

Research Review

PRODUCT REVIEW

Varenicline [Champix®]

About the Reviewer



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Hayden is based both in New Zealand, where he is a Senior Lecturer in the School of Public Health and Psychosocial Studies, Auckland University of Technology and an Honorary Senior Lecturer in the School of Population Health at the University of Auckland, and in London, where he is a Senior Clinical Research Fellow post within the UK Centre for Tobacco Control Studies Queen Mary University of London.

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About Research Review

Research Review is an independent medical publishing organisation producing electronic publications in a wide variety of specialist areas.

Product Reviews feature independent short summaries of major research affecting an individual medicine or technique. They include a background to the particular condition, a summary of the medicine and selected studies by a key NZ specialist with a comment on the relevance to NZ practice.

Research Review publications are intended for New Zealand medical professionals.

Varenicline tartrate (Champix®) is a medication specifically developed for use in smoking cessation and has been available in New Zealand since 2007. It has been fully funded since 1st November 2010 via PHARMAC (New Zealand Pharmaceutical Management Agency) through a Special Authority application from a general practitioner. This selective nicotinic acetylcholine receptor partial agonist is designed to reduce withdrawal symptoms and to lessen the rewards associated with smoking. The efficacy and tolerability of varenicline treatment for smoking cessation is discussed below.

The burden of smoking

Tobacco smoking kills around 5,000 New Zealanders every year, including deaths due to second-hand smoke.¹ On average, adults who smoke cigarettes die 14 years earlier than non-smokers.² Smoking-attributable deaths and disease are more prevalent among Māori than non-Māori non-Pacific New Zealanders; smoking contributes up to 10% to the inequalities in all-cause mortality rate between Māori and other New Zealanders.³

Smoking: The facts

- About 90% of all deaths from chronic obstructive lung diseases are attributable to cigarette smoking.⁴ In New Zealand, 79% of male deaths and 65% of female deaths are due to chronic obstructive respiratory diseases.
- Smoking is a major cause of blindness, with about 1300 people in New Zealand having untreatable blindness due to current and past smoking.⁵
- There are health risks associated with smoking that particularly affect women, including reproductive problems such as cervical cancer,⁶ earlier menopause and a diminished ovarian reserve.⁷
- Women who smoke during pregnancy, compared to women who are nonsmokers, are more likely to have complications during pregnancy,^{8,9} suffer a miscarriage,^{8,9} produce a lower birth weight baby¹⁰ and face a greater risk of foetal and infant mortality.
- Maternal smoking has been linked to birth defects,¹² an increased risk of childhood cancer¹³ and an increased incidence of respiratory illnesses in infants.^{14,15}
- The more the mother smokes after her child is born, the more likely her baby might die from sudden unexplained death in infancy than a baby with a non-smoking mother.¹⁶
- Exposure to second hand smoke worsens asthma symptoms in children¹⁷ and is associated with middle ear effusion.¹⁸
- The contraceptive pill has a combined effect with smoking, increasing the risk of dying of heart attacks and strokes.¹⁹
- Evidence suggests that women are at higher risk (by 1.5 to 2 times) than men of developing smoking-induced lung cancer.²⁰ It appears that cigarette smoking predisposes women to a greater risk of osteoporosis and possible fracture.²¹

Benefits of smoking cessation

Smoking cessation is a very important treatment and disease-prevention strategy, offering not only immediate health benefits to those who already have smoking-related diseases but also future health benefits to all smokers. Smoking cessation reduces overall mortality, cardiovascular mortality and cancer-related mortality within 5 years of quitting, and, in some cases, the risks are reduced to the levels of never smokers.²² The risk of smoking-induced cardiovascular disease is almost completely reversed by smoking cessation, making it potentially the single most effective intervention available for those at risk of and with existing cardiovascular disease.²²

The earlier a person stops smoking the better; however, benefits can be gained at any age. Stopping smoking during pregnancy is associated with a large number of benefits for not only the foetus and pregnancy itself, but also for the mother and infant. Encouraging smoking cessation in women of child bearing age is a priority.

