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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 Reader in Public Health Interventions 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 NZ since 2007. It has been fully funded since November 1st, 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 5000 New Zealanders every year, including deaths due to second-hand smoke.[1] On average, adults who smoke cigarettes die 14 years earlier than nonsmokers.[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 NZ, 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 NZ 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, earlier menopause and a diminished ovarian reserve.[6,7]
- Women who smoke during pregnancy, compared with women who are nonsmokers, are more likely to: i) have complications during pregnancy; ii) experience miscarriage; iii) produce a lower birthweight baby; and iv) face a greater risk of foetal and infant mortality.[8–11]
- Maternal smoking has been linked to: i) birth defects; ii) increased risk of childhood cancer; and iii) increased incidence of respiratory illnesses in infants.[12–15]
- The more the mother smokes after her child is born, the more likely her baby might die from sudden unexplained death in infancy compared with a baby with a nonsmoking mother.[16]
- Exposure to second-hand smoke worsens asthma symptoms in children and is associated with middle ear effusion.[17,18]
- 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 1.5–2 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 (CV) 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 CV disease is almost completely reversed by smoking cessation, making it potentially the single most effective intervention available for those at risk of, or with existing, CV disease.

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 childbearing age is a priority.

Cessation support in NZ

According to the NZ smoking cessation guidelines, the key components of cessation support that have been shown to be most effective include the delivery of multisession behavioural support and stop-smoking medication.[23] Four different pharmacotherapies exist for the treatment of nicotine dependence – all are now subsidised.[24] 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, lozenges, sublingual tablets, nasal spray and inhalators); the patches, gum and lozenges are available in NZ 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 NZ, but are available through pharmacies, with the exception of nasal spray, which is not sold in NZ.

Key Points: NRT[23,26–28]

NRT approximately doubles the chances of long-term abstinence.

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

NRT appears to be as effective as bupropion (amfebutamone) 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 cigarettes per day can start on full-strength patches.

NRT should be used for 8–12 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 smoke-free. 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 CV 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 three 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, 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, 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 NZ and only available on prescription.

Key Points: Bupropion[23,28,29]

Bupropion almost doubles the chances of long-term abstinence.

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

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 CV 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 CV effects. There are a number of contraindications and precautions with its use. Nortriptyline is fully subsidised in NZ and only available on prescription.

Key Points: Nortriptyline[23]

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 CV 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 ten studies (involving a total of 4443 participants) comparing the effects of varenicline with those of placebo for quit rates lasting ≥6 months; these data demonstrate a pooled RR of 2.31 (95% CI 2.01, 2.66).[28] Pooled results from three trials comparing varenicline with bupropion and two studies comparing varenicline with NRT showed superiority of varenicline to bupropion (RR 1.52 [95% CI 1.22, 1.88]), but not to NRT (1.13 [0.94, 1.35]).

Key Points: Varenicline[23,28]

Varenicline at least doubles the chances of long-term abstinence.

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

Pooled data from three trials comparing varenicline with bupropion show higher quit rates with varenicline. Combining data from two studies comparing varenicline with NRT showed no significant difference in long-term quit rates between these medicines.

The effectiveness of varenicline compared with 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 patients aged <18 years.

As of 1 November 2010, varenicline is fully funded in NZ 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 subsidy[32]

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.
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.
3. Either:
   - 3.1. The patient has tried but failed to quit smoking after at least two separate trials of NRT, at least one of which included the patient receiving comprehensive advice on the optimal use of NRT; or
   - 3.2. The patient has tried but failed to quit smoking using bupropion or nortriptyline.
4. The patient has not used varenicline in the last 12 months.
5. Varenicline is not to be used in combination with other pharmacological smoking cessation treatments and the patient has agreed to this.
6. The patient is not pregnant.
7. The patient will not be prescribed >3 months' funded varenicline.

