New drugs

Vortioxetine

Approved indication: major depression
Brintellix (Lundbeck)
5 mg, 10 mg, 15 mg and 20 mg film-coated tablets
Australian Medicines Handbook section 18.1.5

Most antidepressants are presumed to work by increasing the synaptic availability of serotonin or noradrenaline. Based on non-clinical studies, the manufacturers of vortioxetine say it has a multimodal mechanism of action. They claim that it selectively inhibits reuptake of serotonin (5-HT) via the serotonin transporter and acts as an agonist or antagonist at various serotonin receptors (5-HT_{1A}, 5-HT_{1B}, 5-HT_3, 5-HT_{1D} and 5-HT_7).

Numerous short-term clinical trials (6–8 weeks) have compared the efficacy of vortioxetine to placebo with variable results (Table).[1-6] Not all of the studies have been published in full. One randomised trial found that daily vortioxetine at doses of 15 mg or 20 mg was significantly more effective than placebo at lowering scores on a depression rating scale.[1] In other trials, doses of 1 mg, 5 mg and 10 mg also lowered depression scores more than placebo.[2,3] In a trial enrolling people aged 65 years and over, vortioxetine 5 mg was better than placebo.[4] However, in two other trials of younger people (mean age 42–43 years) the 5 mg dose was no better than placebo.[5,6]

In a longer term relapse trial, 396 patients who responded to 12 weeks of vortioxetine 5 mg or 10 mg were randomised to continue treatment or receive placebo. After a total of 24 weeks, fewer patients in the vortioxetine arm than in the placebo arm had relapsed (13% vs 26%, p=0.0013).[7]

Nausea was the most common adverse event with vortioxetine. Its incidence was dose-related, occurring in 32% of patients who received the 15 mg or 20 mg dose. Other common events included diarrhoea, dizziness, constipation and vomiting.

In an analysis of seven placebo-controlled trials, sexual dysfunction was reported by up to a third of men and women taking the 15 mg or 20 mg dose.

Table **Short-term placebo-controlled trials of vortioxetine for major depression**

Trial	Number of patients (mean age)	Daily treatment (active reference comparator)	Outcome: mean change from baseline on depression rating scale at 6–8 weeks compared to placebo
Boulenger 2014[1]	607 (47 years)	vortioxetine 15 or 20 mg placebo (duloxetine 60 mg)‡	15 and 20 mg doses statistically better on MADRS than placebo (p<0.0001)
Henigsberg 2012[2]	560 (46 years)	vortioxetine 1, 5 or 10 mg placebo	All doses statistically better on HAM-D 24 (p<0.001)
Alvarez 2012[3]	429 (43 years)	vortioxetine 5 or 10 mg placebo (venlafaxine 225 mg)‡	5 and 10 mg statistically better on MADRS than placebo (p<0.0001)
Katona 2012[4]	453 (71 years)	vortioxetine 5 mg placebo (duloxetine 60 mg)‡	5 mg statistically better than placebo on HAM-D 24 (p=0.0011)
Jain 2013[5]	600 (42 years)	vortioxetine 5 mg placebo	Not significantly better than placebo on HAM-D 24
Mahableshwarkar 2013[6]	611 (43 years)	vortioxetine 2.5 or 5 mg placebo (duloxetine 60 mg)‡	Not significantly better than placebo on HAM-D 24

MADRS Montgomery–Asberg Depression Rating Scale HAM-D 24 24-item Hamilton Depression Rating Scale
‡ Venlafaxine or duloxetine was included as an active reference comparator which was compared to placebo but not to vortioxetine.

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Sexual problems were also reported in up to 20% of people taking the placebo. As these events are often under-reported, doctors should ask the patients about these possible effects.

Following multiple oral doses, maximum plasma concentrations are reached after 7–8 hours. Bioavailability is 75% and vortioxetine's mean terminal half-life is about 66 hours. Vortioxetine is mainly metabolised by cytochrome P450 (CYP) 2D6 and metabolites are eliminated in the faeces (59%) and urine (26%).

The recommended starting dose of vortioxetine is 10 mg per day. However, because exposure is increased in people over 65 years old, the recommended starting dose is 5 mg per day in this age group.

Dose reduction should be considered if co-administration of strong CYP2D6 inhibitors (e.g. bupropion, fluoxetine) is necessary. Conversely, the vortioxetine dose may need to be increased if strong CYP2D6 inducers (e.g. rifampicin, carbamazepine) are used.

Because of the risk of serotonin syndrome, concomitant use of monoamine oxidase inhibitors is contraindicated during vortioxetine treatment and for 14 days after it is stopped. Consult the product information if switching a patient between a monoamine oxidase inhibitor and vortioxetine, as washout periods are needed. Serotonin toxicity can also occur with other serotonergic medicines such as sumatriptan, tramadol and St John's wort. Prescribers should be vigilant for symptoms if these drugs are taken concurrently. As with other antidepressants, vortioxetine may increase the risk of suicide or mania in some patients.

Vortioxetine is a pregnancy category B3 drug. Although there is no human data, animal studies found that vortioxetine reduced fetal weight and delayed ossification. In rats, survival of pups was lower in mothers receiving vortioxetine.

Vortioxetine offers another option for people with major depression. However, the nausea and sexual adverse effects are common and may put some patients off. In general, vortioxetine reduced symptoms of depression and prevented relapse.

However, it was not clear from the trials how vortioxetine's purported multimodal mechanism of action contributes to its antidepressant effect. The efficacy and tolerability of vortioxetine in comparison with other antidepressants is not currently known.

T manufacturer provided the product information

REFERENCES *†

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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).