Vortioxetine: a New Treatment for Major Depressive Disorder

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1. Introduction

Major depressive disorder (MDD) is a common psychiatric disorder that affects up to 16.2% of individuals over the course of their lives.[1] A wide range of effective antidepressants already exists and, given the considerable societal burden that is caused by MDD, prompt recognition and vigorous treatment of depression is considered a public health priority.[2] Following the serendipitous discovery of the therapeutic effects of the medications that comprise the first generation of antidepressants (i.e. tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]), concerted efforts over the past 40 years have led to the introduction of safer, better tolerated, and easier-to-prescribe antidepressants, most notably selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Nevertheless, at least 50% of patients who begin therapy with newer-generation medications either fail to respond or discontinue therapy because of intolerable side effects, so there remains an ongoing need for antidepressants that are either more effective or better tolerated than existing standards.[3,4] As part of the effort to address this unmet need, several novel drugs have recently been introduced, including the subject of this review, the multimodal serotonergic drug vortioxetine (see Box 1).

2. Market review

Although the dramatic growth in the use of antidepressants in the last 30 years has leveled off in the US, untreated depression remains a significant problem throughout the world and in most settings antidepressant...
medications remain a cornerstone of therapeutics.\[5\] Indeed, despite pessimistic forecasts about the limited commercial viability of new antidepressants in the current climate, nearly US$7 billion are spent on antidepressant medications each year.\[5\] With the SSRIs securely entrenched as the favorite antidepressants for first-line use throughout most of the industrialized world, it is nevertheless interesting that the major shift in the use of antidepressants since the mid-1990s has involved greater use of other types of newer-generation antidepressants, including SNRIs (venlafaxine, duloxetine, milnacipran, desvenlafaxine, and levomilnacipran), mirtazapine, and bupropion. This particular trend underscores the reality that, despite the great utility of SSRIs, there is a considerable need for alternate therapies, specifically medications that work through mechanisms other than selective inhibition of neuronal uptake of serotonin.

Beyond the existing first-line therapies – SSRIs, SNRIs, bupropion, and mirtazapine – several other recently introduced medications might be considered competitors of vortioxetine in a crowded marketplace. These medications include extended-release (XR) trazodone, vilazodone, and levomilnacipran.

### 2.1. Extended-release trazodone

First introduced in the early 1980s, trazodone is arguably both the first drug that could be called a multimodal serotonin modulator and the first member of a so-called second generation of antidepressants. Most of trazodone’s effects on depression and anxiety are thought to derive from antagonism at serotonin 5HT\(_{2A}\) receptors, though partial agonism at serotonin 5HT\(_{1A}\) receptors may also be clinically significant.\[6,7\] However, the original formulation of trazodone was judged to be no easier to use than TCAs and, probably, less effective.\[8\] After the introduction of SSRIs and mirtazapine, trazodone was seldom used in doses adequate to treat depression. Rather, because low doses of trazodone can promote sleep (presumably through antagonism at histamine H\(_1\) and adrenergic \(\alpha_1\) receptors) without concerns about abuse liability, this drug continues to be widely prescribed ‘off label’ in 25–100 mg doses as a hypnotic.\[9\]

An XR formulation of trazodone was developed in the hope of encouraging a re-consideration of this medication’s utility as an antidepressant by addressing some of the side effect concerns that hindered use of higher doses, particularly lightheadedness and sedation.\[8\] Two placebo-controlled studies of this formulation have documented the tolerability and efficacy of once-daily dosing.\[10,11\] Nevertheless, to date, the clinical use of the extended-release formulation of trazodone in the US has been quite limited.

### 2.2. Vilazodone

Vilazodone is, like trazodone, a drug with multimodal serotonergic activity. In this case, vilazodone is a partial agonist of the serotonin 5-HT\(_{1A}\) receptor, in addition to being a potent serotonin reuptake inhibitor.\[12\] Approved by the US FDA in 2011, the efficacy of vilazodone was demonstrated in a pair of double-blind, placebo-controlled, randomized clinical trials (RCTs).\[13,14\] As these trials did not include an active comparator, no assessments of relative efficacy were possible. Nevertheless, the efficacy of vilazodone can be estimated from drug versus placebo differences, which appear to be comparable to other, recently developed antidepressants. For example, the number needed to treat (NNT) for response versus placebo in the pooled sample from the pivotal trials was eight. The NNT value for remission was only 14, which may reflect the fact that vilazodone must be slowly titrated upward to the therapeutic dose (i.e. from 10 mg to 20 mg to 40 mg) during the first 3 weeks of therapy and, as a result, a
somewhat longer course of therapy may be needed for a response to evolve into a remission.

