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New Product Focus

Vortioxetine: more than just another selective serotonin reuptake inhibitor

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Abstract
Major depressive disorder (MDD) is a disabling disease with a high risk of relapse and chronicity. Despite treatment, only 30% of patients with MDD achieve full remission. Vortioxetine is a new multimodal antidepressant. It is a serotonin reuptake inhibitor, but in addition, also has direct effects on several subtypes of serotonin receptors. It has been shown to be as effective as venlafaxine, and more effective than agomelatine in improving the symptoms of MDD. In addition, vortioxetine has been shown to improve cognitive function. It may also improve sexual dysfunction in patients who have experienced antidepressant-related sexual dysfunction with other antidepressants. Vortioxetine is generally well tolerated. The most common adverse events are mild to moderate nausea, and headaches that are usually transient in nature.

Introduction
Major depressive disorder (MDD) most commonly emerges in the third decade of life, and causes symptoms that interfere with a person’s ability to work, sleep, eat and think. Symptoms include feelings of sadness and hopelessness, difficulty concentrating, memory lapses and the inability to make decisions. MDD has a high relapse rate and a high risk of chronicity. Evidence suggests that depression is a neuroprogressive disease, and the persistence of signs and symptoms implies structural changes in the neurons and neural tract. Therefore, it is important to achieve the therapeutic objectives as quickly and effectively as possible. According to the World Health Organization (WHO), depression is currently the second leading cause of disability, expressed as healthy years lost in the age group 15-44 years. The WHO estimates that it will become the second leading cause of disability in all age groups by the year 2020, and by 2030, it is expected to become the leading cause of disability in industrialised countries.

Despite the availability of numerous antidepressants with differing mechanisms of action, many patients with depression do not achieve treatment outcomes in terms of optimal efficacy and remission rates. In addition, treatment with currently available antidepressants is associated with adverse events, such as increased suicide risk, weight gain and sexual dysfunction, while long-term treatment with some antidepressants may increase the risk of bleeding and the development of type 2 diabetes mellitus. Doctors often turn to polypharmacy when treatment with first-line agent fails. Vortioxetine is a new antidepressant with a multimodal mechanism of action that could partially mitigate some of these negative aspects associated with antidepressant therapy.

Mechanism of action
In addition to the inhibition of serotonin reuptake, vortioxetine also has a direct effect on serotonin receptor [5-hydroxytryptamine (5-HT)] activity in the central nervous system. Vortioxetine is a full agonist at the 5-HT1A receptor and a partial agonist at the 5-HT1B receptor. It is an antagonist at the 5-HT1D, 5-HT3 and 5-HT7 receptors.

In order to appreciate the possible clinical effects of drug-receptor interactions, it is important to understand the neuropharmacological effects behind these receptors. Serotonin has seven major receptors, each with several subtypes. The potential physiological and therapeutic effects of serotonin modulation are summarised in Table I.

While the mechanism of action of vortioxetine is not fully understood, the multiple receptor effects of this agent lead to modulation of neurotransmission in the serotonin system as well as the noradrenaline, dopamine, histamine, acetylcholine, gamma-aminobutyric acid and glutamate systems within the forebrain. Activity across all these systems may be responsible for the anxiolytic and antidepressant-like effects, and the improvement in cognitive function, learning and memory observed with vortioxetine.
These patients may initially need closer monitoring. Stable has not been studied in patients with severe hepatic impairment or moderate hepatic or renal impairment. The use of vortioxetine has not been recommended that the elderly and patients who are poor cytochrome P450 (CYP) 2D6 metabolisers start treatment at a dose of 5 mg daily, with a maximum dose of 10 mg per day.8

No dose adjustments are recommended for patients with mild or moderate hepatic or renal impairment. The use of vortioxetine has not been studied in patients with severe hepatic impairment. These patients may initially need closer monitoring. Stable plasma concentrations are reached within two weeks.1 Treatment should continue for at least six months after resolution of the initial episode.7

Discontinuation

Treatment with vortioxetine may be stopped abruptly, and it is not necessary to decrease the dose gradually upon discontinuation. However, patients who were treated with higher doses of vortioxetine (15 or 20 mg/day) reported discontinuation symptoms, including headaches, muscle tension, mood swings, sudden outbursts of anger, dizziness and a runny nose within one week of discontinuation.7,8 If possible, it is advisable that the dose is reduced to 10 mg for a week before complete discontinuation.8

Efficacy

Vortioxetine versus placebo

Twelve clinical trials were performed to assess the short-term efficacy of vortioxetine over a period of 6-8 weeks. Eleven of these trials included a placebo arm, and seven a reference arm. Positive results, with regard to efficacy of vortioxetine, were reported in eight of the 11 placebo-controlled studies.1 Typically, response to treatment with vortioxetine occurred within two weeks of treatment, with maximum results observed from 4-8 weeks of treatment.1,2

