VARENICLINE - Guidance for health professionals on a new prescription-only stop smoking medication

ASH, London, November 2006

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About this guidance

Varenicline, which will be called Champix in the UK, is due to be launched on prescription in early December 2006. We are publishing this guidance to help smoking cessation advisers and other health professionals decide how to manage anticipated demand for this new stop smoking medication. In this paper we briefly describe varenicline, review the evidence that it works, and make recommendations on how to use it, based on the research evidence, the SPC (Summary of Product Characteristics), and expert opinion.

The National Institute for Health and Clinical Excellence (NICE) will be issuing their guidance on varenicline around the late spring or early summer of 2007, and therefore this document gives interim guidance only. Furthermore, because varenicline is a new, centrally acting drug, with limited time yet for adverse effects to emerge, we have not made a recommendation as to whether it should be a first or second line smoking cessation treatment. We think this judgment should be made by the prescribing physician in consultation with the smoker, following a discussion of efficacy and safety profiles of available treatments, contraindications and precautions, and taking into account patient preference and experience of other treatments. When the NICE guidance is published there will be more experience of the drug, including of adverse events.

Key messages to health professionals

1. Varenicline is a new drug developed specifically for smoking cessation.

2. It has a different mechanism of action from the other smoking cessation medications available in the UK.

3. It is thought to work by reducing the strength of the smoker's urge to smoke and by relieving craving and withdrawal symptoms.

4. Two randomised comparative phase 3 clinical trials report good results, in which varenicline is superior to placebo and to bupropion.

5. The main adverse effect is nausea; no serious adverse effects have yet been found.

6. Unlike NRT and bupropion, varenicline does not appear to reduce post-cessation weight gain.

7.It looks to be an effective and welcome addition to our range of medications to help smokers stop.

Prescribing details from the SPC

1. Varenicline has been licensed for use with all smokers except those with severe renal impairment, pregnant or breastfeeding smokers, and those under 18; to date there are no known drug interactions that need to be considered.

2. Treatment with varenicline begins 1 week before the quit date. During this week the dose is titrated until it reaches the treatment dose of 1mg twice daily for 12 weeks after the quit date.

3. If the patient has stopped smoking at the end of the 12 week treatment period, an additional course of 12 weeks treatment at 1mg twice daily may be considered.

4. In the trials, at the end of the treatment period, discontinuation of varenicline was associated with irritability, an urge to smoke, depression and/or insomnia in up to 3% of patients. Because of this the SPC recommends that patients need to be informed and dose tapering considered.

Recommendations

1. As varenicline has not yet been tested in patients with psychiatric illness, we suggest that if it is prescribed to such patients, it is done so only with close surveillance and follow-up by the prescribing physician.

2. Clinical trials have demonstrated efficacy in those receiving weekly support, so as far as possible varenicline should be prescribed to those receiving such support, either through the services or from a health professional. This will also enable prescribing to be contingent on continuing effort to quit smoking.

3. As it is a new drug, patients should be encouraged to report adverse effects.

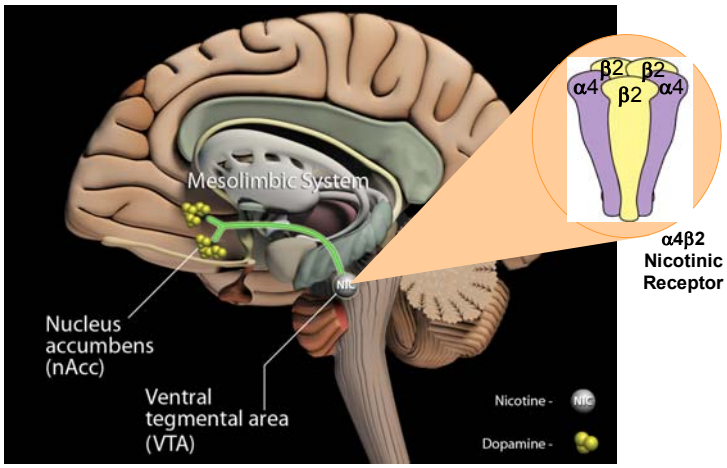
4. If the patient has stopped smoking at the end of the 12 week treatment period, but is not confident of remaining abstinent, we suggest the clinician makes a judgement as to whether the patient will benefit from continued support, bearing in mind the high relapse rates back to smoking. Varenicline can then be continued for a further 12 weeks.

5. The SPC suggests that varenicline be taken with a glass of water to help reduce nausea and experience in the US has indicated that taking the second pill at dinner or supper time rather than bedtime may help reduce insomnia and disturbed dreams.

