

NEW DRUG EVALUATION

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VARENICLINE

Varenicline is a partial nicotinic receptor agonist licensed to aid smoking cessation. To date, there is no published evidence directly comparing varenicline with the most commonly prescribed cessation aid, nicotine replacement therapy. Furthermore, safety has not been established in patients with medication controlled diabetes, significant cardiovascular disease or uncontrolled hypertension. In published trials, 44% of patients taking varenicline for 12 weeks abstained from smoking during weeks 9-12 compared with 30% on bupropion and 18% on placebo. However, all subjects received concomitant motivational support at a level that would not be expected in clinical practice. Current evidence does not suggest that a subsequent 12-week treatment course significantly improves long-term (52-week) cessation rates.

What is it?

Varenicline (Champix[®], Pfizer) is a partial agonist selective for nicotinic acetylcholine receptor subtypes and is licensed as an aid to smoking cessation.^[1] It is available in 0.5 mg and 1 mg tablets with the recommended dose being titration with 0.5 mg tablets for one week, followed by 1 mg twice daily for 11 weeks. Dosing should start one to two weeks before the planned cessation date and tablets can be taken with or without food.^[1]

How effective is it?

Two multi-centre, randomised, double-blind, placebo-controlled trials involving 1,025 and 1,027 patients compared varenicline with bupropion and placebo.^[2, 3] Eligible subjects received either 1 mg varenicline twice daily, 150 mg bupropion twice daily or placebo for 12 weeks (which included dose titration of active treatments for one week). Subjects with medication controlled diabetes mellitus, significant cardiovascular disease or uncontrolled hypertension were excluded.^[2, 3] The primary end point was continuous abstinence during weeks 9 and 12. In both studies varenicline was significantly more effective than both bupropion (44% vs. 29.5%, $p < 0.001$ ^[2] and 43.9% vs. 29.8%, $p < 0.001$ ^[3]) and placebo (44.0% vs. 17.7%, $p < 0.001$ ^[2] and 43.9% vs. 17.6%, $p < 0.001$ ^[3]). Longer-term abstinence was also evaluated by assessing cessation rates from weeks 9 to 52. Varenicline was significantly more effective than bupropion in one trial (23% vs. 14.6%, $p = 0.004$ ^[3]) and placebo in both trials (21.9% vs. 8.4%, $p < 0.001$ ^[2] and 23% vs. 10.3%, $p < 0.001$ ^[3]). These results may be considered to more closely reflect likely differences between interventions in the longer term, as benefits from smoking cessation are realised only over an extended period.

An extension trial compared varenicline with placebo for a further 12-week course from weeks 13 to 24.^[4] All subjects ($n = 1,927$) initially received varenicline 1 mg twice daily for

12 weeks. Subjects who did not smoke during the last seven days of those 12 weeks were subsequently randomised to receive a further 12-week course of varenicline ($n = 603$) or placebo ($n = 607$). The confirmed continuous abstinence rates at 24 weeks were 70.5% and 49.6% for varenicline and placebo respectively ($p < 0.001$). The 52-week abstinence rates were 43.6% and 36.9% respectively ($p = 0.02$).^[4] It is noteworthy that over a third ($n = 691$) of the original participants were not eligible for randomisation after the 12-week open-label phase.^[4] Consequently a large proportion of participants for whom varenicline may have been ineffective were eliminated from the final analysis. This potentially biases the results in favour of treatment with varenicline. If the final analysis includes these ineligible patients as failures ($n = 1,294$) then the 11-to 52-week abstinence rates for those taking the drug for 24 weeks are actually lower than for those taking the drug for 12 weeks in the companion studies.^[5]

Furthermore all patients had access to 18^[2, 3] or 20^[4] ≤10 minute counselling sessions, including one per week for the 12-week treatment phase. This level of support may not be available in practice, which could lead to lower response rates than those observed in the clinical trials.

A recent systematic review of varenicline conducted by the Cochrane Collaboration includes the data discussed here.^[6] It highlights the need for further independent, comparator trials to establish varenicline's relative efficacy and safety.^[6]

How safe is it?

