New drugs

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may have been little experience in Australia of their safety or efficacy. However, the Editorial 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.

Aripiprazole

Abilify (Bristol-Myers Squibb)

10 mg, 15 mg, 20 mg and 30 mg tablets

Approved indication: schizophrenia

Australian Medicines Handbook section 18.2.2

Aripiprazole is a new atypical antipsychotic. These drugs are less likely to cause extrapyramidal adverse effects than typical antipsychotics such as haloperidol.

As aripiprazole is a partial agonist at dopamine (D_2) receptors it may increase neurotransmission if the concentration of dopamine is low and decrease neurotransmission if the dopamine concentration is high. This action may have effects on the positive and negative symptoms of schizophrenia. Aripiprazole is also a partial agonist at serotonin ($5HT_{1A}$) receptors, but an antagonist of $5HT_{2A}$ receptors.

The drug only needs to be taken once a day. After absorption, aripiprazole is converted to an active metabolite. As aripiprazole and its metabolite have long half-lives steady-state plasma concentrations are not reached for approximately two weeks. Dose increases should therefore be at least two weeks apart.

The metabolism of aripiprazole involves cytochrome P450 2D6 and 3A4. This increases the potential for interactions with drugs such as fluoxetine, paroxetine and carbamazepine. Most of the unchanged drug and its metabolites are excreted in the faeces.

The clinical trials of aripiprazole have used rating scales such as the Positive and Negative Syndrome Scale (PANSS) to assess the drug's efficacy. In most short-term studies (4–6 weeks) aripiprazole has had a greater effect than placebo on this scale. One of the trials included haloperidol as an active control. Although haloperidol and aripiprazole reduced the PANSS scores significantly more than placebo, the study was not designed to show a difference between the active treatments.[1]

In clinical trials common adverse events included headache, nausea, anxiety and insomnia. Compared to haloperidol, aripiprazole caused less somnolence and extrapyramidal effects, but more nausea and dizziness.[1] As aripiprazole acts as an antagonist at α_1 adrenergic receptors it may cause orthostatic hypotension, so it should be used cautiously in patients with cardiovascular disease. Patients may gain weight during long-term treatment. As with other antipsychotics, aripiprazole has been reported to cause neuroleptic malignant syndrome.

Although aripiprazole appears to have little effect on prolactin secretion or the QT interval of the ECG, it is unclear if it has significant clinical advantages. Despite being approved for maintenance treatment there is little published information about the long-term safety and efficacy of aripiprazole. It needs to be compared with other atypical antipsychotics in long-term trials to establish its place in therapy.

REFERENCE*

1. Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002;63:763-71.

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

Memantine

Ebixa (Lundbeck)

10 mg tablets

50 mL bottles containing 10 mg/mL oral solution

Approved indication: Alzheimer's disease

Australian Medicines Handbook section 16.4

The currently available drug treatments for Alzheimer's disease are donepezil, galantamine, rivastigmine and tacrine. These drugs inhibit acetylcholinesterase so cholinergic adverse effects can be a problem. Memantine aims to improve the patient's function by a different mechanism – antagonism at the N-methyl-D-aspartate (NMDA) receptors.

The NMDA receptor is one of the receptors for glutamate, a cerebral neurotransmitter. If neuronal dysfunction in dementia is related to increased concentrations of glutamate, then blocking the receptors could slow progression of the disease.

In a clinical trial 252 patients, with moderate or severe Alzheimer's disease, were randomised to take memantine or a placebo for 28 weeks. Although 71 patients did not complete the trial, those given memantine showed less decline on some of the rating scales used to assess efficacy. These patients' scores were significantly different from placebo on the Alzheimer's Disease Co-operative Study Activities of Daily Living Inventory (ADCS-ADL), the Severe Impairment Battery (SIB) and the Functional Assessment Staging scale (FAST). There was also a significant difference in the clinicians' and carers' assessments of the patients.[1]

Many patients in the trial had adverse events including agitation, urinary incontinence, diarrhoea and insomnia.[1] Adverse effects with a higher frequency than placebo include fatigue, headache, dizziness and hallucinations. Approximately 11% of patients will stop treatment because of adverse effects.

To reduce the risk of adverse effects memantine should be started at a low dose and slowly increased over a month. The drug is completely absorbed even if taken with food. Most of the dose is excreted unchanged in the urine, so a lower dose is needed if renal function is reduced. There are potential

interactions with drugs such as cimetidine which use the same renal transport system. Memantine may also interact with antipsychotics, levodopa and other dopaminergic drugs.

Although memantine may have an advantage over placebo, it is important to remember that, on average, all the patients in the clinical trial got worse. There was also no significant difference between memantine and placebo in some of the assessments such as the Mini-Mental State Examination, the Global Deterioration Scale and the Neuropsychiatric Inventory. In addition the results can be influenced by how the data from the 28% of patients who dropped out are analysed. A different analysis negates the significant differences in the clinicians' impressions of change.[1]

Although the options for the treatment of moderate to severe dementia are limited, memantine does not seem to be a major advance. (It has been available in Germany for approximately 20 years.) Further research is exploring whether treating patients with a combination of memantine and an acetylcholinesterase inhibitor will be of greater clinical benefit.

REFERENCE†

1. Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333-41.

† At the time the comment was prepared, a scientific discussion about this drug was available on the web site of the European Agency for the Evaluation of Medicinal Products (www.emea.eu.int).

NEW FORMULATIONS

Desmopressin acetate

Minirin (Ferring)

200 microgram tablets

Follitropin alfa

Gonal-F (Serono)

75 IU, 450 IU and 1050 IU powder for injection

Oestradiol

Aerodiol (Servier)

150 microgram per actuation nasal spray

Progesterone

Crinone 8% (Serono)

90 mg/1.125 g vaginal gel tube

Answers to self-test questions

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

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