Table I: Summary of the effects of serotonin receptor stimulation9

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Type</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT1A</td>
<td>Agonist</td>
<td>Anxiolytic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antidepressant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Light-headedness</td>
</tr>
<tr>
<td>5-HT3/5HT2</td>
<td>Agonist</td>
<td>Low weight gain</td>
</tr>
<tr>
<td>5-HT3</td>
<td>Agonist</td>
<td>Low weight gain</td>
</tr>
<tr>
<td>5-HT2A/7</td>
<td>Antagonist</td>
<td>Beneficial effects on the circadian rhythm and sleep</td>
</tr>
<tr>
<td>5-HT4</td>
<td>Antagonist</td>
<td>A reduction in gastrointestinal effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A reduction in nausea</td>
</tr>
</tbody>
</table>

*5-HT: 5-hydroxytryptamine*

Vortioxetine versus comparators

The efficacy of vortioxetine was also compared to venlafaxine, duloxetine and agomelatine. Vortioxetine was found to be non-inferior when compared to venlafaxine, and superior to agomelatine. It was superior to other comparators in terms of the rate of discontinuation owing to adverse events.4

The study that compared vortioxetine with agomelatine was performed on patients with inadequate response to other selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). These patients presented with moderate to severe MDD, with a substantial level of anxiety. Patients were switched to vortioxetine or agomelatine, since both of these agents have mechanisms that differ from those that the patients had been treated with previously. The scores improved in both treatment groups with regard to clinician-rated assessments, as well as patient-reported outcomes. However, vortioxetine was shown to be superior to agomelatine.5

Cognitive function

Patients treated for depression, and especially the elderly, often complain about impaired cognitive function. This may be a symptom of depression, but treatment with SSRIs or SNRIs may also impair cognitive function, probably due to excessive neuromodulation of the release of catecholamines, which occurs with increased 5-HT function. Cognitive function in elderly patients was assessed as a secondary end-point in a study that compared vortioxetine with placebo and duloxetine as a reference. Baseline testing of processing speed, memory and verbal learning was performed using two different tests. Patients with neurodegenerative disease were excluded. The results of the final tests suggested that vortioxetine does not impair cognitive function, and may actually improve the baseline condition via direct effects, even when patients were non-responders in terms of depression.1 In a subsequent placebo-controlled study, the authors concluded that vortioxetine improved objective and subjective measures of cognitive function. Cognitive improvement was largely due to the direct treatment effects of vortioxetine.10

Tolerability

Vortioxetine was generally well tolerated in clinical studies. Nausea, vomiting, constipation, diarrhoea, backache, fatigue and headaches were the most commonly reported adverse effects.1 These adverse events were usually transient and mild or moderate, and occurred within the first two weeks of treatment.7
Vortioxetine was not associated with significant changes in weight, QT intervals, arterial blood pressure, heart rate, sweating, insomnia or somnolence. Interactions. Although modulation of several of the neurotransmitters indicates that vortioxetine may also have an anxiolytic effect, especially at higher doses, both positive and negative results were reported in studies that evaluated its effect in patients with generalised anxiety disorder and social anxiety disorder.

Serotonin syndrome (see “Interactions” section), seizures, suicidal thoughts, hyponatraemia, mania and hypomania were other serious adverse events reported with the use of vortioxetine.

Sexual dysfunction

Sexual dysfunction is known to be a symptom of depression. A meta-analysis found that only antidepressants without serotonergic action were able to address low levels of sexual dysfunction. However, most patients need serotonergic activity in order to obtain acceptable antidepressant effects. Patients with well-controlled MDD who experienced sexual dysfunction while being treated with SSRIs, including citalopram, sertraline and paroxetine, were switched to either escitalpram or vortioxetine. Vortioxetine was associated with a greater improvement in sexual dysfunction than escitalpram by the second week of treatment.

Interactions

Although vortioxetine is extensively metabolised in the liver by several CYP450 enzymes, it does not inhibit nor activate any of them. It may be necessary to reduce the dose of vortioxetine if strong CYP2D6 inhibitors, such as bupropion, quinidine, fluoxetine or paroxetine, are added to the treatment. The dose of vortioxetine may need to be increased if patients need to be treated with strong CYP450 inducers, such as rifampicin, carbamazepine or phenytoin. Adjustments should be based on individual clinical responses. Serotonin syndrome may occur with the use of vortioxetine, and the risk is increased with the concomitant use of other serotonergic medication. These include monoamine-oxidase inhibitors (MAOIs), linezolid, pethidine, tramadol, sumatriptan and other triptans, as well as St John’s wort. The use of MAOIs is contraindicated with vortioxetine, and vortioxetine should not be started within 14 days of discontinuation of a MAOI. Vortioxetine should be discontinued at least 21 days before starting treatment with a MAOI.

Although vortioxetine does not interact with warfarin, aspirin or other nonsteroidal anti-inflammatory drugs, concomitant use of these medications with vortioxetine may increase the risk of abnormal bleeding.

Conclusion

Most antidepressants negatively impact sexual and cognitive function, and can induce weight gain. This can lead to poor patient compliance and treatment interruption, resulting in an increase in the risk of relapse and chronicity. Vortioxetine is a promising new agent for the treatment of MDD. It does not impair cognitive function, and may even improve cognitive function independently of its antidepressant effect. It may also have a place in treating patients with an inadequate response to other SSRI or SNRI treatments, even at maximum doses, because of its multimodal activity. Clinical studies suggest that vortioxetine has a good safety and tolerability profile, with minimal effects on sexual function and weight gain, especially at doses lower than 20 mg per day.

References