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.
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.
3. The patient has not used varenicline in the last 12 months.
4. Varenicline is not to be used in combination with other pharmacological smoking cessation treatments and the patient has agreed to this.
5. The patient is not pregnant.
6. The patient may not have had >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 concentrations 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.[33]
- <20% of varenicline is plasma protein bound, and >90% is excreted unchanged in the urine and the remainder eliminated in the urine as minor metabolites.[33]
- 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 0.5mg once daily for the initial 3 days with titration to 0.5mg twice daily on days 4–7, followed by 1mg twice daily for 12 weeks.[33] An additional 12 weeks of therapy can be used to aid long-term maintenance of abstinence in those who are having difficulty abstaining, but extended treatment is not 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 (CYP) family of metabolising enzymes.[31] The pharmacokinetics of digoxin, transdermal nicotine, bupropion, metformin, warfarin and cimetidine are unchanged after varenicline administration.

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.[34]

Other commonly reported side effects include flatulence, constipation, dry mouth, abnormal dreams, mood disturbance and irritability.[31,33] 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.[35–39] 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.[36]

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.[35,40] The varenicline datasheet 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."[41] Patients should also be advised to *"use caution driving or operating machinery until they know how quitting smoking and/or varenicline may affect them"*.

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 nonsmokers, and heavy smokers are at higher risk than light smokers.[34] 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). Several of the papers summarised below investigate this issue, although none to date can provide a definitive answer. However, we cannot ignore the reports of neuropsychiatric adverse events that have occurred in people taking varenicline, and so care should be taken, especially with patients with a history of psychiatric illness. For further information please refer to the Champix® Datasheet on the MedSafe website.

Major studies on efficacy and safety of varenicline

Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: a randomized trial[42]

Summary: This RCT involved 714 smokers with stable cardiovascular (CV) disease, without a history of depression or psychiatric disease, who were randomised to receive varenicline (1mg 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 CV mortality (0.3% vs. 0.6%), all-cause mortality (0.6% vs. 1.4%), CV events (7.1% vs. 5.7%) or serious adverse events (6.5% and 6.0%). In total, 9.6% of varenicline and 4.3% of placebo participants discontinued the study drug because of adverse events.

Comment: Varenicline selectively binds to the of $\alpha_4\beta_2$ subtype nicotinic acetylcholine receptors (nAChRs), which are the predominant form of receptors in the reward pathway that nicotine acts upon. This relative selectivity suggests that varenicline would not have significant action on nAChRs in the CV system, making it suitable for use in people with CV disease. 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 it was well tolerated by people with stable CV disease. As noted above, the occurrence of CV adverse events was slightly higher in the varenicline group compared with placebo (1.4% difference), although this difference was not statistically significant (95% CI –2.3, 5.0). These findings suggest that varenicline can be considered for use in smokers with stable CV disease. However, it is important to note that postmarketing surveillance has detected reports of serious CV adverse events (e.g. myocardial infarction and stroke), and although in most cases smokers have had underlying CV disease, the use of varenicline as a contributing factor to these events cannot be ruled out.

Risk of serious adverse cardiovascular events associated with varenicline[43]

Summary: This was a systematic review and meta-analysis of 14 RCTs (n=8216; duration 7–52 weeks) from MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, websites of regulatory authorities and clinical trial registries with reports of serious cardiovascular (CV) events associated with the use of varenicline. Compared with placebo, varenicline was found to be associated with a significantly higher CV event rate (1.06% vs. 0.82%; Peto odds ratio 1.72 [95% CI 1.09, 2.71; I^2=0%]); sensitivity analyses were consistent with the main analysis, and no publication bias was evident on a funnel plot. The number of deaths did not allow meaningful between-group mortality comparisons.

