Varenicline: effectiveness and safety

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Introduction

The need for this briefing was established when the National Centre for Smoking Cessation and Training (NCSCT) accompanied the Department of Health (DH) Tobacco Control Delivery Team on a number of regional seminars. Commissioners and managers of local stop smoking services stated that, despite the evidence on safety and efficacy, getting primary care trusts to accept varenicline as an equal 'first line' treatment option was in some cases difficult.

This briefing is intended as a resource for commissioners, managers and staff of stop smoking services and is set out as answers to a series of questions. For more information on the NCSCT and on the NCSCT ethical policy please visit our website: www.ncsct.co.uk

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Varenicline (Champix)

1. Is varenicline more effective than NRT?

Answer: It is certainly more effective than NRT used in single forms (e.g. patch or gum). Its advantage over a combination of more than one NRT product (patch plus a fast-acting form) is likely to be smaller.

The evidence: In a Cochrane review of 12 reviews on smoking cessation medication,[1] varenicline was more effective than single NRT (OR = 1.57; 95% CredI = 1.29 to 1.91) but not more effective than combination NRT (OR = 1.06; 95% CredI = 0.75 to 1.48). Another meta-analysis of trials found very similar results.[2] Data from clinical practice indicate that varenicline is superior to single NRT, while the difference in effectiveness between varenicline and combination NRT appears to vary considerably between clinics. A study comparing 52-week abstinence in smokers attending a behavioural support programme in a Czech clinic found that 31.0% of those using NRT were abstinent compared with 42.8% of those using varenicline and this remained significant after adjusting for other factors associated with abstinence (adjusted odds ratio = 2.03; 95% CI = 1.46 to 2.82). Outcomes were better for varenicline compared with either single form NRT (adjusted OR = 1.39; 95% CI = 1.31 to 2.79) or dual form NRT (adjusted OR = 2.19; 95% CI = 1.44 to 3.35).[3] In the English Stop Smoking Services, the advantage for varenicline was much smaller but still existent when adjusting for client and treatment characteristics (adjusted OR = 1.08; 95% CI = 1.00 to 1.16; adjusted absolute percentage difference of 1.86% (95% CI, 0.07% – 3.67%). This study also indicated that the relative effectiveness of the two medications varied considerably across services.[4]

2. Does varenicline increase risk of suicide?

Answer: While it is never possible to rule out a very small increased risk the evidence to date shows no evidence of this.

The evidence: There have been media reports of cases of suicide and suicidal thoughts in people taking varenicline. However in epidemiology, case reports are seen as very weak evidence of an association and can be misleading. The crucial question that needs to be answered is whether the risk is greater than it would have been in the same individuals had they not taken this medication.

A number of studies have now been performed and none has found evidence of an increased risk of suicide or suicidal ideation due to varenicline.

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One study looked at whether the reported number of suicides on varenicline was more than would be expected given the number of smokers using varenicline for a number of weeks.[5] The modelling showed that varenicline use was not associated with an increased risk of suicide. A study examining GP prescription data for records of 81,000 users of stop smoking medication found no difference in the incidence of suicide related events.[6] Another study used 12,000 patient records from Denmark and found no association between varenicline and suicidal ideation.[7]

In addition to this, studies have examined the association between varenicline use and psychiatric events and not found an increased risk.[6–10] One of these studies examined the occurrence of psychiatric adverse events in the randomised placebo controlled trials of varenicline versus placebo. Combined, these studies randomly allocated 3,901 smokers to varenicline and 2,005 to placebo. The number of adverse mood-related or agitation-related events was similar on varenicline to on placebo and the confidence intervals excluded any substantial risk (RR = 1.02; 95% CI: 0.86–1.22).[8] Other studies involving tens of thousands of patients found no difference in neuropsychiatric events between patients on varenicline or NRT patch[9] or between those on varenicline or bupropion.[10]

Whilst it is impossible to rule out any effect at all, these studies indicate that if there is an increased risk it must be very small.

Notwithstanding this, it is important to remain vigilant to this and other possible rare neuropsychiatric side effects while not losing sight of the fact that because of its high level of effectiveness varenicline is an important life-saving medication.

The Medicines and Healthcare products Regulatory Authority (MHRA) issues the following advice:[11]

- Patients and their family or caregivers should be made aware of the possibility that trying to stop smoking might cause symptoms of depression
- Patients who are taking varenicline who develop suicidal thoughts or behaviour should stop their treatment and contact their doctor immediately
- Varenicline should be discontinued immediately if agitation, depressed mood, or changes in behaviour are observed that are of concern for the doctor, patient, family, or caregiver
- Patients with serious psychiatric illness did not participate in the premarketing studies of varenicline, and the safety and efficacy of varenicline in such patients has not been established. Care should be taken when prescribing varenicline to patients who have a history of psychiatric illness.