Cessation support in New Zealand

According to the New Zealand smoking cessation guidelines, the key components of cessation support that have been shown to be most effective include the delivery of multi-session behavioural support and stop-smoking medication.²³ Four different pharmacotherapies exist for the treatment of nicotine dependence;²⁴ all are now subsidised. Smoking cessation treatments are very cost-effective and in fact are more cost-effective than most other public health and clinical activities.²⁵

Nicotine Replacement Therapy

Nicotine replacement therapy (NRT) is a safe and effective pharmacotherapy for smoking cessation. It replaces some of the nicotine that smokers would have otherwise received from tobacco and thereby reduces the severity of tobacco withdrawal symptoms associated with smoking cessation. NRT includes a range of delivery systems (patches, gum, sublingual tablets, nasal spray and inhalators); the patches, gum and lozenges are available in New Zealand under subsidy and can be obtained on prescription or *Quitcards* (the nicotine replacement exchange card system). The other types of NRT are not subsidised in New Zealand, but are available through pharmacies, with the exception of nasal spray which is not sold in New Zealand.

Key Points: NRT^{23,26,27}

NRT approximately doubles the chances of long-term abstinence.

The number needed to treat to benefit is 23 (95% CI 20 to 27).²⁸

NRT appears to be as effective as bupropion and nortriptyline.

The choice of NRT product can be guided by client preference. Healthcare workers should advise people that:

- oral products have an unpleasant taste initially
- use of the gum requires a special technique (chew, then rest in the side of the mouth, then chew)
- patches can leave a slight reddening and itching of the skin and they should be put on a different site each day

More dependent smokers (e.g. those who smoke within an hour of waking) should use the higher dose oral products (e.g. 4mg gum and 2mg lozenge, instead of the 2mg and 1mg strengths).

Smokers of 10 or more cigarettes a day can start on full-strength patches.

NRT should be used for 8 to 12 weeks, but a small number of smokers may need to use it for longer (some 5% may continue to use it for up to a year).

Combining NRT products (e.g. patch and gum, or patch and lozenge) increases abstinence rates compared with just a single product.

There are no safety concerns with combining NRT products.

NRT can be considered for use in pregnant women who are having difficulty becoming smokefree. Intermittent NRT (e.g., gum, inhaler, microtab and lozenge) are preferred products; however, patches can be considered if these oral products are not tolerated (daytime use only).

NRT can be used by young people (aged 12–18 years) who are dependent on nicotine and it is believed that the NRT may help with stopping smoking.

NRT can be safely used by people with cardiovascular disease.

Bupropion

Bupropion is an antidepressant medication that almost doubles the chances of long-term abstinence from smoking.²⁹ Its activity in smoking cessation is independent of its antidepressant effects. Like NRT, it primarily helps by reducing the severity of withdrawal symptoms, but it may also have other actions that help people stop. Bupropion appears to have similar efficacy to NRT and nortriptyline. In a Cochrane meta-analysis of data from 3 trials (1622 participants), varenicline was associated with higher long-term cessation rates, with a pooled risk ratio (RR) for varenicline versus bupropion at 1 year of 1.52 (95% CI 1.22 to 1.88).²⁸ There are a number of contraindications and cautions that need to be considered before use (e.g., bupropion is contraindicated in patients with hypersensitivity to bupropion or any of the other components of the preparation, and is also contraindicated in patients with a current seizure disorder or any history of seizures, and should be used with caution in patients with liver impairment, and with extreme caution in patients with severe hepatic cirrhosis.³⁰ Bupropion is fully subsidised in New Zealand and only available on prescription.

Key points: Bupropion^{23,29}

Bupropion almost doubles the chances of long-term abstinence.

The number needed to treat to benefit is 20 (95% CI 16 to 26).²⁸

Insufficient evidence exists as to the efficacy of bupropion in combination with any other smoking cessation medications.

Bupropion appears to be safe and effective in patients with stable cardiovascular and respiratory disease.

There are a number of contraindications and cautions that need to be considered before use.

Nortriptyline

Nortriptyline is a tricyclic antidepressant that has been shown to be as effective as bupropion and NRT in aiding smoking cessation. Its action in helping people to stop smoking is independent of its antidepressant effects, and it works in those without a history of depression.

The main concern with using nortriptyline, like other antidepressants in its class, is the risk of adverse cardiovascular effects. There are a number of contraindications and precautions with its use. Nortriptyline is fully subsidised in New Zealand and only available on prescription.

Key Points: Nortriptyline²³

Nortriptyline almost doubles the chances of long-term abstinence.

There is insufficient evidence to recommend the combination of nortriptyline with any other smoking cessation medications.

There are a number of contraindications and cautions that need to be considered before use.

Nortriptyline should not be used by pregnant women or adolescents who smoke.

People with cardiovascular disease should use nortriptyline with caution.