Comment: Following the publication of the paper by Rigotti et al (2010),[42] the US FDA noted that *"varenicline may possibly increase the risk of cardiac events, both ischaemic and arrhythmic, particularly over a longer treatment period"*. The mechanism of action by which varenicline would do this is not absolutely clear, however vasoconstrictive effects have been postulated as a potential mechanism. This issue deserves further investigation. The authors of this systematic review and meta-analysis of 14 randomised placebo-controlled trials of varenicline reported a 72% increase in risk of CV adverse events. However, the absolute risk of a CV adverse event in the varenicline group was 52/4908 (1.06%) compared with 27/3308 (0.82%) in the placebo group, which is a difference in risk of 0.24%. The number-needed-to-harm is 417 (calculated as 1/0.0024). The risks of using varenicline need to be balanced with the risks of continuing to smoke and the benefits of quitting.

Effects of varenicline on smoking cessation in mild-to-moderate COPD[44]

Summary: This multinational RCT enrolled 504 patients with mild-to-moderate COPD (postbronchodilator FEV_1/FVC <70% and FEV_1% predicted normal value ≥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 nontreatment 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%).[45] Data from this and the previously summarised cardiovascular disease studies suggest that varenicline may be particularly useful in highly dependent smokers.

Psychiatric adverse events in randomized, double-blind, placebo-controlled clinical trials of varenicline: a pooled analysis[46]

Summary: These researchers analysed data from all smoking cessation phase II, III and IV RCTs of varenicline (n=3091) versus placebo (n=2005) completed as of 31 December 2008 on file with the manufacturer (Pfizer, Inc.); all studies have been published. 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 1.02). The relative risks versus placebo of psychiatric adverse events with an incidence ≥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 following review provides good advice regarding the use of varenicline in people with mental health illness.

Suicidal behavior and depression in smoking cessation treatments[47]

Summary: This analysis of data from the US FDA's Adverse Event Reporting System (AERS) from 1998 to September 2010 included 9757, 1751 and 1917 serious case reports associated with the use of varenicline, bupropion (for smoking cessation) and nicotine replacement therapy (NRT) products, respectively. Among the 3249 reports of suicidal/self-injurious behaviour, 90%, 7% and 3% were associated with varenicline, bupropion and NRT, respectively; the respective odds ratios for varenicline and bupropion versus NRT were 8.4 (95% CI 6.8, 10.4) and 2.9 (2.3, 3.7). Moreover, these increased risks persisted after reports involving concomitant use of any of the 58 drugs that carry warnings or precautions of suicidal behaviour were excluded, and a comparison with antibiotic users revealed a rare risk of suicidal/self-injurious behaviour or depression in healthy individuals receiving such short-term drug regimens.

Comment: Postmarketing surveillance has raised concern that the use of varenicline might be associated with neuropsychiatric adverse events. Since the first reports in 2006/07, there have been an increasing number of serious adverse events (SAEs) reported to regulatory bodies. The authors of this study looked at a series of SAEs (e.g. events that resulted in hospitalisation, disability or death) reported to the FDA since 1998 in people taking varenicline, bupropion and NRT, and then within these looked at the number of cases of SAEs that reflected depression and suicidal behaviour. Since smoking cessation may result in depressed mood, a comparison group of SAEs reported in people using antibiotics was also included. The authors report that 25% of the cases using smoking cessation medications reported SAEs related to depression and/or suicidal behaviour compared with only 1% of the cases using antibiotics. NRT, bupropion and varenicline were all associated with a higher proportion of psychiatric SAEs compared with antibiotics; however, those using varenicline were most likely to have a higher proportion of these SAEs. Again these data are a signal for appropriate prescribing and, most importantly, good follow-up of people who are being assisted to stop smoking. However, these data do not prove causality or indeed give an indication of the frequency of such events.

In a safety announcement made on October 24th 2011, the FDA reported on two studies looking at the risk of neuropsychiatric adverse events associated with varenicline or NRT use (www.fda.gov/Drugs/DrugSafety/ucm276737.htm). Neither found any increase in risk with varenicline use, but the studies could not rule out an increased risk either. As these studies were both retrospective cohort designs that only assessed neuropsychiatric AEs resulting in hospitalisation, these results need to be interpreted with caution. The FDA concluded, *"Healthcare professionals and patients should continue to follow the recommendations in the physician label and the patient medication guide, and to monitor for neuropsychiatric symptoms when prescribing or using Champix"*. The FDA has directed the manufacturer of varenicline to undertake a large RCT to help establish the risk associated with the use of this medication.

