Vortioxetine
A new option for depression

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Vortioxetine was approved by the TGA in 2014 for treatment of adults with major depressive disorder. It adds to the repertoire of antidepressants available for individualising treatment and may have particular benefits for patients with cognitive impairment associated with depression.

Vortioxetine is a new antidepressant that appears generally well tolerated; the most common side effect is nausea.[1] It has been shown to be effective in relieving depression, anxiety and associated cognitive symptoms in depressed patients.[2-4] It is suitable for use in adult patients with depression, including the elderly, in general practice as well as specialist psychiatric practice.

What is vortioxetine?

Vortioxetine is an antidepressant that inhibits the serotonin transporter and also directly modulates serotonin receptor activity.[1] In vitro studies indicate that it is an inhibitor of serotonin reuptake and acts as an agonist at the serotonin 5-HT_{1A} receptor, partial agonist at the 5-HT_{1B} receptor and antagonist at the 5-HT_{1D}, 5-HT_3 and 5-HT_7 receptors.[1] Vortioxetine provides a new antidepressant option and has the potential to also improve cognitive symptoms associated with depression.[5] It is not listed on the PBS.

What is different about vortioxetine?

Vortioxetine may help improve cognition as well as depressed mood and anxiety.[2-4] Cognitive impairment often occurs with depressive illness, and may include a diminished ability to think or concentrate or indecisiveness. Objective deficits in measures of executive function, processing speed, attention, learning and memory during and after resolution of a major depressive episode have been reported. Commonly used depression rating scales for clinical studies do not assess cognition in detail, or even at all. This does not stop depressed patients feeling they cannot think as well as normally. Depressive-related cognitive impairment can also be seen with so-called 'pseudodementia'.

An eight-week study of vortioxetine in around 600 adults at doses of 10 mg (n=195) or 20 mg (n=207) showed that it significantly improved cognition across a number of distinct cognitive domains compared with placebo (n=196).[4] Improved cognition significantly influences functional recovery from a major depressive episode, suggesting that this is a useful quality of vortioxetine.

Studies of most other antidepressants have not focused on cognitive impairment accompanying depression and the effect of treatment on this. Only one other large study has primarily aimed to compare the efficacy of a conventional antidepressant versus placebo for improving cognition. This study, of duloxetine in the elderly, used a composite cognitive score and suggested that duloxetine significantly improved cognition compared with placebo.[5] It has not yet been shown whether other antidepressants similarly improve cognition with clinical recovery.

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Who is suitable and how is vortioxetine used?

Vortioxetine has been approved by the TGA for treatment of major depressive disorder in adults, including the elderly. This includes prevention of relapse. A study has shown vortioxetine to be effective in patients who have had an inadequate response to treatment with a single course of a selective serotonin receptor inhibitor (SSRI) or a serotonin and noradrenaline receptor inhibitor (SNRI).[6] The safety and efficacy of vortioxetine in patients under the age of 18 years have not been established.

In adults, the usual starting dose of vortioxetine is 10 mg once daily, taken with or without food at any time of day.[1] In patients aged 65 years or over, an initial starting dose of 5 mg is recommended. Depending on tolerability and response, the dose can be increased to 20 mg daily, or reduced to 5 mg daily (caution is advised for doses above 10 mg in elderly patients).

Vortioxetine is available as film-coated, almond-shaped tablets at doses of 5, 10, 15 or 20 mg[1]. The tablets are not scored and should not be halved or quartered, as the consequent dose may be variable and unreliable.

Studies of vortioxetine have been based on daily administration. The elimination half-life is approximately 66 hours. If patients miss a dose then they should take the next dose at the usual time. They should not take a double dose to make up for a missed dose.[1] Vortioxetine can be stopped abruptly without the need for a gradual reduction in dose.[1]

How long should vortioxetine treatment continue?