Background

Varenicline is a new type of medication specifically designed for smoking cessation. In this respect it differs from bupropion, an anti-depressant which had been on the market for many years when it was discovered, by chance, to have an effect on smoking rates. Varenicline was approved by the FDA in the US in May 2006 (under the trade name Chantix) and by the European Medicines Evaluation Agency (EMEA) in September 2006 (under the trade name Champix). It is a nicotinic acetylcholine receptor partial agonist and is thought to work by reducing the strength of the smoker's urge to smoke and relieving withdrawal symptoms. Furthermore, if a person smokes a cigarette while using varenicline, it has the potential to diminish the sense of satisfaction associated with smoking.

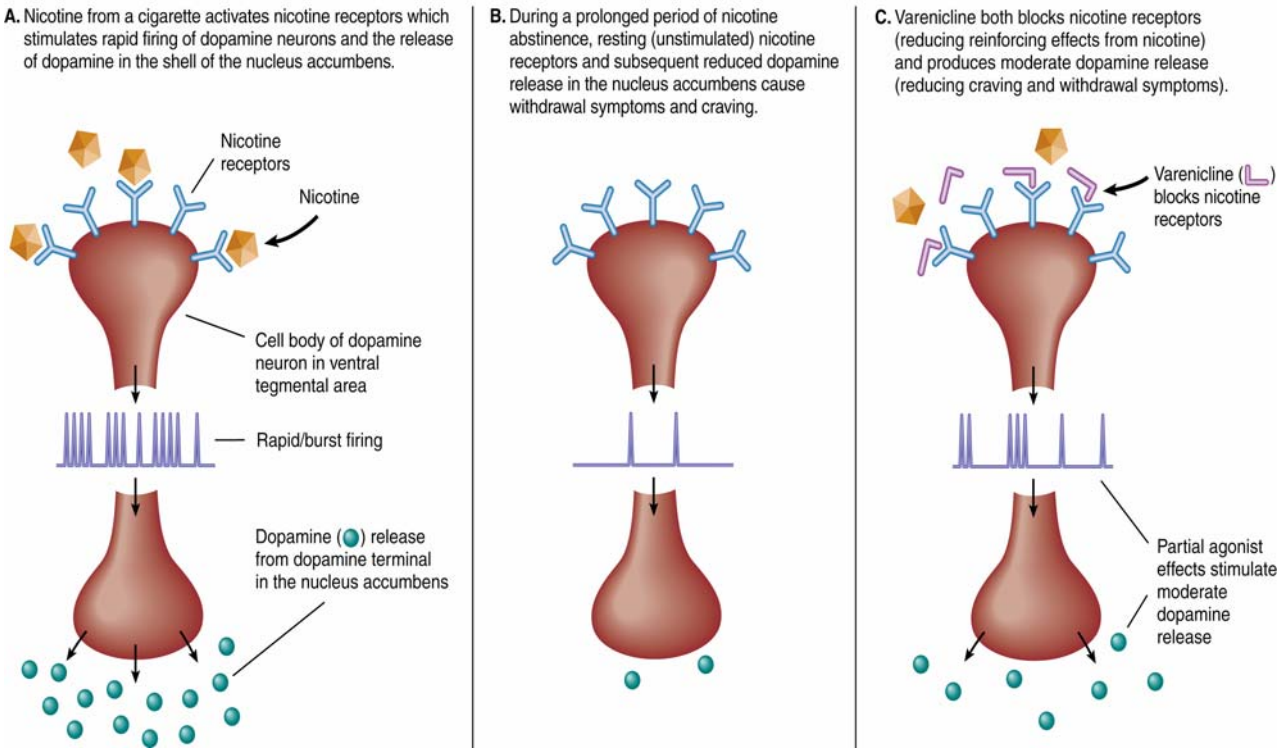
The neurochemistry of varenicline is complex. It is an α4ß2 nicotinic acetylcholine receptor partial agonist. Being a partial agonist means that is has both a stimulating *and* a blocking effect on the receptor it is attracted to. It is structurally similar to cytisine, a naturally occurring substance used as a starting point to develop varenicline (1). Cytisine has been licensed as a stop smoking medication for around forty years in central and eastern Europe. The α 4ß2 receptor subtype is thought to mediate the rewarding properties of nicotine by modulating the release of dopamine in the nucleus accumbens, the so called “pleasure centre” of the brain (2) (see diagram).