Psychiatric adverse events associated with varenicline: an intensive postmarketing prospective cohort study in New Zealand[48]

Summary: This observational prospective cohort study of 3415 patients who were prescribed varenicline during the first year of monitoring in NZ included follow-up by record linkage to national morbidity and mortality datasets for 98%. Questionnaires were completed by the patients' doctors for 1394 patients, of which 1310 were valid and defined the 'responder' population. Reports of psychiatric adverse reactions in this population included: i) sleep disorders in 56 (the most frequently reported); ii) new-onset depression, worsening of depression and impaired motivation in 24, 14 and 1, respectively; and iii) withdrawal reactions after varenicline cessation in 6. Serious psychiatric adverse reactions included suicide (1 patient), suicidal ideation (2) and psychotic reactions (3). There were six reports of self-harm events in the total cohort (0.18%).

Comment: Data from NZ broadly reflect what has been reported in other parts of the world. Many readers will be familiar with NZ's Intensive Medicine Monitoring Programme (IMMP). These data reported in this paper come from a cohort of people that were dispensed varenicline over a 12-month period. The IMMP identified adverse events from questionnaires sent to patients' doctors, cases reported to the NZ Pharmacovigilance Centre and by linking with the national mortality datasets. The results show that around 3% of cases from the survey responses reported symptoms of depressed mood. Most of these (24/39) were new in onset. There were six cases of psychiatric serious adverse reactions, including one completed suicide. However, the most commonly reported neuropsychiatric adverse reaction was sleep disorders (4.3% among the survey responses). Sleep disorders, which includes vivid dreams and insomnia, can be troublesome for some, and healthcare professionals should advise people about these and also enquire on their occurrence at follow-up. Anecdotally, advising people not to take the second tablet of the day too late in the evening may help reduce sleep disorders. A dose reduction, or stopping treatment, may be required in those who report more severe sleep disorders. However, the quit attempt should not be abandoned and people can be switched to nicotine replacement therapy.

A double-blind randomized placebo-controlled pilot study of neuropsychiatric adverse events in abstinent smokers treated with varenicline or placebo[49]

Summary: Smokers with no history of psychiatric illness (n=110) were randomised 1:1 to receive varenicline 1mg twice daily or placebo. There were no significant between-group differences for neuropsychiatric adverse events or scores for the Montgomery-Åsberg Depression Rating Scale, Hamilton Anxiety Scale, Overt Aggression Scale-Modified aggression or irritability subscale or Profile of Mood States. No attempted suicides were reported.

Comment: In an effort to try and estimate and characterise neuropsychiatric adverse events in people quitting smoking, Garza and colleagues conducted this small exploratory RCT. One-hundred and ten smokers, without any history of psychiatric illness, were randomised to a standard treatment course of varenicline or placebo and were closely followed throughout their quit attempt. In fact for the first 2 weeks of this study, participants were required to stay in an inpatient facility for assessment. They were then seen on a weekly basis as outpatients. The results showed no differences in the incidences of neuropsychiatric adverse events, except for insomnia and abnormal dreams, between active and placebo treatment. However, this study was not powered to detect a difference in such events between these groups, and so does not change the current recommendations for varenicline use.

