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.

Agomelatine

Valdoxan (Servier)

25 mg tablets

Approved indication: major depression

Australian Medicines Handbook section 18.1

Agomelatine is a synthetic analogue of melatonin. The manufacturers claim that as well as agonising melatonin, it also antagonises the serotonin $5HT_{2C}$ receptors.

Numerous placebo-controlled trials have assessed the efficacy of agomelatine for major depression.[1–5] The primary endpoint in these studies was based on the 17-item Hamilton rating scale for depression. At baseline, average scores were around 27 out of a possible 52. After 6–8 weeks, both agomelatine (25 or 50 mg) and placebo had reduced the scores (to between 12.8 and 19.6). Although agomelatine reduced the score significantly more than placebo in most comparisons, the mean difference between agomelatine and the placebo was never more than a few points. For example in a trial of 503 randomised patients, mean scores were reduced to 17.1 with placebo and to 15.0 and 15.9 with agomelatine 25 mg and 50 mg.[5]

Agomelatine has also been compared with other antidepressants. A comparative trial with sertraline favoured agomelatine after six weeks, however, the difference in mean scores (Hamilton rating scale) between treatments was only 1.68.[6] Agomelatine has also been compared to fluoxetine and paroxetine. However, superiority of the active treatments over placebo was not consistently shown and most of these studies have not been published.

The ability of agomelatine to prevent relapse of major depression has also been investigated in a 24-week trial of patients who had already responded to 8–10 weeks of agomelatine treatment. Relapse rates were significantly lower for patients who continued agomelatine (after 8–10 weeks) compared to those who switched to placebo (20.6% vs 41.4%).[7] However in a similar but unpublished study, relapse rates for agomelatine and placebo were not significantly different (25.9% vs 23.5%).

After oral administration, agomelatine is rapidly absorbed with peak plasma concentrations reached within 1–2 hours. Bioavailability is low and varies considerably between individuals. It is increased by oral contraceptives and female gender and decreased by smoking. Agomelatine is rapidly metabolised by the cytochrome P450 isoenzyme CYP1A2, and to a lesser extent by CYP2C9 and CYP2C19. The inactive metabolites are mainly eliminated in the urine. Potent inhibitors of CYP1A2, such as fluvoxamine or ciprofloxacin, are contraindicated with agomelatine and caution is urged if patients are taking a moderate inhibitor such as propranolol.

Over 3900 patients took agomelatine in the depression trials. The most common adverse effects were headache (14.1%), nausea (7.7%), dizziness (5.5%), dry mouth (3.5%), diarrhoea (3.1%), somnolence (2.9%), fatigue (2.6%), abdominal pain (2.4%) and insomnia (2.4%). These were mostly mild to moderate. There were four deaths out of 3956 patients who took agomelatine and one out of 826 patients who took placebo – these were all due to suicide. There were more suicide attempts with agomelatine than with placebo (0.6% vs 0.4%).

Increases in liver enzymes (more than three times the upper limit of normal range) occurred in around 1% of people taking agomelatine. This effect seemed to be dose-related. Serious hepatic reactions included hepatitis and a transaminase elevation more than 10 times the upper limit of the normal range. Agomelatine should not be given to people with cirrhosis or active liver disease. Liver function tests should be performed before a patient starts treatment and at regular intervals during treatment. Consuming alcohol with agomelatine is not advisable.

Caution is urged in patients with impaired renal function and those aged 65 or over. Agomelatine should not be used in elderly patients with Alzheimer's disease.

Although agomelatine reduces symptoms of depression on the Hamilton rating scale, its effect seems to be only marginally better than placebo, if at all. This questionable efficacy coupled with the potential risk of adverse hepatic reactions suggests that doctors are probably better continuing with the more established antidepressants.

T T manufacturer provided additional useful information

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Indacaterol

Onbrez Breezhaler (Novartis)

capsules containing 150 microgram and 300 microgram as dry powder for inhalation

Approved indication: chronic obstructive pulmonary disease

Australian Medicines Handbook section 19.1.1

Patients with chronic obstructive pulmonary disease (COPD) who have symptoms despite using short-acting bronchodilators may obtain relief by adding a long-acting bronchodilator. The choice of drug includes beta$_2$ agonists such as eformoterol, salmeterol and now indacaterol.

A specific device is used to inhale indacaterol. Bronchodilation begins within five minutes of inhalation, with a peak effect after 2–4 hours. This action is prolonged so indacaterol is suitable for once-daily dosing. Some of the dose is absorbed into the circulation and then metabolised with very little being excreted in the urine.

Indacaterol was compared with placebo in a 28-day study of 163 patients with moderately severe COPD. From the first day the mean improvement in the forced expiratory volume in one second (FEV_1) with indacaterol was significantly greater than with placebo. On day 28, FEV_1 was 220 mL greater than placebo with 400 microgram indacaterol and 210 mL greater with 800 microgram once-daily.[1]

A lower dose (150 microgram) was used in a 12-week placebo-controlled trial involving 416 patients. FEV_1 increased with indacaterol from day 1 and at the end of the study was 160 mL greater than with placebo. The trough FEV_1, measured 24 hours after the final dose, was 130 mL higher than with placebo. The patients given indacaterol needed to use sulbutamol less often as a 'rescue' medication for their symptoms.[2]

In the placebo-controlled studies adverse events occurred with a similar frequency in all groups, although inhaling indacaterol was more likely to cause the patients to cough.[1,2] From all the studies of indacaterol, the adverse events which have occurred more frequently than with placebo include upper respiratory tract infections, cough, muscle spasms and headache. At therapeutic doses, indacaterol does not appear to significantly affect the heart rate. There may be small changes in blood glucose and potassium.