Vortioxetine has been shown to be effective in achieving remission of depression in short-term studies of up to eight weeks.[3] It was also shown to be effective in maintaining a response in a six-month relapse prevention study and an open-label 12-month study.[2,7] In the six-month study, relapse occurred in 26% of patients who stopped vortioxetine after an acute response compared with 13% of patients who continued vortioxetine treatment.[2] In the one-year study, around 60% of 535 patients completed the year of open-label treatment; responders increased from 63% at six months to 94% at one year and those in remission from 42% to 83%.[7] Although response and remission rates were lower (84% and 71%, respectively) when patients who withdrew during the extension phase of the study were included in a last observation carried forward analysis, these outcomes are better than those seen for escitalopram in a similar study.[8]

These results are typical of the maintenance of the acute response and potential improvement in the longer term seen with extended antidepressant treatment. The manufacturer recommends if symptoms resolve, continuing vortioxetine treatment for at least six months. In clinical practice it is useful to continue treatment until the patient has been well for about a year, although for those who have had relapses, longer term treatment may be warranted.

Monitoring and side effects

No special monitoring is needed when using vortioxetine beyond routine clinical monitoring of depression and for the possible emergence of any side effects that might warrant dose adjustment or other intervention.

The most common side effects are nausea and headache, which are mostly transient, mild to moderate in severity, and did not generally lead to cessation of therapy in trials.[1] There was a low rate of the adverse effects of insomnia, sedation, cardiovascular effects or sexual dysfunction, and no association with weight gain in either short- or long-term clinical studies.

Important precautions and interactions

The risk of suicide attempts should be considered and managed in patients taking vortioxetine, as in any depressed patients. Concurrent use of vortioxetine with irreversible nonselective monoamine oxidase inhibitors or other serotonergic agents, including SSRI and SNRI antidepressants and herbal preparations of St John's wort, should be avoided because of the risk of serotonin syndrome.

Vortioxetine is extensively metabolised in the liver, with in vitro evidence that its metabolism involves a range of cytochrome p450 isozymes (CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5).[1] Consequently, concurrent use of strong CYP450 inhibitors, such as bupropion, or broad CYP450 inducers, such as rifampicin, should be avoided or the dose of vortioxetine adjusted. No dose adjustment is necessary in patients with mild or moderate renal or hepatic impairment. The major metabolite of vortioxetine is pharmacologically inactive.

Other precautions typical of any antidepressant with serotonin activities, including SSRIs and SNRIs, are needed in certain patients because of the risk of activation of mania in those with bipolar disorder, seizures, haemorrhage, or hyponatraemia with inappropriate antidiuretic hormone production.

Use in pregnancy and breastfeeding

Vortioxetine should not be used during pregnancy unless the benefit outweighs the risk because of lack of data (category B3). Vortioxetine also appears in breast milk and is not recommended for women who are breastfeeding. In animal studies (in rats) it did not appear to adversely affect fertility, even with exposures 20 times the maximum human recommended dose.

Benefits of vortioxetine

Antidepressants are not substitutable. Patients who tolerate and respond to one antidepressant will not necessarily tolerate or respond to another. In consequence, it is desirable to have a range of antidepressants to increase the chance of finding an effective tolerated treatment to help optimise outcomes for each patient. Overcoming cognitive difficulties seen with depression, such as impairments of attention, concentration and memory, can help

patients engage in psychosocial interventions to aid recovery and rehabilitation from an episode of depression. This may, or may not, occur with treatment with other antidepressants.

Access to vortioxetine

Vortioxetine is available on prescription but is not listed on the PBS. The cost of a pack of 28 tablets is currently around $60, regardless of the dose. Vortioxetine is the second antidepressant with potential advantages for some patients to be approved recently but not subsidised by the PBS, the other being agomelatine. The financial impediment may deny access to these new treatments to patients with depression who are living on a pension or have limited financial resources.

Conclusion

Vortioxetine is a new antidepressant that is generally well tolerated in adults. It may help to improve the cognitive impairments seen with depression, as well as improving depressed mood and anxiety, thereby facilitating functional recovery. Once-a-day dosing is sufficient. Vortioxetine appears to be a useful addition to our range of antidepressant treatments. MT

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COMPETING INTERESTS: Professor Tiller is a member of the Faculty of the Lundbeck International Neuroscience Foundation (LINF) and the Australian LINF Board. He has acted as a consultant to and given presentations for Lundbeck (the manufacturer of vortioxetine) and Servier. He has not received any research or other grant funding from either company.