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## Further reading

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*Conflict of interest: none declared*

### Self-test questions

*The following statements are either true or false (answers on page 27)*

7. The cognitive impairment reported by some patients after chemotherapy may be caused by depression.
8. Erythropoietin prevents the cognitive impairment associated with chemotherapy.

# New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained either from the manufacturer's approved product information, a drug information centre or some other appropriate source.

## Nitric oxide

INOmax (Delpharm)

2 and 10 litre gas cylinders containing 800 parts per million

Approved indication: neonatal respiratory failure

Australian Medicines Handbook Appendix A

Nitric oxide has a physiological role in several systems of the body. One of its actions is to cause vasodilation. When it is administered as a gas it dilates the vessels in the lung. There is little effect on the systemic circulation as nitric oxide is inactivated when it binds to oxyhaemoglobin. This has led to the study of inhaled nitric oxide in conditions where there is pulmonary vasoconstriction.

Pulmonary hypertension can cause hypoxic respiratory failure in neonates. The pulmonary vascular resistance causes deoxygenated blood to be shunted from the right to the left heart through the foramen ovale. In severe cases extracorporeal membrane oxygenation is needed, but this procedure is very specialised and mortality remains high. If nitric oxide can reduce the pulmonary hypertension it could reduce the need for extracorporeal membrane oxygenation.

The Neonatal Inhaled Nitric Oxide Study (NINOS) involved 235 babies, of at least 34 weeks gestation, who needed ventilation for hypoxic respiratory failure. In about half the cases this resulted from meconium aspiration while 16–18% of the babies had persistent pulmonary hypertension of the newborn. There was a significantly greater improvement in the oxygenation of the babies randomised to receive nitric oxide. Extracorporeal membrane oxygenation was needed by 39% compared with 55% of a control group who received 100% oxygen.[1]

Another study randomised 58 full-term neonates with persistent pulmonary hypertension of the newborn, confirmed by echocardiography, to receive either nitric oxide or nitrogen. Extracorporeal membrane oxygenation was needed by 12 of the 30 babies given nitric oxide and by 20 of the 28 babies in the control group.[2]

The Clinical Inhaled Nitric Oxide Research Group studied 248 babies, born after 34 weeks gestation, who had clinical or echocardiographic evidence of pulmonary hypertension. Extracorporeal membrane oxygenation was needed by 38% of the babies given low-dose nitric oxide and 64% of the control group. The median duration of successful treatment was 44 hours.[3]

Nitric oxide should not be used if the baby is dependent on a right to left shunt. It should also not be stopped suddenly as the pulmonary artery pressure may rebound, reducing oxygenation.

A complication of ventilating patients with nitric oxide is the formation of methaemoglobin. As neonates have a limited amount of methaemoglobin reductase they need to be monitored to avoid methaemoglobinaemia. Some of the toxicity of nitric oxide may be the result of oxidation to nitrogen dioxide. Monitoring is needed to ensure that nitrogen dioxide concentrations are minimised.

Adverse events are common in sick neonates. Those reported in trials of nitric oxide include hypotension, haematuria, infection and atelectasis. Hypokalaemia and thrombocytopenia occur frequently.

While nitric oxide may spare babies from extracorporeal membrane oxygenation it does not improve their survival. In NINOS 14% of the nitric oxide group and 16% of the control group died.[1] With low doses the mortality in the first 30 days of life was 7% with nitric oxide and 8% in the control group.[3]

A Cochrane review has evaluated the evidence for giving nitric oxide for respiratory failure in infants born at or near term. It found that nitric oxide improves oxygenation in approximately 50% of cases. A combined end point including extracorporeal membrane oxygenation and death was less frequent with treatment, but this was mainly accounted for by a reduced need for extracorporeal membrane oxygenation. Babies with diaphragmatic hernias did not benefit.[4]

Nitric oxide is only approved for babies over 34 weeks gestation. Trials in preterm babies have not shown a clear benefit and in this group nitric oxide has been described as a therapy in search of an indication.[5]

T manufacturer provided only the product information

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## Varenicline tartrate

Champix (Pfizer)

0.5 mg and 1 mg film-coated tablets

Approved indication: smoking cessation

Australian Medicines Handbook section 18.7

Smoking is addictive. Although many smokers try to stop, very few succeed without assistance. Some people need nicotine replacement therapy or bupropion to help them quit.[1]

Varenicline is a drug which binds to nicotinic receptors. It is a partial agonist so it provides some stimulation at the receptor, but also blocks nicotine. These actions may help to reduce withdrawal symptoms and the craving smokers have for nicotine.

Once someone has committed to stop smoking, they begin varenicline one or two weeks before the date they have set to quit. They gradually increase the dose from 0.5 mg daily to 1 mg twice daily which they continue until the end of the 12-week period of treatment.

The tablets are well absorbed and undergo little metabolism. Most of the dose is excreted in the urine with an elimination half-life of approximately 24 hours.