Varenicline

Varenicline (Champix) is a partial agonist of $\alpha_4\beta_2$ nicotinic acetylcholine receptors (nAChRs) and binding results in dopamine release in the reward pathways of the brain. Although varenicline has less dopaminergic activity than nicotine, it is sufficient to reduce tobacco withdrawal symptoms, thereby making it easier to stop smoking. Varenicline also exhibits antagonist effects, in that it dose-dependently blocks nicotine-induced dopamine increase, theoretically decreasing the reinforcing effects of smoking satisfaction and psychological reward associated with nicotine use.³¹ The Cochrane Group pooled the results of 10 studies (involving a total of 4443 participants) comparing the effects of varenicline with those of placebo for quit rates lasting 6 months or longer; these data demonstrate a pooled RR of 2.31 (95% CI 2.01 to 2.66).²⁸ Pooled results from three trials also show a RR for varenicline versus bupropion at 1 year of 1.52 (95% CI 1.22 to 1.88).²⁸

Key Points: Varenicline²³

Varenicline almost triples the chances of long-term abstinence.

The number needed to treat to benefit is 10 (95% CI 8 to 13).

Pooled data from three trials comparing varenicline with bupropion show higher quit rates with varenicline with varenicline use.²⁸

One study has shown that abstinence from smoking was greater and craving, withdrawal symptoms and smoking satisfaction were less after a 12-week standard regimen of varenicline than after a 10-week standard regimen of transdermal NRT, but this difference was not significant at a year.³² The effectiveness of varenicline compared to nortriptyline is unknown.

There is currently insufficient evidence to recommend its combination with any other smoking cessation medications.

There is insufficient evidence to recommend its use by pregnant women or adolescents who smoke. Varenicline should not be used in pregnant or lactating women or in children under 18 years.

From 1 November 2010, varenicline is fully funded in New Zealand as a smoking cessation treatment, subject to Special Authority criteria, for patients who have previously had two trials of NRT or a trial of bupropion or nortriptyline.

Varenicline: Special Authority criteria for subsidy³³

Initial application from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

- 1 Short-term therapy as an aid to achieving abstinence in a patient who has indicated that they are ready to cease smoking; and
- 2 The patient is part of, or is about to enrol in, a comprehensive support and counselling smoking cessation programme, which includes prescriber or nurse monitoring; and
- 3 Either:
 - 3.1 The patient has tried but failed to quit smoking after at least two separate trials of nicotine replacement therapy, at least one of which included the patient receiving comprehensive advice on the optimal use of nicotine replacement therapy; or
 - 3.2 The patient has tried but failed to quit smoking using bupropion or nortriptyline; and
- 4 The patient has not used varenicline in the last 12 months; and
- 5 Varenicline is not to be used in combination with other pharmacological smoking cessation treatments and the patient has agreed to this; and
- 6 The patient is not pregnant.

Renewal from any relevant practitioner. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

- 1 Short-term therapy as an aid to achieving abstinence in a patient who has indicated that they are ready to cease smoking; and
- 2 The patient is part of, or is about to enrol in, a comprehensive support and counselling smoking cessation programme, which includes prescriber or nurse monitoring; and
- 3 The patient has not used varenicline in the last 12 months; and
- 4 Varenicline is not to be used in combination with other pharmacological smoking cessation treatments and the patient has agreed to this; and
- 5 The patient is not pregnant.

The patient may not have had more than 1 prior approval in the past 12 months.

Varenicline pharmacology and pharmacokinetics

- Varenicline has a half-life of 20–30 hours and repeated oral dosing achieves steady-state levels within 4 days.³¹
- Co-administration of varenicline with food, smoking and time of dosing does not appear to affect the pharmacokinetics of the drug.³⁴
- Less than 20% of varenicline is plasma protein bound, and over 90% is excreted unchanged in the urine and the remainder eliminated in the urine as minor metabolites.³⁴
- Varenicline exposure increased 1.5-fold in patients with moderate renal impairment (estimated CrCl, 30–50 mL/min) and 2.1-fold in patients with severe renal impairment (estimated CrCl, <30 mL/min).³¹ Varenicline was efficiently removed by haemodialysis in patients with end-stage renal failure.

Dosing details

Varenicline is started at least a week before the target quit date (TQD) at a recommended dose of 0.5 mg once daily for the initial 3 days with titration to 0.5 mg twice daily on days 4–7, followed by 1 mg twice daily for 12 weeks.³⁴ An additional 12 weeks' therapy can be used to aid long-term maintenance of abstinence in those who are having difficulty abstaining, but extended treatment is not currently subsidised.