One of the more interesting aspects of the clinical pharmacology of vilazodone is that the serotonin partial agonism would be expected to convey greater therapeutic effects for anxiety symptoms, as well as possibly protective effects against sexual side effects mediated by serotonin reuptake inhibition.[12] A pooled analysis of the impact of vilazodone therapy on the symptoms of anxiety associated with MDD demonstrated that the drug’s effect on anxiety symptoms was comparable to its effect on core depressive symptoms.[15] Of course, head-to-head trials are necessary to confirm that this effect differs from that of SSRIs or SNRIs. The RCTs of vilazodone have used structured scales to collect information on sexual adverse effects and found the rates of these effects to be only marginally greater than placebo.[13,14,16] However, these data were not judged to be sufficient by the FDA to permit the manufacturer to market this product as having a ‘low risk of sexual dysfunction.’ A second group of studies that may provide necessary additional evidence pertaining to anxiolytic properties and sexual side effects is nearing completion.

2.3. Levomilnacipran

Levomilnacipran is the more potent stereoisomer of the racemic compound milnacipran, a drug that has been approved for antidepressant therapy in several regions of the world for more than a decade. Among SNRIs, in vitro studies suggest that milnacipran and levomilnacipran might be the most noradrenergically active members of this drug class, because these drugs have greater potency for inhibition of norepinephrine than serotonin.[17] Although the manufacturer of milnacipran did not pursue an indication for treatment of depression in the US, a second US-based company did the requisite research to obtain an indication for treatment of fibromyalgia and, in turn, levomilnacipran was approved by the FDA for treatment of MDD in late 2013. The summary basis of approval for levomilnacipran consisted of five placebo-controlled RCTs. Although not all of the individual studies are yet published, Montgomery and colleagues recently published a meta-analysis of the five placebo-controlled RCTs, summarizing the efficacy of this drug in doses of 40–120 mg/day.[18] This analysis found that levomilnacipran XR versus placebo resulted in greater improvement in Montgomery–Åsberg Depression Rating Scale (MADRS) score (−15.8 versus −12.9; LS mean difference, −2.9; P < .001), higher response rates (44.7% versus 34.5%; P < .001), and higher remission rates (27.7% versus 21.5%; P < .05) in the overall population.

3. Introduction to vortioxetine

Vortioxetine, previously called Lu AA21004, was developed as a partnership between H. Lundbeck A/S and Takeda Global Research & Development Center, Inc.

3.1. Chemistry

Vortioxetine is chemically identified as 1-(2-((2,4-dimethyl-phenylthio)phenyl)piperazine; the compound belongs to the arylpiperazine class.[19] Along with trazodone, nefazodone, vilazodone, and buspirone, vortioxetine shares a piperazine group as part of its structure; this family of compounds shows significant effects on multiple serotonin receptors.

3.2. Pharmacodynamics

Although classified by the FDA as an SSRI, vortioxetine has a number of effects on serotoninergic neurotransmission and, as such, can be described as a ‘multimodal serotonin modulator’ (see Table 1). In addition to blockade of the serotonin transporter (SERT), the compound has affinity for 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>6</sub>, and 5-HT<sub>7</sub> receptors. In concert, these effects increase extracellular serotonin, acetylcholine, norepinephrine, and histamine in animal models.[19]

Table 1. Summary of effects of vortioxetine on serotoninergic targets.