Stopping smokeless tobacco with varenicline[50]

Summary: This trial randomised patients who used smokeless tobacco ≥8 times daily, and had not abstained for >3 months over the 12 months prior to enrolment, to receive 12 weeks of varenicline titrated to 1mg twice daily during week 1 (n=213) or placebo (n=218), and followed them for an additional 14 weeks. Compared with placebo, varenicline was associated with significantly higher rates of 4-week cotinine-confirmed continuous abstinence (primary endpoint; 59% vs. 39%; relative risk 1.60 [95% CI 1.32, 1.87; p<0.001]; number-needed-to-treat 5) and continued abstinence over weeks 9–26 (45% vs. 34%; 1.42 [1.08, 1.79; p=0.012]; 9). Common adverse events in the varenicline versus placebo group were nausea (35% vs. 6%), fatigue (10% vs. 7%), headache (10% vs. 9%) and sleep disorders (10% vs. 7%), with few adverse events leading to discontinuation (9% vs. 4%) and serious adverse event rates of 1% in each group.

Comment: This Scandinavian study sought to determine the efficacy of varenicline in helping people cease the use of oral tobacco. Sweden, in particular, has a high prevalence of snus use compared with smoked tobacco (19% vs. 11%, reported in this paper). Snus is a form of smokeless tobacco, and although not 100% risk free, it is considered safer than smoking. Like most people who smoke tobacco, the majority of those who use smokeless tobacco want to give it up. However, there are relatively few interventions that have been examined to help those who use smokeless tobacco.

This study randomised 431 users of smokeless tobacco to a standard 12-week course of treatment with varenicline or placebo. The results confirmed that quit rates were significantly higher in the varenicline group at both the end of treatment (59% vs. 39%) and at 6 months (45% vs. 34%). It is interesting to note the high quit rates in both groups, and the authors suggest that users of smokeless tobacco may be less resistant to treatment than people who smoke. The adverse effect profile was similar to that seen in other studies, nausea being the most commonly reported symptom. Varenicline is not currently licensed for use in users of smokeless tobacco.

Varenicline treatment for smoking cessation in Asian populations: a pooled analysis of placebo-controlled trials conducted in six Asian countries[51]

Summary: These researchers undertook a pooled analysis of smokers from three phase IIb/III RCTs conducted in Japan, Taiwan, Korea, China, Singapore and Thailand who had been randomised to receive varenicline 1mg twice daily (n=447) or placebo (n=446) for 12 weeks; post-treatment follow-up was ≥12 weeks. Compared with placebo, varenicline was associated with significantly greater carbon monoxide-confirmed continuous abstinence rates at 9–12 and 9–24 weeks (58.6% vs. 34.3%; odds ratio 2.74 [95% CI 2.08, 3.60; p<0.0001] and 41.4% vs. 25.3%; 2.08 [1.56, 2.77; p<0.0001], respectively). Nausea (31.5%), headache (8.5%), dizziness (7.8%), insomnia (7.4%) and upper abdominal pain (5.4%) were the most frequent adverse events in the varenicline compared with placebo group. Serious adverse events were reported in four and five of the varenicline and placebo recipients, respectively, and the respective rates of discontinuation due to adverse events were 3.6% and 1.6%. Abstinence rates were numerically higher in both groups in the Asian studies compared with Western studies, but treatment effects were similar as were adverse events.

Comment: Smoking prevalence across Asia is diverse. For example, some 60–70% of Chinese men smoke, compared with 20% of men in Hong Kong. There are some notable differences also between Asian and Western countries. For example, smoking prevalence in women is lower in Asian (typically <5%) than Western countries. In general, people of Asian descent metabolise nicotine more slowly due to differences in the CYP2A6 enzyme, which is the enzyme primarily responsible for metabolising nicotine. Slow nicotine metabolisers tend to smoke fewer cigarettes.

This paper combined the results for three RCTs examining the efficacy of varenicline for smoking cessation in Asian populations. Of the 894 smokers randomised, 41% of varenicline users versus 25% of placebo users achieved abstinence for 6 months. The quit rate seen in this population is higher than what was seen in Western studies (30% vs. 12% at 6 months), which may reflect either differences in smoking behaviour or culture. For example, most participants in the Western studies had tried to quit before, whereas only a third of smokers in the Asian cohorts had tried to quit in the past. Nonetheless, the odds ratios of quitting at 6 months on varenicline relative to placebo are similar between the populations (Asian 2.08 [95% CI 1.56, 2.77] and Western 3.14 [2.36, 4.10]).