Drug interactions

Varenicline does not have any clinically meaningful interactions with other drugs. Varenicline does not undergo significant hepatic metabolism in humans and does not appear to act as a substrate, inhibitor, or inducer of the cytochrome P450 family of metabolising enzymes.³¹ The pharmacokinetics of digoxin, transdermal nicotine, bupropion, metformin, warfarin and cimetidine are unchanged after varenicline administration.³¹

Tolerability

The most commonly reported adverse effect is nausea, which occurs in approximately 30% of people. It is mostly mild to moderate in intensity and can be limited by taking varenicline with food. If this does not help, then a lower dose can be used, which is still likely to roughly double the chances of quitting.³⁵

Other commonly reported side effects include flatulence, constipation, dry mouth, abnormal dreams, mood disturbance, and irritability.^{31,34} It is important to note that some of these symptoms, e.g. irritability, low mood and constipation are also tobacco withdrawal symptoms.

Postmarketing reports of new onset of depressed mood, aggressive and erratic behaviour, suicidal thoughts and suicide within days to weeks of starting varenicline include patients with and without pre-existing psychiatric illness.^{36–40} In 2009, the US FDA approved safety labelling revisions for varenicline tartrate tablets that include a black-box warning regarding the risk for serious neuropsychiatric events.³⁷

Guidelines recommend careful monitoring of all patients with underlying psychiatric illnesses who are quitting smoking. Varenicline is not contraindicated in patients with mental health illness, but smoking cessation (with or without pharmacotherapy) may exacerbate an underlying psychiatric illness.^{36,41} The varenicline data sheet states that:

"Patients and their families should be advised that the patient should stop taking CHAMPIX and contact a health care professional immediately if changes in behaviour or thinking, agitation or depressed mood, that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behaviour".⁴²

Is there a link between varenicline use and suicide? Researchers have noted how difficult it is to quantify the risk of suicidal ideation or suicidal behaviour from the published reports; the risk of suicide is higher among smokers than non-smokers, and heavy smokers are at higher risk than light smokers.³⁵ It remains unclear as to whether the link is 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).³⁵

Major studies on efficacy and safety of varenicline

Nicotine receptor partial agonists for smoking cessation²⁸

Summary: This recently published Cochrane Review established that varenicline increases the chances of successful long-term smoking cessation between two- and three-fold compared with placebo. More participants quit successfully with varenicline than with bupropion. Varenicline demonstrated a modest benefit over NRT.

A search of the Cochrane Tobacco Addiction Group's specialised register for trials, MEDLINE, EMBASE, PsycINFO and CINAHL, up to March 2008, revealed nine trials that assessed the efficacy and tolerability of nicotine receptor partial agonists, including varenicline, for smoking cessation. In seven trials that compared varenicline with placebo for smoking cessation, three also included a bupropion experimental arm. One relapse prevention trial comparing varenicline with placebo was included, as well as one open-label trial comparing varenicline with NRT. The nine trials included 7267 participants, 4744 of whom used varenicline. The pooled risk ratio (RR) for continuous abstinence from smoking after at least six months from the beginning of varenicline treatment versus placebo was 2.33; the pooled RR for varenicline versus bupropion at one year was 1.52. The RR for varenicline versus NRT at one year was 1.31. In two trials that examined the use of varenicline beyond the 12-week standard regimen, varenicline showed good long-term tolerability. The main adverse effect of varenicline was nausea, which was mostly mild to moderate in intensity and usually subsided over time.

Comment: Meta-analyses such as this provide sound evidence of the efficacy of varenicline in assisting smokers achieve long-term abstinence. The absolute long-term quit rate seen in those using varenicline was 26% versus 11% for placebo. This gives a number needed to treat of seven for one long-term quitter. Varenicline appears to be the most effective pharmacotherapy currently available, with it outperforming bupropion and nicotine patch in head-to-head trials, although the difference to patch was modest. This medicine provides another option for smoking cessation that will be especially welcomed by smokers who have tried and failed on NRT and bupropion.

Immediate versus delayed quitting and rates of relapse among smokers treated successfully with varenicline, bupropion SR or placebo⁴³

Summary: This analysis shows that a substantial proportion of smokers who become 'successful quitters' during 12 weeks of cessation treatment smoke during one or more weeks during the first eight weeks. The study authors urge clinicians and patients to realise that 'real-world' quit rates may be significantly increased just by motivated smokers continuing cessation treatments without interruption despite a lack of success early in the treatment.

Data were reviewed from two identically-designed studies published in 2006^{44,45} that included a total of 2,052 generally healthy adult smokers, randomised to receive 12 weeks of treatment with either varenicline, bupropion sustained-release (SR), or a placebo plus 40 weeks of follow-up.