<table>
<thead>
<tr>
<th>Target</th>
<th>Action at Target</th>
<th>Potential Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERT (serotonin transporter)</td>
<td>Antagonist, (K&lt;sub&gt;i&lt;/sub&gt; 1.6 nM, increases synaptic serotonin, SSRI-like action)</td>
<td>Antidepressant &amp; anxiolytic</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1A&lt;/sub&gt;</td>
<td>Near-full agonist (K&lt;sub&gt;i&lt;/sub&gt; 15 nM, unclear in vivo effect, agonism at postsynaptic receptors would lead to serotonin-like effect, partial antagonism at inhibitory autoreceptors may enhance serotonin release)</td>
<td>Antidepressant &amp; anxiolytic. May also speed symptomatic response. May reduce risk of sexual side effects</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;1B&lt;/sub&gt;</td>
<td>Partial agonist (K&lt;sub&gt;i&lt;/sub&gt; 33 nM)</td>
<td>Modulates release of monoamines, acetylcholine, glutamate and GABA; uncertain clinical impact</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Antagonist, (K&lt;sub&gt;i&lt;/sub&gt; 3.7 nM)</td>
<td>Antimetic, possible antidepressant/anxiolytic effects, possible effects on memory and learning Possible effects on memory and learning</td>
</tr>
<tr>
<td>5-HT&lt;sub&gt;7&lt;/sub&gt;</td>
<td>Antagonist, (K&lt;sub&gt;i&lt;/sub&gt; 19 nM)</td>
<td></td>
</tr>
</tbody>
</table>

*K<sub>i</sub> = inhibitory constant. Adapted from information published in Arenberg et. al, 2011 [20], Bang-Andersen et. al, 2011 [21], and Sanchez et al., 2014.[19] GABA: gamma-aminobutyric acid.*
3.3. Pharmacokinetics and metabolism

Vortioxetine is metabolized in the liver into four major metabolites via cytochromes 2D6, 2C19, 3A4, 2C9, and 2B6, as well as alcohol and aldehyde dehydrogenases; 2D6 seems to catalyze the rate-limiting step overall.[19] The compound does not appear to significantly induce or inhibit cytochrome oxidase enzymes. Vortioxetine is 75% bioavailable orally, is extensively protein-bound, and has an elimination half-life (t1/2) of 60 hours. [19,22] Thus, when it is necessary to discontinue therapy, it will take several weeks to fully wash out the effects of the drug, which warrants caution when switching to an MAOI. On the positive side, a drug with this pharmacokinetic profile is unlikely to be associated with problematic discontinuation symptoms. Cytochrome-related drug interactions are likely to be unusual given the multiple metabolic pathways involved in the metabolism of vortioxetine, though butyrophion may significantly increase vortioxetine levels, while rifampicin may lower these levels significantly. [22] Coadministration with other strong cytochrome 2d6 inhibitors (e.g. fluoxetine, paroxetine, and quinidine) or inducers (carbamazepine and phenytoin) should also prompt consideration of dose modification. When treating patients known to be poor 2D6 metabolizers, dose reduction is advised. [From manufacturer’s prescribing information]

3.4. Special populations

Vortioxetine is approved in the US only for use in adult patients and has not been investigated in child and adolescent populations. As vortioxetine is currently listed as category ‘C’ in pregnancy and as its transmission into the breast milk of nursing mothers is not yet characterized, caution is advisable when considering this medication for women who are or who plan to become pregnant. No dosage adjustment is necessary for elderly patients or those with renal impairment or mild to moderate hepatic impairment. [From manufacturer’s prescribing information]

3.5. Preclinical studies

In animal in vivo microdialysis studies, vortioxetine has been shown to increase extracellular serotonin in key depression-related areas, such as the hippocampus and medial prefrontal cortex (mPFC), to a greater degree than SSRIs.[23,24] Vortioxetine also increases the extracellular concentration of norepinephrine, dopamine, acetylcholine, and histamine (HA) in rat prefrontal cortical areas, presumably though modulation of serotonin receptors.[23,24] In addition to these effects, vortioxetine has also demonstrated significantly greater effects on synaptic plasticity, long-term potentiation, and glutamatergic signaling than escitalopram in animal studies, suggesting a potential for a specific effect on cognitive functioning.[25,26]

4. Vortioxetine premarketing clinical trials

Eleven premarketing clinical trials submitted to the FDA were considered for this review of the efficacy of vortioxetine: all nine short-term efficacy trials and one 6-month relapse prevention trial submitted to the FDA and one Phase 2 study conducted in the EU were identified. Phase 1 trials have largely not reported or published results, or were focused on pharmacokinetic properties (NCT01299805, and assay of serotonin and metabolites in plasma and CSF, and, NCT01607125, NCT02112903, NCT01676571, and NCT02072278, which have been completed but have not posted results).