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3. Does varenicline increase risk of cardiovascular events?

Answer: There does not appear to be an increase in risk in cardiovascular serious adverse events associated with the use of varenicline.

The evidence: An earlier published meta-analysis looked at the number of cardiovascular events seen in 8,216 clients taking either varenicline or placebo.[12] It found that events were rare in both groups but that there was a slightly increased number in the people taking varenicline: 1.06% (52 out of 4,908) compared with 0.82% taking placebo (27 out of 3,308). However, a number of limitations of this meta-analysis have been identified, including the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which nobody had an event.

A more recent meta-analysis also evaluated the association of the use of varenicline with cardiovascular serious adverse events.[13] This study provides up-to-date risk estimates and included all published placebo-controlled trials of varenicline with a total of 9,232 participants. It confirmed that the risk of cardiovascular events was extremely rare for those using varenicline (0.63%, 34 out of 5,431) or placebo (0.47%, 18 out of 3,801). This meta-analysis, which relied on a more robust methodology to mitigate the limitations of the previous review, concluded that the difference in cardiovascular risk between groups was small (0.27%. 95% confidence interval -0.10–0.63, p=0.15) and not statistically significant or clinically meaningful. This was again supported by more recent studies not included in the review.[14,15]

Taking these findings together, there is currently little reason to avoid this medication on these grounds. This view is in line with the European Medicines Agency that confirmed a positive benefit-risk balance for varenicline and concluded that its benefits as a smoking cessation medicine outweigh any potential slight increase in cardiovascular events.[16]

Nevertheless, the Summary of Product Characteristics for Champix[17] now includes a statement that patients should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

NCSCT briefing no. 4 – Cardiovascular disease and varenicline (Champix) gives more detail about this topic.

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4. Is varenicline safe to be used by people with mental health problems?

Answer: There are no good grounds for excluding patients with mental health problems from taking varenicline and because of its high level of effectiveness it may be their best chance of stopping smoking, especially given their generally high level of nicotine dependence.

The evidence: There has been no suggestion in the published studies or case reports that smokers with pre-existing mental health problems are more vulnerable to neuropsychiatric side effects than other patients.

In a study[18] of over 500 patients followed up for 12 months, varenicline increased smoking cessation in smokers with stably treated current or past depression without exacerbating depression or anxiety.

A recent review[19] of the use of varenicline in patients with mental health problems states:

'Although the risk of potential neuropsychiatric events is evident through voluntary reporting systems and reported cases in the literature, multiple studies and case reports support the use of varenicline in the mental health population'

The authors recommend that when using varenicline in smokers with mental health illness that there should be:

- Cautious treatment initiation
- Patient education
- Close follow-up
- Monitoring for mood and behaviour changes during therapy

More recent studies have specifically looked at varenicline in patients with stable schizophrenia or schizoaffective disorders and found it not to be associated with changes in psychiatric symptoms.[20–22]

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5. Varenicline is a 'black triangle' drug. Are not such drugs considered potentially unsafe?

Answer: New medications are often tested in clinical trials that have a relative small number of users. This means that clinical trials may not show all possible side effects of the new medication. This does not mean that these medicines are unsafe, but only when large numbers of people have taken the medication do rare or long-term adverse effects become known. Therefore when these new medications are introduced to the market the Commission on Human Medicines (CHM) and the MHRA encourages the reporting of all suspected reactions to new medicines which are denoted by an inverted Black Triangle symbol (▼).

Varenicline has been examined by NICE and advised for use in the NHS[1] and no further consideration of this is planned.

6. Varenicline is more expensive than other medications, is it cost-effective?

Answer: Varenicline typically costs more than other smoking cessation medications. However, it is also more effective, so when examined as cost per quitter, the figures are very similar. Comparisons of cost-effectiveness have found varenicline to be at least as cost-effective as NRT or bupropion.[23,24]

All smoking cessation pharmacotherapies are amongst the best buys in modern medicine, being hugely more cost-effective per quality adjusted life year gained (QALY) than other commonly used NHS treatments.[25]

7. What is varenicline's role in treatment?

Answer: NICE has indicated that it should be a first line treatment and smokers should be routinely offered it as one of the options available to them.[26] It should not be necessary for people to have failed to stop smoking with other medication before using varenicline. Given that it is almost certainly more effective than single forms of NRT, to deny smokers access to this treatment will lead to avoidable loss of life. After the age of 35 years, every year that cessation is delayed results in a loss of three months' life expectancy[27] so every quit attempt must be given the best possible chance of success and it is not appropriate to wait for quit attempts to fail before offering effective help.

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