenicline increased by 2- to 3-fold the chances of stopping smoking, compared with placebo. The benefit remained stable beyond the treatment phase, with scant evidence of differential relapse rates over the long term (up to 12 months), compared with the placebo group. The treatment and follow-up phases included regular monitoring and brief advice at every contact, either face to face or by telephone, in accordance with public health guidelines.

These trials evaluated a standard dose administration regimen of 1 mg twice daily. There is some evidence from phase II trials that a lower dose (0.5 mg twice daily) can also assist with quitting and may reduce the incidence of withdrawal symptoms in the first few weeks. Low-dose treatment nearly doubled the chances of quitting, making it comparable to results achieved for NRT and bupropion.

In direct comparisons, varenicline at standard dose outperformed both NRT and bupropion, and improved the chances of quitting by approximately 50%. Like bupropion, varenicline is currently a prescription-only drug, making it less readily available than NRT. That seems likely to remain the case while varenicline's safety profile continues to be developed and tested.

There is consistent evidence that varenicline reduces levels of craving and withdrawal symptoms, and that it also reduces the physical and psychological satisfaction and rewards of smoking in those who continued to smoke while receiving treatment.

Users are at increased risk of adverse effects during the first few weeks of treatment. These may include nausea, abnormal dreams, insomnia and headaches. However, these are usually at mild to moderate levels, with low attributable rates of discontinuation. Titration during the first week is recommended, and appears to reduce the level of discomfort. For those who find the adverse effects unacceptable, a lower dose may be better tolerated and is still likely to roughly double the chances of quitting. Trial participants who were free to regulate their own dose in response to adverse effects settled on a mean dosage of 1.35 mg daily, i.e. between the recommended low and standard regimens.[32]

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.

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