

Varenicline, a new treatment option in smoking cessation

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PRODUCT PROFILE

Proprietary name: Champix

Constituent: varenicline tartrate

Indication: smoking cessation in adults

Dosage and method of administration: for oral use only; treatment to be started one to two weeks before the patient's set quit date; recommended dose: days 1-3, 0.5mg once daily; days 4-7, 0.5mg twice daily; day 8-end of treatment, 1mg twice daily; patients who cannot tolerate adverse effects may have the dose lowered temporarily or permanently to 0.5mg twice daily

Contraindications: hypersensitivity to the active substance or to any of the excipients

Precautions: physiological changes resulting from smoking cessation, with or without treatment, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin); as smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates; smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness, eg depression – care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly; at the end of treatment, discontinuation was associated with an increase in irritability, urge to smoke, depression and/or insomnia in up to 3 per cent of patients – the prescriber should inform the patient accordingly and discuss or consider the need for dose tapering

Pregnancy and lactation: not recommended during pregnancy; a decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy should be made taking into account the benefit of breastfeeding to the child and the benefit of therapy to the woman

Interactions: based on varenicline characteristics and clinical experience to date, varenicline has no clinically meaningful drug interactions

Side-effects: no attempt has been made in either the design or the analysis of the varenicline studies to distinguish between adverse events associated with study drug treatment or those possibly associated with nicotine withdrawal; *very common:* abnormal dreams, insomnia; headache; nausea; *common:* increased appetite; somnolence, dizziness, dysgeusia; vomiting, constipation, diarrhoea, abdominal distension, stomach discomfort, dyspepsia, flatulence, dry mouth; fatigue

Presentation/cost: starter pack – 11 x 0.5mg tab and 14 x 1mg tab, £27.30; 0.5mg, 1mg tablets; 0.5mg – 56, £54.60; 1mg – 28, £27.30; 56, £54.60



Varenicline is a well-tolerated novel treatment to aid smoking cessation in adults that is generally more effective than existing smoking cessation aids. In our New products review Steve Chaplin presents the clinical trial results relating to its efficacy and adverse effects, and Professor Robert West comments on its place in smoking cessation.

Every year, about half a million people try to stop smoking with the NHS Stop Smoking Service.¹ Self-reported cessation rates four weeks after an agreed quit date are around 50 per cent,^{1,2} but this declines to 15 per cent remaining abstinent at 12 months.³

The National Institute for Health and Clinical Excellence (NICE) recommends that people who want to stop smoking should be offered nicotine replacement therapy (NRT), bupropion (Zyban) or the newly available drug varenicline (Champix), the choice depending on their motivation and likely adherence, access to counselling or support, previous use of smoking cessation products, contraindications and risk of adverse effects, and personal preference.

study	Continuous abstinence weeks 9-12 (primary end-point)		Continuous abstinence weeks 9-24		Continuous abstinence weeks 9-52	
	Gonzales, <i>et al</i> ⁷	Jorenby, <i>et al</i> ⁸	Gonzales, <i>et al</i> ⁷	Jorenby, <i>et al</i> ⁸	Gonzales, <i>et al</i> ⁷	Jorenby, <i>et al</i> ⁸
varenicline	44.0%	43.9%	29.5%	29.7%	21.9%	23.0%
bupropion	29.5%	29.8%	20.7%	20.2%	16.1%*	14.6%
placebo	17.7%	17.6%	10.5%	13.2%	8.4%	10.3%
Odds ratios (CI 95%)						
V vs B	1.93 (1.40-2.68)	1.90 (1.38-2.62)	1.63 (1.14-2.33)	1.69 (1.19-2.42)	1.46 (0.99-2.17)	1.77 (1.19-2.63)
V vs P	3.85 (2.70-5.50)	3.85 (2.69-5.50)	3.68 (2.42-5.60)	2.83 (1.91-4.19)	3.09 (1.95-4.91)	2.66 (1.72-4.11)
Rates with varenicline statistically significantly different from both comparators at all time points except* V – varenicline B – bupropion P – placebo						

Table 1. Summary of primary and secondary end-points in two comparative trials with bupropion^{7,8}