Successful quitters were those who achieved continuous abstinence for weeks 9–12. Two patterns of successful quitting were identified: "immediate quitters" were those who quit and remained abstinent from the TQD (day 8) through the end of week 12; "delayed quitters" smoked during 1 or more weeks for weeks 2–8 prior to attaining continuous abstinence.

The cumulative rates of continuous abstinence increased similarly for all treatments during weeks 3–8. Overall, there were significantly greater percentages of immediate quitters and delayed quitters for varenicline (24%; 20%) versus bupropion (18.0%, $p=0.007$; 11.6%, $p<0.001$) or placebo (10.2%, $p<0.001$; 7.5%, $p<0.001$). When 'successful quitters only' were analysed, quitting patterns among delayed quitters were similar regardless of treatment group (varenicline 45%; bupropion 39%; placebo 42%) and accounted for approximately one-third of those remaining continuously abstinent at 12 months. No gender differences were observed by quit pattern. Post-treatment relapse was similar across groups.

Comment: This study highlights the fact that not all smokers manage to achieve abstinence from the target quit date; some people appear to be 'late starters'. The antagonistic actions of varenicline, rendering smoking less rewarding, may be particularly important in these delayed quitters. Smokers who initially struggle to achieve abstinence in the first few weeks of their quit attempt should be encouraged to continue and keep on using their chosen smoking cessation medicine.

Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial⁴⁶

Summary: This randomised, placebo-controlled trial demonstrated the efficacy of varenicline for smoking cessation in smokers with cardiovascular disease (CVD). It did not increase cardiovascular events or mortality.

The trial involved 714 smokers with stable CVD, without a history of depression or psychiatric disease, who were randomised to receive varenicline (1 mg twice daily) or placebo, as well as smoking-cessation counselling, for 12 weeks. Follow-up lasted 52 weeks. The carbon monoxide-confirmed continuous abstinence rate was higher for varenicline than placebo during weeks 9–12 (47.0% vs 13.9%) and weeks 9–52 (19.2% vs 7.2%). No significant between-group differences were seen for varenicline and placebo in cardiovascular mortality (0.3% vs 0.6%), all-cause mortality (0.6% vs 1.4%), cardiovascular events (7.1% vs 5.7%), or serious AEs (6.5% and 6.0%). In total, 9.6% of varenicline and 4.3% of placebo participants discontinued study drug because of AEs.

Comment: Varenicline selectively binds to the $\alpha_4\beta_2$ subtype nicotinic acetylcholine receptors (nAChRs), which are the predominant form of receptors in the reward pathway that nicotine acts upon. This selectivity suggests that varenicline would not have significant action on nAChRs in the cardiovascular system, making it suitable for use in people with CVD. The results of this study support this. Not only was varenicline associated with significantly higher quit rates in the group of highly dependent smokers, but its use was not associated with an increase in cardiovascular events. These findings, along with the fact that varenicline has no known drug interactions, make it a suitable smoking cessation aid for smokers with CVD.

Effects of varenicline on smoking cessation in mild-to-moderate COPD: a randomized controlled trial⁴⁷

Summary: This randomised, placebo-controlled trial in patients with mild-to-moderate chronic obstructive pulmonary disease (COPD) showed that varenicline was more efficacious than placebo for smoking cessation and a safety profile consistent with that observed in previous trials.

This multinational study enrolled 504 patients with mild-to-moderate COPD (post-bronchodilator $FEV_1/FVC < 70\%$ and FEV_1 predicted normal value $\geq 50\%$), who were without known psychiatric disturbances, and randomly allocated them to receive varenicline ($n=250$) or placebo ($n=254$) for 12 weeks, with a 40-week non-treatment follow-up.

From weeks 9–12 of treatment, 42.3% of those taking varenicline remained abstinent (as assessed by carbon monoxide-confirmed continuous abstinence rate), compared with 8.8% of those taking placebo ($p < 0.001$). A significantly higher number of varenicline recipients also remained abstinent from weeks 9–52 (18.6% vs 5.6%; $p < 0.001$). Nausea, abnormal dreams, upper respiratory tract infection, and insomnia were the most commonly reported adverse events (AEs) for varenicline. Serious AEs were infrequent in both treatment groups. Two varenicline patients and one placebo patient died during the study. Reports of psychiatric AEs were similar for both treatment groups.