4.1. Phase 2

The first study of vortioxetine in MDD was conducted in the EU and included venlafaxine XR at 225 mg/day as an active comparator.[27] In this 6-week, four-arm, parallel-group RCT, 429 moderate-to-severely depressed outpatients were randomly assigned to receive one of two doses of vortioxetine (5 or 10 mg/day), venlafaxine XR, or placebo. Both doses of vortioxetine were found to be significantly superior to placebo, as was the comparator. Attrition due to adverse events was comparable in the placebo (4%) and 5 mg vortioxetine (3%) groups. About twice as many patients dropped out because of side effects in the 10 mg vortioxetine group (7%), which in turn had a drop-out rate of about half that observed in the venlafaxine 225 mg group (14%). The results of this study were sufficiently positive for the manufacturer to pursue Phase 3 studies and suggested that the 5 mg/day dose of vortioxetine might offer comparable efficacy as an SNRI with better tolerability.

4.2. Phase 3 studies and FDA review

In addition to the Phase 2 study described above, nine other, short-term, placebo-controlled RCTs were submitted for regulatory review, along with one 6-month long relapse-prevention trial. The FDA review of this body of work is nicely summarized by Zhang and colleagues.[28] All of these studies enrolled adult outpatients with MDD (DSM-IV-TR criteria); one study focused
specifically on patients aged 65 and older. All studies required that patients were medically stable and were not taking concomitant medications that might complicate study treatment. For most studies, the MADRS was the primary dependent measure. The studies differed in the minimum or threshold level of symptom severity required for eligibility, with minimum required pretreatment MADRS scores ranging from ≥22 to ≥30 to be eligible for randomization. Thus, the portfolio includes depressed outpatients ranging from milder to more severe depressive states. The study of older patients also required that patients have a Mini-Mental State Examination score of at least 24 to exclude patients with more advanced levels of cognitive impairment and all patients with a clinical diagnosis of dementia. The studies evaluated vortioxetine in doses ranging from 1 to 20 mg/day. In addition to the Phase 2 study that included venlafaxine XR as an active control, five studies employed duloxetine as the active comparator.

Looking across the regulatory submission portfolio (see Zhang et al., 2015 [28]), it is apparent that the studies were conducted in two waves. In the first wave, the maximum dose of vortioxetine studied was 10 mg/day. Although in aggregate these studies showed that the 5 and 10 mg/day doses were effective, neither of the studies conducted in the US demonstrated efficacy. Therefore, a second wave of studies was undertaken, focusing on the safety and efficacy of higher doses of vortioxetine (15 and 20 mg). In the second wave of studies, the efficacy of the 20 mg/day dose of vortioxetine was established in the US. Across both waves, 6 of the 10 RCTs met the FDA’s a priori review criteria for novel antidepressants; specifically, they were judged to be positive on the basis of a statistically significant effect for at least one dose of vortioxetine as compared to placebo (see Table 2).

Among the four studies that did not find significant treatment effects, the FDA concluded that one study was considered to be a failed study because the active comparator (duloxetine 60 mg per day) also did not statistically separate from placebo. As the current success rate for psychiatric medications in Phase 3 RCTs hovers around 50%, the FDA concluded that the preponderance of the evidence supported the efficacy of vortioxetine 20 mg/day.[28,38]