The technology

Varenicline is an oral, centrally acting, alpha4beta2 nicotinic acetylcholine receptor partial agonist. It binds to the same receptor as nicotine, but with greater affinity. It has sufficient agonist activity to stimulate the receptor, reducing craving and withdrawal symptoms, but it does not share the rewarding and reinforcing properties of nicotine.⁵

NICE recommends varenicline (within the licensed indication) for smokers who express a desire to stop smoking as part of a programme of behavioural support.⁴

A quit date should be agreed one to two weeks after starting treatment. Treatment is initiated at a dose of 0.5mg per day for days 1-3, increasing to 0.5mg twice daily for days 4-6, then to 1mg twice daily.

The recommended duration of treatment is 12 weeks but an additional 12-week course is licensed for those who have successfully quit within the initial treatment period.⁵

Varenicline is licensed for smoking cessation in adults; its safety

during pregnancy and while breastfeeding is unknown.

Clinical trials

Three one-year, placebo-controlled, double-blind trials have evaluated the effectiveness of varenicline 1mg twice daily,⁶⁻⁸ two of which compared it with modified-release bupropion 150mg twice daily.^{7,8}

The study populations were broadly similar, comprising 50-60 per cent men, mean ages in the range 42-45 and smoking 21-23 cigarettes per day for 24-27 years. None had achieved more than three months' abstinence within the previous year; those who had used bupropion were excluded from the trials involving this agent because the therapeutic response is reduced after previous use. All patients also received brief counselling for up to 10 minutes at weekly visits.

In the comparative trials with bupropion (n=1025⁷ and 1027⁸), patients were treated for 12 weeks and followed up for a further 40 weeks. The primary end-point was the four-week continuous absti-

nence rates during weeks 9-12 (*ie* the end of the treatment period), confirmed by measuring expired carbon monoxide. Secondary end-points included continuous abstinence rates over 24 and 52 weeks, and the effects of treatment on craving and smoking enjoyment.

After 52 weeks the proportion of patients who completed the studies were 61 and 70 per cent with varenicline, 56 and 65 per cent with bupropion and 54 and 60 per cent with placebo.

The results of the two comparative trials were very similar (see Table 1); with time, the differences between varenicline and bupropion diminished but point prevalence rates for seven days' abstinence were always greater with varenicline than bupropion or placebo (see Figure 1).

Both varenicline and bupropion reduced craving and urge to smoke compared with placebo; in one trial⁸ their effects were similar, whereas the other⁷ found the effect size of varenicline was about twice as great. Both also reduced the psychological enjoyment of smoking

but only varenicline reduced enjoyment of respiratory tract sensations.

The third trial evaluated the efficacy of a second 12-week treatment period in patients who had achieved abstinence after taking one nonblinded 12-week course of varenicline.⁶ A total of 1210 patients were randomised to varenicline or placebo and followed up for a further 28 weeks (to a total of 52 weeks); 82 per cent of those taking varenicline and 76 per cent of those assigned to placebo completed the study.

Continuous abstinence over weeks 13-24 (the primary endpoint), confirmed by measurement of expired carbon monoxide, was achieved in 70.5 per cent of patients taking varenicline and 49.6 per cent with placebo. The number needed to treat (NNT) was five. After 52 weeks, confirmed abstinence rates were 43.6 per cent with varenicline and 36.9 per cent with placebo (NNT=14). The median time to first lapse was 198 days with varenicline and 87 days with placebo.

Adverse effects

The commonest adverse effects associated with varenicline were nausea (varenicline 28-34 per cent of patients, bupropion 7-13 per cent, placebo 8-10 per cent) and abnormal dreams (10-14 per cent *vs* 6 per cent and 4-6 per cent); other GI events (dry mouth, dyspepsia, flatulence, constipation) tended to be more frequent with varenicline. Bupropion was more frequently associated with insomnia (21-22 per cent *vs* 12 and 4 per cent with varenicline and placebo).

Weight gain among patients who achieved abstinence was 2-3kg in all groups, with a trend to greater weight gain with placebo.