Varenicline has been compared with placebo and bupropion. In one trial, which randomised 1025 people, 44% of those given varenicline had stopped smoking by the end of the 12-week treatment period. This was significantly better than the 30% of the bupropion group and the 18% of the placebo group who stopped smoking. The patients were followed for a further 40 weeks. At the end of the year, the continuous abstinence rates were 22% for varenicline, 16% for bupropion and 8% for placebo.[2]

Using the same design, another trial randomised 1027 smokers. In the last month of treatment (weeks 9–12 of the study) 44% of the varenicline group, 30% of the bupropion group and 18% of the placebo group were no longer smoking. When followed up at 52 weeks the continuous abstinence rate was 23% with varenicline, 15% with bupropion and 10% with placebo.[3]

Many of the people who restarted smoking resumed soon after stopping treatment. Another trial therefore investigated if abstinence rates could be improved by a longer duration of treatment. People who had stopped smoking after a 12-week course were randomised to continue varenicline for another 12 weeks or take a placebo. During this maintenance phase 71% of the varenicline group did not smoke compared with 50% of the placebo group. After a year the rates were 44% and 37%.[4]

Many people dropped out of the smoking cessation trials.[2,3] In the varenicline group 4–9% of people discontinued because of adverse effects. Nausea is the most common problem, affecting approximately 30% of those taking varenicline compared to approximately 10% of the placebo group. Other adverse effects which occurred more frequently with varenicline than placebo included vomiting, constipation, abnormal dreams and insomnia. Patients who cannot tolerate these adverse effects could try a reduced dose. It is not known if the elderly are more prone to adverse effects as few people over 65 years old were included in the trials of varenicline. It is not recommended for people under 18 years old. Following the marketing of varenicline in the USA, there have been reports of patients experiencing suicidal thoughts and aggressive and erratic behaviour.

Varenicline does not prevent the weight gain associated with stopping smoking. After 12 weeks of treatment, patients taking varenicline gained 2–3 kg.[2,3] The safety of varenicline in pregnancy and breastfeeding is unknown.

All the participants had weekly counselling[2,3] so it may not be possible to achieve the same results in routine practice. Although varenicline achieved higher rates of abstinence than bupropion, the difference was not statistically significant in the long term. There do not appear to be any published comparisons of varenicline and nicotine replacement therapy.

T T T manufacturer provided clinical evaluation

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## Zoster virus vaccine

Zostavax (Merck Sharp & Dohme)

vials containing lyophilised virus for reconstitution

Approved indication: prevention of herpes zoster infection

Australian Medicines Handbook section 20.1

Herpes zoster (shingles) results from a reactivation of varicella zoster virus, which primarily causes chickenpox. Shingles is characterised by a painful blistering skin rash. Over half of all cases involve people over 60 years of age as viral reactivation is associated with waning cellular immunity.

Complications associated with herpes zoster are common. From June 1999 to July 2000, there were 1918 admissions to Australian hospitals due to herpes zoster; 1142 of these patients had complications.[1] The most frequent complication is postherpetic neuralgia, a painful condition which can persist for years and diminish the quality of life.

The vaccine, which has been registered in Australia, is a live attenuated strain of varicella zoster virus. It is to be given as a single subcutaneous dose.

The safety and efficacy of the vaccine have been assessed in a single placebo-controlled trial of 36 716 adults aged 60 years or older in the USA. Most of the participants (95%) were actively followed for three years after vaccination for signs of herpes zoster. There were 642 confirmed cases of herpes zoster in 18 357 control patients compared with only 315 confirmed cases in 18 359 vaccinated patients. The median duration of pain was 21 days in the vaccine group compared with 24 days in the control group. Similarly, the severity of disease was less in the vaccine group compared to the control group. There were 107 cases of postherpetic neuralgia; 27 in the vaccine group and 80 in the placebo group.[2]

The numbers of deaths and serious adverse events were similar in the vaccine and control groups. Safety was more closely monitored for 42 days following injection in a sub-group of 6616 people. In the vaccine group, 1604 people (48%) had at least one adverse event at the injection site compared with 539 people (16%) in the placebo group. Systemic adverse events related to the intervention were more frequently reported by vaccinated individuals than by people who received the placebo (209 vs 160).[2]

People for whom the vaccine is not recommended include:

- immunodeficient patients or patients on immunosuppressive therapy, such as high-dose corticosteroids
- patients with a history of anaphylaxis to neomycin
- patients with untreated tuberculosis.

There is a theoretical risk that the vaccine virus could be transmitted from a vaccinated person, who has developed a varicella-like rash, to a susceptible contact.

Although this vaccine will decrease the incidence of herpes zoster, its efficacy is only around 51%. Its duration of protection beyond four years is unknown, so it is unclear if people will need to be revaccinated.

Most of the efficacy data for this vaccine are from people aged 60 years or over. However, the vaccine has also been approved for individuals aged 50–59 based on immunogenicity data alone.

T manufacturer provided only the product information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2007;30:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.emea.europa.eu).

## Answers to self-test questions

| | | | |
|---|---|---|---|
| 1. True | 3. True | 5. False | 7. True |
| 2. True | 4. False | 6. True | 8. False |

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