Comment: This study demonstrates the efficacy of varenicline in people with mild-to-moderate COPD. A rather striking observation is that the long-term quit rates in this group (19%) are close to quit rates seen in the general population of smokers using varenicline. Smokers with COPD are typically highly tobacco dependent and despite being motivated to quit smoking, find this difficult. A study that tested the efficacy of bupropion, compared with placebo, in smokers with mild-to-moderate COPD found no difference in 1-year continuous abstinence rates (10% vs 9%).⁴⁸ Data from this and the CVD study summarised above suggest that varenicline may be particularly useful in highly dependent smokers.

Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial⁴⁹

Summary: Smokers who achieved abstinence after 12 weeks of varenicline treatment and were randomised to receive an additional 12 weeks of varenicline had significantly higher continuous quit rates through week 24 than those who received placebo. This advantage was maintained through the nontreatment follow-up to week 52.

This Phase III study consisted of an initial 12-week open-label period where 1927 smokers were treated with oral varenicline 1 mg twice daily. Of the 1236 that remained abstinent at the end of the 12 weeks, 1210 were randomised for an additional 12 weeks to receive oral varenicline 1 mg twice daily or placebo. The continuous quit rates for weeks 13–24 of the trial were 70.5% and 49.6% for varenicline and placebo, respectively ($p < 0.001$). For weeks 13–52, the continuous quit rates were 43.6% and 36.9% for varenicline and placebo, respectively ($p = 0.02$).

Comment: Using an additional 12 weeks of varenicline was associated with a significant increase in 1-year quit rates among people who had managed to stop at the end of the first 12 weeks of treatment. However, despite this positive effect on quit rates, not all smokers will want to continue treatment for six months and there are of course associated costs (only 12 weeks of treatment is currently subsidised in New Zealand). So which smokers would benefit most from extended treatment? To try and answer this, the investigators reanalysed these data [published in Hajek et al, *Addiction* 104(9):1597–602] and found that compared with people who quit on their target quit day, smokers who are late starters are at of increased risk of relapse and so are more likely to benefit from extended treatment. Other who are likely to benefit are those who have only recently quit, are still having occasional lapses, are worried about stopping the treatment, or are still struggling with urges to smoke and withdrawal.

Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis⁵⁰

Summary: According to this analysis of data from 10 placebo-controlled trials of varenicline among smokers with no current psychiatric problems, varenicline is not associated with any significant increase in overall psychiatric disorders, other than sleep disorders and disturbances.

Data were obtained from all smoking cessation phase II, III and IV randomised controlled trials (RCTs) of varenicline versus placebo completed as of 31 December 2008, on file with the manufacturer (Pfizer, Inc.). All studies have been published. The analysis included all 3091 participants who received at least one dose of varenicline and all 2005 placebo recipients. The cohort consisted of men and women smoking ≥ 10 cigarettes/day, aged 18–75 years and without current psychiatric disease who received varenicline or placebo for 6 (1 study), 12 (8 studies) or 52 (1 study) weeks. The incidence of psychiatric disorders other than only sleep disorders and disturbances was 10.7% in subjects treated with varenicline and 9.7% in subjects treated with placebo (relative risk [RR], 1.02). The RRs versus placebo of psychiatric adverse events with an incidence $\geq 1\%$ in the varenicline group were 0.86 for anxiety disorders and symptoms, 0.76 for changes in physical activity, 1.42 for depressed mood disorders and disturbances, 1.21 for mood disorders and disturbances not elsewhere classified and 1.70 for sleep disorders and disturbances. There were no cases of suicidal ideation or behaviour among varenicline recipients. However, there were three reports of serious psychiatric adverse events (two cases of suicidal ideation and one completed suicide) among three trials that were excluded from the analysis because of their open-label design.

Comment: Following the launch of varenicline, a number of serious psychiatric adverse events were reported. Was this something not detected in the clinical trials? Whilst the RCTs were not designed to detect differences in psychiatric adverse events, this study suggests that there is no causality between varenicline use and serious psychiatric adverse events. As already discussed in this review paper, smokers are at higher risk of depression, suicidal ideation, and suicide. Depression is also a well-documented tobacco withdrawal symptom. With an increasing number of smokers around the world using varenicline, and stopping smoking, psychiatric adverse events are likely to occur. The review below provides good advice regarding the use of varenicline in people with mental health illness.

Varenicline use in patients with mental illness: an update of the evidence⁵¹

Summary: This comprehensive review of the literature up to December 2009 assessed all neuropsychiatric adverse drug events reported in pre-marketing trials and postmarketing surveillance, varenicline case reports, evidence surrounding the use of varenicline in patients with psychiatric diagnoses, and varenicline and suicidality. It established that while there is a risk of potential neuropsychiatric events, as demonstrated by voluntary reporting systems and reported cases in the literature, a great deal of data support the use of varenicline in the mental health population. The review recommends cautious treatment initiation, patient education, and close follow-up, and monitoring for mood and behaviour changes during therapy, especially in the psychiatric setting.