Summary

Varenicline is a novel treatment to aid smoking cessation in adults. In

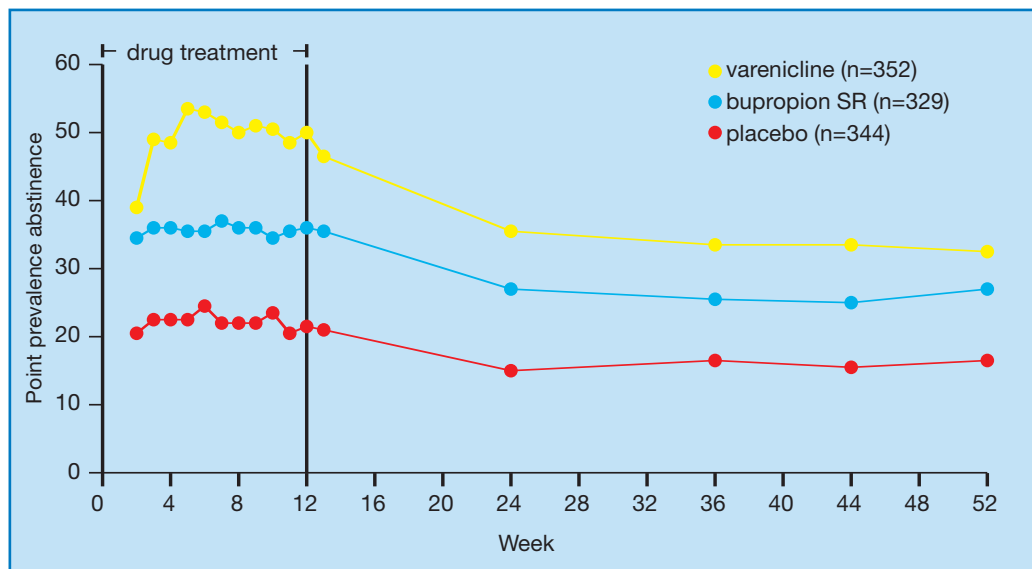


Figure 1. Point prevalence of seven-day abstinence with varenicline, bupropion and placebo⁷

middle-aged heavy smokers, a 12-week course increases the odds of successfully stopping smoking almost fourfold compared with placebo and almost twofold compared with bupropion, achieving abstinence rates greater than 40 per cent.

After one year, over 20 per cent of patients remain abstinent – a two- to threefold improvement over placebo and a 50-77 per cent improvement compared with bupropion.

Varenicline is associated with nausea and abnormal dreams; weight gain among those who stop smoking is less marked than with placebo.

References

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By Steve Chaplin, a pharmacist who specialises in writing on therapeutics

Place in therapy

It is important for smokers to stop as young as possible. Every year that they smoke increases their chances of COPD in later life and after the age of about 40, every year that stopping is delayed loses the smoker an average of three months of healthy life.

To treat nicotine dependence and so aid smoking cessation, we already have nicotine replacement therapy (NRT) in the form of transdermal patches, gum, lozenges, sublingual tablets, inhaler and nasal spray; we also have a tablet, bupropion. So the question is whether varenicline brings anything new to the table.

The answer is that it does – for two reasons. First of all, it is generally more effective and at least as safe. Following a systematic review of randomised controlled

trials, NICE concluded that the overall level of effectiveness of varenicline is greater than bupropion and probably greater than NRT.

Postregistration experience with more than two million patients has supported the findings of clinical trials that the drug does not produce any serious adverse events and the most common minor side-effect, nausea, is rarely sufficient to cause patients to discontinue treatment.

Varenicline also has very few contraindications (only pregnancy in fact) and no known drug interactions. In contrast, bupropion is contraindicated in a range of conditions, including those that predispose to seizure.

Secondly, varenicline offers an additional, potentially effective treatment option for smokers who have not succeeded with existing

treatments, who do not find these attractive or for whom they are contraindicated.

Varenicline does cost more than bupropion and NRT, but because it is more effective the cost-effectiveness for preventing premature death is similar and far greater than medication to treat hypercholesterolaemia.

Reference

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By Robert West, professor of health psychology and director of tobacco studies at the Cancer Research UK Health and Behaviour Research Centre, Department of Epidemiology and Public Health, University College London; Professor West also undertakes consultancy work for Pfizer