The most commonly reported adverse effect was nausea with a markedly higher rate in subjects taking varenicline than bupropion and placebo (28-29%, 7-13%, 8-10% respectively).^[2, 3] Most reports were however of mild to moderate severity. Abnormal dreams were also more common in subjects taking varenicline (10-13%, 6%, 4-6% respectively).^[2, 3] The incidences of headache and insomnia

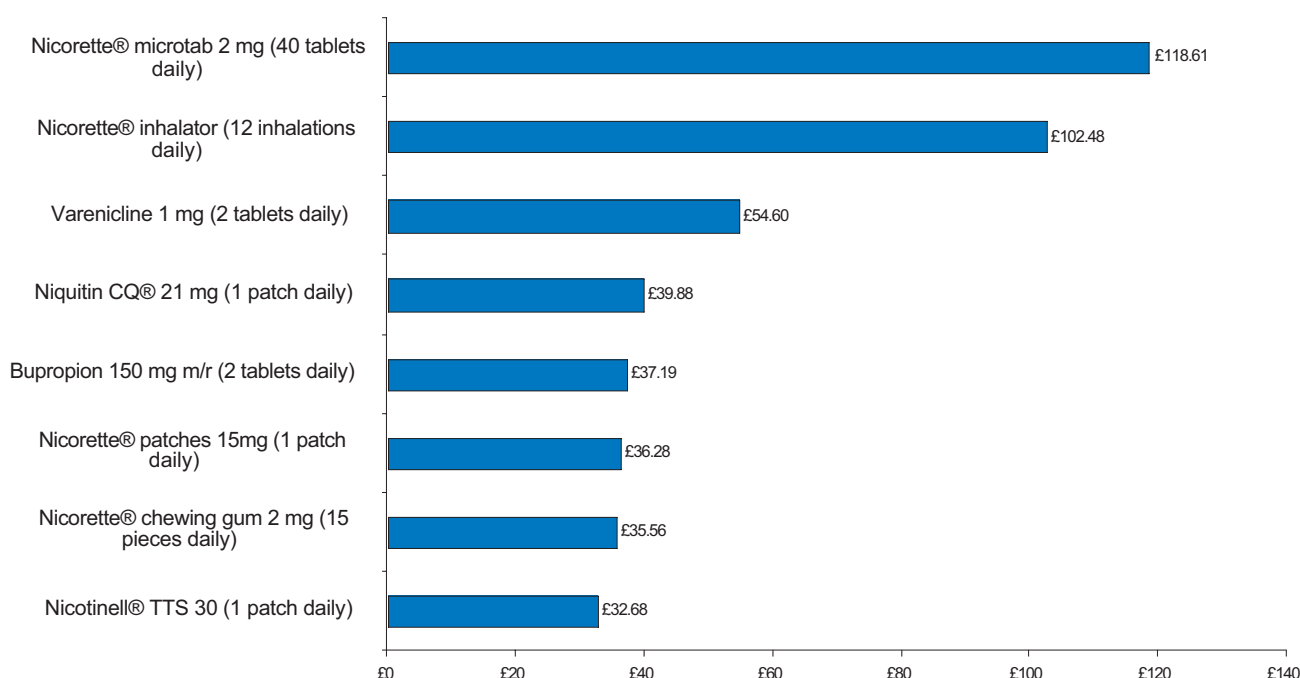
were also high although levels were only slightly higher for those on varenicline than placebo. Despite these side effects, discontinuation rates with varenicline were comparable with bupropion and placebo.^[2-4]

What other options are there?

Current licensed alternative smoking cessation aids are nicotine replacement therapy (NRT) and bupropion. It is recommended that smoking should stop completely before starting a smoking cessation regime with NRT. Counselling should also be available for behavioural support.^[7] The National Institute for Health and Clinical Excellence (NICE) has published guidance on the use of NRT and bupropion in smoking cessation, recommending either for smokers who have expressed a desire to quit smoking.^[8]

How much does it cost?

Cost of 28 days treatment (Drug Tariff / eMIMS January 2007)



The NRT preparations selected were the most commonly prescribed NRT preparations in the North of England in the 2005/06 financial year. Doses shown are for general comparison only and do not imply therapeutic equivalence.

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KEY: RCT - randomised controlled trial, E - editorial, G - guideline, R- review

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