- **Nicotine binds predominantly to nicotinic acetylcholine (nACh) receptors in the CNS; the primary is the α4β2 nicotinic receptor in the Ventral Tegmental Area (VTA)**
- **After nicotine binds to the α4β2 nicotinic receptor in the VTA, it results in a release of dopamine in the Nucleus Accumbuns (nAcc) which is linked to reward**

“Agonist” means that when varenicline binds to the nicotinic receptor it has an effect similar to that of nicotine in stimulating the release of dopamine, although varenicline produces a slower, longer lasting and smaller increase in dopamine release than nicotine. Thus it partially mimics the effect of nicotine and this is thought to explain why it reduces craving when smokers abstain and are deprived of nicotine. However varenicline also binds to the receptor and partially blocks it (hence “partial” agonist), which reduces the binding site availability for nicotine, and so results in a weaker response if people smoke while using the drug. Thus the smoker may experience less satisfaction from smoking. And because varenicline has a higher affinity for the α4ß2 nicotinic acetylcholine receptor than nicotine, it will displace nicotine on the receptor in the same way that carbon monoxide displaces oxygen from haemoglobin, and thus limit the effect of nicotine. Because varenicline doesn’t have as strong an effect as nicotine in releasing dopamine, the addiction potential is likely to be lower.

Figure 3. Highly simplified scheme showing effects of (a) nicotine from cigarettes (b) nicotine withdrawal and (c) varenicline, on nicotine receptors and dopamine release.



We are grateful to Jonathan Foulds and Blackwell Publishing, Oxford, England, for permission to use this diagram, which is from: Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. International Journal of Clinical Practice 2006;60:571-576.

The evidence

There are three standard phases of clinical trials required by regulatory authorities for marketing authorization for a new drug, common across almost all products and all companies. Phase 1 studies usually involve initial dose ranging studies in healthy volunteers to test tolerability and initial adverse effects. Phase 2 studies use patients to fine tune dosing and look in more depth at adverse effects; they also give an initial indication of efficacy, although usually in small numbers of patients. Phase 3 is the key for approval of a new product. Phase 3 trials use large numbers of patients to establish outcome (in this case cessation rates) and the adverse effect profile.

Varenicline has undergone two dosing trials (3,4), two randomised comparative trials measuring efficacy (5,6), and a trial with a maintenance phase, to see if taking the drug for longer reduces relapse rates (7). There have thus been five trials in all, the last three including almost 3,980 smokers of whom 2,623 used varenicline.

The two main outcome trials, which were identical in design, compared 12 weeks of varenicline 1mg twice daily to matching placebo and included an extra comparison with 150 mg twice daily of bupropion (5,6). The varenicline dose of 1mg twice daily with initial titration (see *Instructions for use* below) during the first week was derived from the phase 2 dosing studies (3,4). Patients in these studies were also provided with educational materials and received approximately 10 minutes smoking-cessation counselling at each weekly clinic visit during the 12 week treatment phase. They were then followed up for an additional 40 weeks

without treatment after the initial 12 week treatment period. Subjects also received a telephone call three days after the target quit day, which was one week after the first visit.

Trial entry criteria included good health, male and female smokers aged 18 to 75, smoking at least 10 cigarettes per day during the past year, no prior use at all of varenicline or bupropion for any indication, and being motivated to stop smoking. Smokers were excluded if they had had serious or unstable disease within six months, weighed less than 7st 2lbs (100lbs / 45kg) or had a BMI of less than 15 or more than 38, had a history of drug or alcohol abuse in the past year, had used another form of tobacco, or marijuana, in the past month, had used NRT, clonidine or nortriptyline in the past month, had received any treatment for major depression in the previous 12 months, had a history of or current panic disorder, psychosis or bipolar disorder, or had contraindications for bupropion. Subjects had smoked an average of just over 20 cigarettes per day for approximately 25 years. Examples of serious or unstable disease would be recent heart surgery, unstable diabetes, emphysema – anything serious or unstable enough to prevent the patient living a normal life.

The first main outcome study (5) enrolled 1,025 smokers (352 used varenicline) and the second (6) 1,027 (344 used varenicline). The main outcome measure was self-reported continuous abstinence from smoking (not even one puff) for the last 4 weeks on the drug, ie. weeks 9-12, confirmed by expired air carbon monoxide (10 ppm or less) (*end of treatment* in the table below). The second outcome measure was CO validated self-reported continuous abstinence from weeks 9 to 52 (*one year follow up* in the table below). The numbers in the table are percent abstinent (rounded).