Once-daily indacaterol has been studied with twice-daily (e)formoterol in a year-long trial. There were 437 patients randomised to inhale 300 microgram indacaterol, 428 to inhale 600 microgram, 435 to inhale 12 microgram formoterol (twice daily) and 432 to inhale placebo. Both doses of indacaterol had increased the trough FEV_1 by 170 mL more than placebo and 100 mL more than formoterol, when assessed after 12 weeks. The differences between the active treatments and placebo remained significant after 12 months. Both drugs improved the control of symptoms and reduced the requirement for rescue doses of salbutamol. However, the study was not primarily powered to detect significant differences between indacaterol and formoterol.[3]

Another option for maintenance treatment of COPD is the long-acting anticholinergic drug tiotropium. This drug is also taken as a once-daily inhalation of dry powder. Tiotropium 18 microgram and indacaterol 150 microgram or 300 microgram were compared with placebo in a study of 1683 patients with moderate to severe COPD. After 12 weeks trough FEV_1 had increased by 140 mL with tiotropium and by 180 mL with both strengths of indacaterol compared to placebo. The difference between treatments was still present after 26 weeks. Indacaterol had a greater effect on some symptoms than tiotropium did, but, as tiotropium was given open-label, any differences in efficacy will need confirmation.[4]

Although indacaterol has been studied in asthma, it has not been approved for this indication and it is also not recommended for mixed airways disease. While indacaterol is an efficacious bronchodilator in patients with moderate–severe COPD, the extent of long-term clinical benefit is unknown.

☒ manufacturer declined to supply data

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Plerixafor

Mozobil (Genzyme)

vials containing 20 mg/mL

Approved indications: lymphoma, multiple myeloma

Australian Medicines Handbook section 14.4

High-dose chemotherapy is used in the treatment of cancers such as non-Hodgkin's lymphoma and multiple myeloma. As this suppresses the bone marrow, the patient may be transfused with stem cells to improve survival. Autologous transplants use the patient's own previously collected stem cells. Normally there are not many stem cells in the peripheral blood, but they can be mobilised from bone marrow by colony stimulating factors such as granulocyte colony stimulating factor (G-CSF).

In some patients, G-CSF does not mobilise enough stem cells. By inhibiting a chemokine receptor, which has a role in holding cells within the bone marrow, plerixafor helps to release stem cells into the blood. Plerixafor was originally studied as a treatment for patients infected with HIV, but was found to cause an increase in white blood cells associated with stem cell mobilisation.

An open-label pilot study gave patients with multiple myeloma and non-Hodgkin's lymphoma different regimens of G-CSF and plerixafor. Most of the 40 patients who were given plerixafor had enough cells mobilised for transplantation.[1]

A phase III trial randomised 298 patients with non-Hodgkin's lymphoma to receive G-CSF with or without plerixafor. G-CSF was given daily for up to eight days, with patients starting plerixafor or a placebo on the fourth day and continuing it for up to four days. The target was the collection of at least 5×10^6 CD34+ cells per kg body weight within four days. This outcome was achieved by 59.3% of the 150 patients randomised to plerixafor, but by only 19.6% of those who added placebo. The response enabled 90% of the plerixafor group to have transplantation compared to 55.4% of the placebo group.[2]

Another study compared G-CSF with or without plerixafor in 302 patients with multiple myeloma. The target was the collection of 6×10^6 CD34+ cells per kg within two days. This was achieved by 71.6% of the 148 patients randomised to receive plerixafor and 34.4% of the placebo group. Transplantation took place in 95.9% of the plerixafor group and 88.3% of the placebo group.[3]

The main trials did not give plerixafor alone. It is therefore only approved for use in combination with G-CSF.

There is a concern that plerixafor could mobilise tumour cells as well as stem cells. In a study of seven patients with multiple myeloma, G-CSF alone increased the frequency of tumour cells in five patients. Three patients given plerixafor after G-CSF had an increase in tumour cells in their peripheral blood, so plerixafor appears unlikely to have a significantly greater effect on tumour cell mobilisation.[4]

Plerixafor is given by subcutaneous injection and injection-site reactions are more common than with G-CSF alone. The drug is not metabolised and most of the dose is excreted in the urine. A reduced dose is given if the patient has moderate to severe renal impairment (creatinine clearance 20–50 mL/min). Patients complaining of upper abdominal or scapular pain should be investigated as animal studies show splenic enlargement. Some patients given plerixafor will have excess white cell production, while others will develop thrombocytopenia. Other adverse events which occur more frequently with G-CSF and plerixafor than with G-CSF alone include nausea, vomiting and diarrhoea.

While plerixafor increases the mobilisation of stem cells, it does not have much impact on the patients' survival. After a year, 88% of the patients with non-Hodgkin's lymphoma given plerixafor had survived compared with 87.2% of those given G-CSF alone.[2] In multiple myeloma, 95.3% of the plerixafor group had survived compared with 96.1% of the patients given G-CSF alone.[3]

T T manufacturer provided additional useful information

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The T-score (T) is explained in 'New drugs: transparency', Aust Prescr 2009;32:80–1.

* 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.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/pmeds/auspar.htm)

Answers to self-test questions

1. False
2. True
3. True
4. False

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