This review acknowledges that the majority of published clinical trials of varenicline for smoking cessation excluded patients with an active mental illness, so therefore, the efficacy and safety of varenicline in a psychiatric population remain relatively unknown. It notes that much of the evidence concerning risk for neuropsychiatric adverse drug events has been supplied by case reports; unequivocal evidence is lacking from prospective controlled study data. Information is also lacking as to issues including medication adherence, continuation of smoking and numbers of cigarettes smoked during varenicline use, effect of smoking cessation on psychotropic drug levels and varenicline treatment duration. The reviewers advise that clinicians must balance decreasing morbidity and mortality associated with smoking and the risks of possible adverse drug events for all patients, including those with mental illness.

Varenicline in the routine treatment of tobacco dependence: a pre–post comparison with nicotine replacement therapy and an evaluation in those with mental illness⁵²

Summary: In the setting of a National Health Service (NHS) tobacco dependence clinic in London, UK, varenicline achieved higher short-term cessation rates than did NRT, and proved equally effective in those with and without mental illness.

Outcomes are reported for 412 subjects receiving routine care in an NHS tobacco dependence clinic between May 2006 and April 2007, each of whom attended seven weekly group support sessions lasting 1–1.5 hours, plus NRT (n=204) or varenicline (n=208).

Short-term cessation rates were significantly higher with varenicline than with NRT based on carbon monoxide-verified abstinence 4 weeks after quit day (72.1% vs 61.3%), and also according to Department of Health self-report abstinence (80.3% vs 69.6%). Varenicline was equally effective in those with and without mental illness. Craving to smoke, but not adverse mood, was less severe with varenicline than NRT. The cost per successful short-term quitter was similar for varenicline and NRT. There was a higher incidence of adverse effects among those taking varenicline, but these were tolerated by most smokers. There was no evidence that varenicline exacerbated mental illness.

Comment: Although these data are less robust than those from a RCT, the findings give us some insight into the 'real-world' use of varenicline. These data are from a large NHS Stop Smoking Service that treats highly dependent smokers, many of whom have co-morbidities. The service measures short-term outcome (abstinence at 4 weeks post quit day). A four-week quit rate of 50% translates approximately to 15% at 1 year. The results reflect the findings from the RCTs with higher quit rates in those using varenicline compared to single-product NRT. It is important to note that there was no significant difference in quit rates in those using varenicline compared to combination NRT (e.g. patch and gum). If we are using NRT in our patients who smoke then we should recommend combination use. These observational data need to be interpreted with some caution, but they provide some 'real-life evidence' of varenicline use in smokers with a history of mental health illness. It is interesting to observe that these people were just as likely to quit using varenicline compared to smokers without mental health illness, and without any increase in adverse events.

Behavioral counseling and varenicline treatment for smoking cessation⁵³

Summary: This study compared three ways to deliver a smoking-cessation programme using varenicline in a real-world setting: by phone, Web, or both. Phone counselling had greater treatment advantage for early cessation and appeared to increase medication adherence, but abstinence outcomes did not differ at 6 months.

Current treatment-seeking smokers (n=1202) were recruited from a large healthcare organisation between October 2006 and October 2007 and were randomised to one of three smoking cessation interventions: Web-based counselling (n=401); standard proactive telephone-based behavioural counselling (PTC; n=402); or combined PTC and Web counselling (n=399). All participants received a standard 12-week FDA-approved course of varenicline.

Intent-to-treat analyses revealed relatively high percentages of abstinence at 3 months (38.9%, 48.5%, 43.4%) and at 6 months (30.7%, 34.3%, 33.8%) for the Web, PTC, and PTC-webgroups, respectively. The PTC group had a significantly higher percentage of abstinence than the web group at 3 months (odds ratio, 1.48), but no between-group differences in abstinence outcomes were seen at 6 months.

Gastrointestinal disturbances and abnormal dreams were the most common varenicline side effects, similar to the proportion of study participants reporting side effects in the phase III trials. No serious neuropsychiatric incidents attributable to varenicline use occurred during the trial.

Comment: There is good evidence to show that telephone-based smoking cessation counselling is effective in helping people to quit long-term and there is growing evidence that web-based counselling is also effective. This study demonstrates that varenicline can be combined with these behavioural support approaches and together produce very respectable 6-month quit rates. Furthermore, the adverse event profile was similar to that seen in the face-to-face RCTs.