Cessation rates of the two randomized controlled outcome trials (5,6)					
	end of treatment			one year follow up	
	study one	study two		study one	study two
Varenicline	44	44		22	23
Bupropion	30	30		16	15
Placebo	18	18		8	10

Note: conventional rounding, 0.1 - 0.4 rounded down, 0.5 - 0.9 rounded up.

Cessation rates in the varenicline group were statistically significantly better than placebo and bupropion at the end of treatment in both studies (5,6). The long term quit rates for varenicline were significantly higher than placebo in both studies, significantly higher than bupropion in the second study (6), and just failed to reach significance in the first study (5). When the long term results of the two studies are pooled, varenicline more than doubled the odds of stopping compared with placebo (OR 2.82, 95% CI 2.06 – 3.86) and was significantly better than bupropion (OR 1.56, 95% CI 1.19 – 2.06) (8). At the time of writing no trials comparing varenicline directly with NRT have been published.

In the maintenance of abstinence study (7), 1,210 smokers who were abstinent from smoking during the last 7 days of 12 weeks of open label treatment with varenicline 1mg twice daily (1,927 Ss), and who were deemed appropriate for study participation, were randomized to an additional 12 weeks of varenicline 1mg twice daily or matching placebo. During this period both groups received five brief counselling sessions. The relapse rate (confirmed by expired air carbon monoxide) from week 13 to week 24 was significantly lower for subjects continuing with varenicline (30%) than for subjects switching to placebo (50%) (OR=0.4, 95% CI 0.33 – 0.52). In the subsequent 12 week period however (weeks 25-36), immediately after varenicline treatment ceased, more from the varenicline maintenance group relapsed than from the placebo group. A modest but significant advantage in abstinence rates of varenicline over placebo remained at the one-year follow up (again confirmed by carbon monoxide), 44% c/w 37%.

Other effects, adverse effects, safety

Both varenicline and bupropion reduced craving compared with placebo and there was some evidence that varenicline reduced smoking satisfaction, although these findings need confirmation in further studies. Nausea, insomnia, abnormal dreams, headaches and flatulence were the most commonly reported adverse effects in the two main outcome studies (5,6). The most common adverse effect was nausea, reported by approximately 30% of subjects taking 1mg of varenicline twice daily. It was usually mild to moderate in intensity and generally resolved with continued treatment. Only 3% of subjects discontinued treatment because of it. However this rate was higher than with bupropion or placebo. It would appear that nausea is dose related and titration – for example to 0.5 mg daily – appears to reduce the incidence (4) (see on). There were more reports of abnormal dreams in the varenicline group.

Of those subjects who were abstinent during the 9-12 week period (used to define end of treatment abstinence) in the Jorenby et al study (6), the average weight gain was 2.89kg in those on varenicline, 1.88kg in those on bupropion and 3.15kg in those on placebo.

Overall around 10% of people on varenicline across the three phase 3 trials stopped using the drug because of adverse effects. In the two main outcome studies (5,6) the incidence of adverse effects emerging during treatment was similar for varenicline, bupropion and placebo. Other adverse effects noted in the SPC (9) included increased appetite, headache, dizziness and fatigue.

No significant drug-drug interactions associated with the use of varenicline have so far been identified, nor do there appear to be any contra-indications. However, because varenicline is excreted almost entirely by the kidney, precautions should be taken with patients who have severe renal impairment. The following advice is summarised from the SPC (9), which we recommend you consult for further details.

“For patients with moderate renal impairment who experience adverse events that are not tolerable, dosing may be reduced to 1 mg once daily. For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience in patients with end stage renal disease, varenicline is not recommended in this patient population.”

Comment on the evidence

The authors of the first main outcome study (5) draw attention to potential limitations of these results: “First, participants who volunteer for clinical trials of investigational drugs tend to be in better general health and are by definition more motivated than those in a typical primary care population. The external validity of the trial is also limited by the fact that individuals with serious medical illness or current or recent depression were excluded from the trial. Second, all participants received 12 weeks of brief individual smoking cessation counseling along with the study drug. Therefore, this study does not assess the efficacy of varenicline in the context of more minimal counseling support, which is common in health care settings.” (5) A JAMA editorial agrees with these cautions, particularly that the special study population may limit the generalisability of the results, and also notes the higher rates of nausea and abnormal dreams reported by those on varenicline. The editorial concludes however that these are good results and that varenicline represents a useful new tool in our attempts to help smokers stop (10).

Early experience from the USA

Although patient demand for varenicline in the US was low it is now increasing rapidly. So far there has been no direct advertising to smokers. This is expected to start early in 2007. In the US advertising of prescription medicines direct to consumers is allowed but the advertising has to be approved by the FDA. The delay in advertising varenicline was to give doctors time to learn about it before demand increased significantly. In general varenicline seems to have been well received, with nausea common but usually manageable, often by adjusting the dose (see on).

