Varenicline for smoking cessation

MATTHEW PETERS MD, FRACP

Able to block the pleasant sensation of smoking while activating nicotine receptors enough to ease cravings, the latest addition to the smoking cessation armamentarium is unique. However, varenicline is not side effect free, and careful patient selection for this treatment is essential.

PHOTOLIBRARY

Tobacco dependence is a complex process characterised by repeated cycles of stimulation, followed after a period of time by withdrawal and relief of withdrawal symptoms from the next cigarette providing a further stimulatory effect.[1]

Chemically, a surge in brain nicotine levels after smoking activates specific nicotine receptors within the so-called 'brain reward system' that functions as the common central pathway for pleasurable experiences such as sexual activity and satiety from eating.[2] Dopamine is the critical mediator in this process and nicotine, cocaine, opiates and amphetamines all act on their own specific receptors in the 'brain reward system'.

Nicotine replacement therapies (NRTs) and bupropion hydrochloride (Clorprax, Prexaton, Zyban SR) increase dopamine levels and ease cravings but cannot prevent the reinforcement associated with smoking. A better drug to treat smoking dependence would do both. A simple receptor blocking agent would prevent reinforcement but produce uncomfortable withdrawal that would not be ameliorated by nicotine intake from smoking.

Varenicline (Champix) is the first smoking cessation product that acts at the same brain receptor targeted by nicotine inhaled from smoke. It became available in Australia on the PBS from 1 January 2008. Varenicline is a partial receptor agonist, the first to be developed and marketed for smoking cessation.[3] It specifically activates the nicotine receptor sufficiently to ease craving but prevents full activation of the reward system should the smoker lapse with a cigarette.

Dr Peters is a Clinical Associate Professor of Medicine at The University of Sydney, Concord Clinical School, and a Senior Staff Specialist at Concord Hospital, Concord, Sydney, NSW.

Clinical studies

Relief of cravings and withdrawal, and prevention of reinforcement

In clinical trials varenicline and bupropion hydrochloride eased withdrawal symptoms to a similar extent but insomnia was more prominent among patients taking bupropion.[4,5] The trials showed that varenicline significantly reduced smoking satisfaction, psychological reward from smoking and, for patients who smoked during treatment, enjoyment of respiratory tract sensations (such as flavour and taste). In the same studies, smoking satisfaction and relief of cigarette cravings were not changed in the group taking bupropion. These findings suggest that varenicline inhibits reinforcement from smoking *in vivo* in a fashion consistent with conceptual design and preclinical studies.

Smoking cessation

The major comparative effectiveness studies involving varenicline included a three-way blinded comparison with bupropion and placebo. After 12 weeks of treatment, the seven-day confirmed abstinence rate with varenicline was approximately 50.3%. This compared favourably with use of bupropion (approximately 36.1%) and placebo (approximately 21%).[4,5] Abstinence rates climbed slowly through the 12-week standard treatment period in the study for patients taking varenicline, indicating that failure to quit early in a cessation attempt should not lead to abandonment of the drug. It is plausible that this steady increase in quit success during treatment is related to the absence of reinforcement from further smoking.

In another study in which all patients received varenicline openly for 12 weeks, the seven-day quit rate at the end of treatment was even higher at 64%.[6] This may be related to the so-called 'nocebo' effect that occurs when the thought that a subject might be taking placebo treatment is removed.

In all major studies of smoking cessation treatments or strategies, about half of those who have quit at the end of treatment will relapse in the next 12 months. In the studies above, after 12 months, 29.3% of the varenicline group, 23.1% of those who had been on bupropion and 15.6% of those taking placebo were still abstinent.[4,5] If patients are treated for 24 weeks, as opposed to the standard 12 weeks of treatment, relapse is delayed but not prevented (when relapse is measured from the time treatment ends).[6]

Dosing and precautions

Treatment with varenicline starts with a dose titration phase of 0.5 mg daily for the first three days, followed by a dosage of 0.5 mg twice daily for the next four days and then 1 mg twice daily for a total of 12 weeks' treatment. Patients require two prescriptions: one for the first four weeks and another for the remaining eight weeks. This is similar to the existing arrangement for bupropion on the PBS.