Smoking outcome by psychiatric history after behavioral and varenicline treatment⁵⁴

Summary: This study provides some evidence that having a prior psychiatric diagnosis, particularly anxiety or depression, does not result in worse outcomes nor is it less effective for smokers treated with varenicline and behavioural intervention, compared with smokers without a psychiatric history.

This study examined the association between psychiatric history and smoking cessation in a secondary analysis of data from the above-mentioned study. The sample cohort included participants with (positive psychiatric history [PH+]; n=271) and without (PH-; n=271) a prior psychiatric diagnosis based on medical record evidence of anxiety, depression, psychotic disorder, or bipolar disorder. All participants received behavioural counselling plus varenicline and were followed for 6 months post quit date. PH+ smokers used varenicline for fewer days on average (59.4 vs 68.5; p<0.01) but did not differ in their use of behavioural treatment. PH+ smokers were more likely to report anxiety and depression, but side effect intensity ratings did not differ after adjusting for multiple comparisons. Overall, all side effects were rated as moderate intensity or less. Thirty-day abstinence rates were similar between the groups at 6 months (31.5% PH+ vs 35.4% PH-; p=0.35).

Comment: These results are from a secondary analysis of the data from the behavioural counseling study above. As with the clients seen in the NHS Stop Smoking Clinic, a significant proportion of clients had a history of mental health illness (MHI). People with MHI who smoke are typically more highly tobacco dependent and so find quitting more difficult. Smokers with MHI were just as likely to quit as smokers without MHI and there was no increase in psychiatric adverse events in this group. Like the NHS study above, these data do not confirm the safety of varenicline use in smokers with mental health illness. Cautious treatment initiation and close follow-up and monitoring of mood in this group of smokers is recommended.

Utilization of the smoking cessation medicine varenicline: an intensive post-marketing study in New Zealand⁵⁵

Summary: In this 'real-life' investigation of varenicline use, most patients did not receive 12 weeks of varenicline treatment as recommended in the Champix product information. Failure to complete the course may have implications for the effectiveness of this smoking cessation treatment.

This investigation analysed dispensing records for all New Zealand patients prescribed varenicline collected by the Intensive Medicines Monitoring Programme (IMMP) during the first year that varenicline was available in New Zealand.

Of 3415 patients in the first year IMMP cohort, only 125 patients (4%) were dispensed the recommended 12 weeks of varenicline treatment. 1299 (38%) were dispensed 14 days treatment (most often as a Starter Pack), 766 (22%) were dispensed 6 weeks, 411 (12%) were dispensed 4 weeks and 332 (8%) patients were dispensed more than 12 weeks treatment as a continuous course. The most common reasons for stopping varenicline prematurely were adverse reactions and cost of treatment. In a subgroup of 1299 patients for whom follow-up information was available, varenicline was reported to have been effective for 359 (28%) patients.

Comment: Varenicline is currently on the IMMP and the data collected by the programme demonstrate the difficulty in getting many smokers to adhere to treatment. Cost of treatment was a contributing factor to low treatment adherence, which will be less of a barrier now that varenicline is subsidised. However, many smokers will discontinue treatment early because they lapse, feel that they have now 'beat' their addiction, or experience adverse effects. It is therefore important that healthcare professionals encourage their patients to use the full course of treatment even if they lapse or feel that they do not need it any more. Patients should also be advised on the most common adverse effects (e.g. nausea, vivid dreams, sleep disturbance) and be followed-up to monitor progress with stopping smoking and the occurrence of adverse events.

Dr McRobbie has undertaken research and consultancy for, and received honoraria for speaking at meetings, from the manufacturers of smoking cessation medications.

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Conclusion

New Zealanders who smoke have access to all medications that have been shown to be effective in aiding long-term abstinence. NRT (in the form of patches, gum and lozenges), bupropion, nortriptyline and varenicline are all available on prescription and fully subsidised. These medicines are no silver bullets for smoking cessation but they will at least double the chances of long-term abstinence. Absolute quit rates are highest when medicines are used in combination with behavioural support, but are still effective when

used on their own. Smoking cessation medications are strongly recommended in those smokers who show signs of high nicotine dependence (e.g. those who smoke their first cigarette of the day within an hour of waking).

Varenicline is the newest medicine to be added to our armamentarium to better help our patients who smoke to quit. It will provide another welcome option to many smokers, especially those who have tried and failed on the other products in the past.

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