Recommendations for smoking cessation advisers and other health professionals in the UK

Instructions for use and precautions from the Summary of Product Characteristics (SPC) (9)

The information in the next two paragraphs is from the SPC. We have made one comment in *italics*.

Instructions for use: Varenicline comes in film coated tablets, each tablet containing 0.5mg of varenicline tartrate. The SPC notes that patients who are provided with additional support and advice are more likely to succeed. Treatment is started one week before the target quit date. The recommended titration pattern is 0.5mg daily for the first three days, 0.5mg twice daily on days four to seven, and then the treatment dose, 1mg twice daily for 12 weeks, one in the morning and one in the evening. Patients should be advised to take varenicline after eating and with a full glass of water. For those who are successful in quitting smoking at the end of 12 weeks, an additional 12 weeks of treatment can be used to reduce the chance of relapse. Patients who cannot tolerate side effects from varenicline should notify the prescribing physician and could have the dose temporarily or permanently lowered, as varenicline is available in 1mg and 0.5mg tablets. *We note however the efficacy of varenicline does appear to be dose related*.

Precautions: There are no specific contra-indications mentioned in the SPC but patients with severe renal impairment are recommended to use a reduced dose of 1mg daily, and because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient. Varenicline is not recommended for use in children or adolescents below 18, nor in pregnancy, because there are no data yet in these groups. At the end of treatment, discontinuation of varenicline was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients, so the prescriber should inform the patient accordingly and discuss or consider the potential need for dose tapering.

The SPC recommendation for smokers with psychiatric illness is as follows: “Smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.”

How and to whom should varenicline be prescribed?

Choice of medication, which should be discussed with a doctor, can be guided by factors such as patient preference and previous experience. As NRT and bupropion have been on the market for so long, especially NRT, many smokers are likely to want to try this new drug, so demand is likely to be high.

As varenicline is a new drug, it is possible that with greater experience of its use, drug interactions or rare adverse effects may be identified, so we recommend that patients should be encouraged to report potential side effects to health professionals.

As the clinical trials have demonstrated efficacy in people having weekly support, we recommend that varenicline should be prescribed to people, as far as possible, who are receiving regular support through the NHS treatment services, or will receive at least 10 minutes support each week from a health professional. This will also enable prescribing to be contingent on continuing efforts to quit smoking.

As varenicline has not yet been tested in patients with psychiatric illness, given the dopaminergic action of the drug and the caution in the SPC, we suggest that if varenicline is prescribed to such patients, it is done so only with close surveillance and follow-up.

We believe it is unwise to prescribe a brand new drug to a pregnant smoker when there are drugs with a known risk profile available. We also support the SPC caution that varenicline should not be prescribed to people under 18.

The efficacy and safety of varenicline used alongside bupropion or NRT has not been studied thus prescribing such combination therapies is not recommended at the moment.

Smokers who have stopped smoking at the end of the 12 week treatment period but are not yet confident of remaining abstinent, only managed to stop recently, or have been having minor slips, or feel they would like to continue, can be given varenicline for a further 12 weeks.

Experience from the USA so far suggests that in general varenicline is very well tolerated. We recommend that it be taken with food and a glass of water to help reduce nausea (this is in the SPC), and experience in the US has suggested that taking the second pill at dinner or supper time rather than bedtime may help reduce insomnia and disturbed dreams.

Packaging and cost

Varenicline will be sold in 2 and 4 week packs. There will be a 2 week initial titration pack, a 2 week continuation pack, a 4 week continuation pack 1mg twice a day, and a 4 week pack 0.5mg twice a day.

Varenicline is likely to cost about £1.95 per day and £164 for a full three month course. The cost of NRT depends on the format used but if you assume the 24 hour patch given in four one week lots (a frequently prescribed format), and bupropion at almost £40 a month, then the approximate monthly costs are likely to be:

Varenicline £55
Bupropion £40
NRT £40.

Cost effectiveness

It seems likely that patient demand will determine the popularity of varenicline, but in the current funding climate it is difficult to predict how trusts will make spending decisions in relation to the new drug. Since all smoking cessation treatments are highly cost effective compared with almost all other healthcare interventions (11), varenicline will also be very cost effective. However until we have cost and effectiveness data in less restricted

populations of smokers, we think it premature to comment on its cost effectiveness in real life settings compared with NRT and bupropion.

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