The target 'quit date' is between seven and 10 days after the first dose. If a patient develops problematic nausea during titration, dose increases can be delayed.

Varenicline is excreted largely unchanged in urine. For patients who have moderate renal impairment, the dose should be halved, and in those with severe renal failure, it may be more sensible to consider another smoking cessation strategy although varenicline is dialysable. Drug to drug interactions are minimal, and there is no need to make dose adjustments with varenicline for patients with hepatic disease. However, smoking cessation itself can alter levels of some drugs such as olanzapine (Zyprexa) and monitoring may be required.

There are no safety or efficacy data available for the use of varenicline in pregnancy or in children and for this reason it should not be used in these settings. Varenicline should not be used in combination with other smoking cessation therapies such as bupropion or NRTs.

Adverse effects

Nausea is the most commonly reported adverse event, occurring in up to 30% of patients. Patients should be specifically warned about the potential for nausea to develop and be counselled that it will settle in time. Only 3% of patients cease treatment because of nausea when the dose is titrated in the first week of treatment. Vivid but not necessarily unpleasant dreams are also common. In those people who have quit successfully at the conclusion of treatment, there is a 2% increase in reports of irritability but withdrawal from varenicline is otherwise well tolerated.

Use in clinical practice

At a community level, we should firstly encourage smokers to make a quit attempt and, secondly, make efforts to increase the chance of success. The high success rates described with varenicline have been achieved with standard counselling, amounting to five minutes at each study visit. At the very least, it is sensible that a patient starting treatment should receive a phone call from his or her GP or practice nurse on their designated quit date. A clinic visit is a good alternative.

Both sponsored support lines and state-based Quitlines should be able to provide appropriate advice for patients attempting smoking cessation with varenicline. Counselling will be useful both to achieve cessation and to prevent relapse during and after treatment.

In acute medical settings, NRT offers immediate relief of symptoms for those who cannot smoke or those who wish to quit. Varenicline does not offer such immediate relief and should be reserved for suitable patients who cannot quit or those who quit on NRT but later relapse.

No data are available to support the safety or effectiveness of varenicline in patients who have significant depression, panic disorder, psychosis or bipolar disorder or those who abuse drugs other than nicotine. A small number of adverse psychiatric events in patients taking varenicline have been reported. Whilst causation has not been proven in these cases, carefully monitored use of NRT is generally the preferred approach with such patients until the nature and extent of risks are clarified.

Patients who do not have a diagnosed mental illness should be told to contact their GP if they experience mood swings or agitation.

Summary

Studies of varenicline have shown that this new agent has improved efficacy compared with existing treatments that aid smoking cessation. Compared to bupropion, it matches control of withdrawal symptoms but also reduces cigarette satisfaction and it is safe when used in suitable patients. Despite these benefits, varenicline is neither side effect free nor a guarantee of successful smoking cessation. What is important is that clinicians caring for smokers develop competence and confidence with the use of this new drug. MT

References

1. Jarvis MJ. ABC of smoking cessation: why people smoke. BMJ 2004; 328: 277-279.
2. Dani JA, Harris RA. Nicotine addiction and comorbidity with alcohol abuse and mental illness. Nat Neurosci 2005; 8: 1465-1470.
3. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an α4β2 nicotinic receptor partial agonist for smoking cessation. J Med Chem 2005; 48: 3474-3477.
4. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 47-55.
5. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an α4β2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006; 296: 56-63.
6. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA 2006, 296: 64-71.

DECLARATION OF INTEREST: Dr Peters has served on advisory boards for smoking cessation products for Pfizer and GlaxoSmithKline and has received honoraria for lectures presented.