Efficacy of a flexible quit date versus an a priori quit date approach to smoking cessation[52]

Summary: This cross-study analysis compared effect sizes and quit rates seen in one placebo-controlled study that allowed participants randomised to varenicline or placebo to set a flexible quit date (FQD) with those seen in nine previous RCTs that required participants to set a fixed target quit date (TQD). The analysis showed that the FQD study results produced an odds ratio for varenicline versus placebo that was ranked the fourth highest of the ten trials, and the incidence of continuous abstinence was fifth highest. The authors noted that as cross-study analyses have hidden biases, an RCT investigating FQD versus TQD would be more valid, and that a study exploring the two approaches in different subpopulations is also indicated.

Comment: Most smoking cessation treatment protocols recommend that smokers set a TQD prior to commencing treatment. The rationale for this is that it gives smokers something to aim for and may engender commitment to the quit attempt. This also makes some sense when using medications that are started when smoking stops, e.g. nicotine replacement therapy. An alternative to setting a TQD is to let people choose a date that they want, and feel most ready, to quit after they have started treatment. This might be beneficial when using medication started prior to quitting, especially when using the medication whilst still smoking might help uncouple the 'reward' from the behaviour. For example, using nicotine patches and varenicline for longer periods prior to quitting might increase long-term quit rates. Rennard et al (2011) published a study showing that varenicline was more effective than placebo when a FQD was allowed, but this does not inform us if the FQD approach is better than a TQD.

In this paper, Hughes and others attempt to examine the difference in the approaches more closely by comparing the quit rates in the FQD study with those seen in nine studies using a TQD. They found that 56% of people in the FQD study planned their quit date only a day in advance and 42% quit spontaneously. However, overall the odds ratios for abstinence for varenicline versus placebo were similar, suggesting that either approach could be recommended to people. Currently, the FQD approach is not included in the varenicline product license.

Nicotine receptor partial agonists for smoking cessation[28]

Summary: This 2011 Cochrane Review reported that varenicline at standard dosage was superior to placebo for continuous abstinence at ≥6 months (ten trials; n=4443), as was varenicline at lower or variable dosages (four trials; n=1272). Varenicline was also significantly superior to bupropion (three trials; n=1622), but not significantly different to nicotine replacement therapy (NRT) for point prevalence abstinence (two trials; n=778). Varenicline for >12 weeks was found to be well tolerated (two trials), and its main adverse event was mild-to-moderate nausea, which usually subsided with time. The authors commented that to date there are little data from surveillance reports and secondary analyses of trials to support a causal relationship between varenicline and depressed mood, agitation or suicidal behaviour/ideation.

Comment: This systematic review is an update of the 2008 Cochrane Review, and the results reported in this recent version do not significantly change what was previously known. The authors were able to include ten randomised placebo-controlled trials in the meta-analysis, and showed that varenicline, compared with placebo, at least doubles long-term abstinence rates (risk ratio [RR] 2.31 [95% CI 2.01, 2.66]). The absolute quit rate seen in those using varenicline was 24% versus 11% for placebo. There were no new trials comparing varenicline with bupropion, and the pooled risk ratio remains at 1.52 (95% CI 1.22, 1.88). Since the 2008 review, there has been one further open-label study comparing varenicline to NRT. Combining data from two studies showed no significant benefit of varenicline over NRT (RR 1.13 [95% CI 0.94, 1.35]). The numbers-needed-to-treat for a benefit with the use of these medications are now 23 (95% CI 20, 27) for NRT, 20 (16, 26) for bupropion and 10 (8, 13) for varenicline.

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 another option for those who have tried and failed on other cessation products in the past. It is an effective treatment that at least doubles the chances of quitting long-term. However it is not appropriate for all people who smoke and is associated with some common side effects. Prescribers should give adequate information to smokers to ensure they understand how to use it and to report any adverse effects.

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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