<table>
<thead>
<tr>
<th>Study number</th>
<th>NCT identifier</th>
<th>Location</th>
<th>Study length</th>
<th>Key inclusion criteria</th>
<th>Main result (primary outcome)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>11492A</td>
<td>NCT00839423</td>
<td>Non-US</td>
<td>6 weeks</td>
<td>MADRS ≥ 30 MDE ≥ 3 months and &lt;12 months</td>
<td>Significant reduction in MADRS vs. placebo of 5.9 (5 mg), and 5.7 (10 mg)</td>
<td>Alvarez et al., 2012 [27]</td>
</tr>
<tr>
<td>11984A</td>
<td>NCT00635219</td>
<td>Non-US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 MDE ≥ 3 months</td>
<td>‘Failed’ study. Neither duloxetine nor vortioxetine demonstrated a significant reduction in MADRS vs. placebo</td>
<td>Baldwin et al., 2012 [29]</td>
</tr>
<tr>
<td>305</td>
<td>NCT07337509</td>
<td>Non-US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 MDE ≥ 3 months</td>
<td>Significant reduction in HDRS-24 vs. placebo of 3.52 (1 mg), 4.12 (5 mg) and 4.93 (10 mg)</td>
<td>Henigsberg et al., 2012 [30]</td>
</tr>
<tr>
<td>12541A</td>
<td>NCT00811252</td>
<td>US and non-US</td>
<td>8 weeks</td>
<td>Aged ≥65 years MADRS ≥ 26 MDE ≥ 4 weeks, recurrent</td>
<td>Significant reduction in HDRS-24 vs. placebo of 3.3</td>
<td>Katona et al., 2012 [31]</td>
</tr>
<tr>
<td>303</td>
<td>NCT00672958</td>
<td>US</td>
<td>6 weeks</td>
<td>MADRS ≥ 30 MDE ≥ 3 months</td>
<td>No significant difference was found between vortioxetine and placebo in reduction of HDRS-24</td>
<td>Jain et al., 2013 [32]</td>
</tr>
<tr>
<td>304</td>
<td>NCT00672620</td>
<td>US</td>
<td>8 weeks</td>
<td>MADRS ≥ 22 MDE ≥ 3 months</td>
<td>No significant difference was found between vortioxetine and placebo in reduction of HDRS-24</td>
<td>MahableshwarKar et al., 2013 [33]</td>
</tr>
<tr>
<td>13267A</td>
<td>NCT01140906</td>
<td>Non-US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months, recurrent</td>
<td>Significant reduction in MADRS vs. placebo of 5.5 (15 mg) and 7.1 (20 mg)</td>
<td>Boulenger et al., 2014 [34]</td>
</tr>
<tr>
<td>316</td>
<td>NCT01163266</td>
<td>US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months, recurrent</td>
<td>Significant reduction in MADRS vs. placebo of 3.64 (20 mg), no significant difference seen with 10 mg vs. placebo</td>
<td>Jacobsen et al., 2015 [35]</td>
</tr>
<tr>
<td>315</td>
<td>NCT01153009</td>
<td>US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months, recurrent</td>
<td>Significant reduction in MADRS vs. placebo of 4.07 (20 mg), no significant difference seen with 15 mg vs. placebo</td>
<td>MahableshwarKar et al., 2015 [36]</td>
</tr>
<tr>
<td>317</td>
<td>NCT01179516</td>
<td>US</td>
<td>8 weeks</td>
<td>MADRS ≥ 26 CGI-S ≥ 4 MDE ≥ 3 months, recurrent</td>
<td>No significant difference was found between vortioxetine and placebo in reduction of MADRS</td>
<td>MahableshwarKar et al., 2015b [37]</td>
</tr>
</tbody>
</table>

*n represents all randomized participants who took at least one dose of study drug. CGI-S: Clinical Global Impression-Severity of Illness; DUL: duloxetine; MADRS: Montgomery-Åsberg Depression Rating Scale; MDE: major depressive episode; PBO: placebo; VEN: venlafaxine; VOR: vortioxetine; HDRS: Hamilton Depression Rating Scale.

Adapted from FDA CDER 2013 [4].
The results of the single longer-term, relapse-prevention study also were consistent with the FDA’s appraisal of efficacy.[39] In this trial, a total of 693 depressed outpatients were treated for up to 12 weeks with 5–10 mg of vortioxetine, of which 396 responded and were then blindly randomized to continuation treatment or placebo. Across the 24 weeks of double-blind preventive therapy, the subjects who stayed on active vortioxetine had a significantly lower relapse rate (13%) than those who were switched to placebo (26%). The observed magnitude of reduction of risk is comparable to what has been observed in other studies of newer-generation antidepressants using similar designs.[40,41] However, because this study used doses of vortioxetine that are below the current recommended dose in the US, the FDA requested that the manufacturer perform an additional longer-term study to document the safety and efficacy of the 20 mg/day dose for recurrence prevention.

4.2.1. Dose–response relationship
Careful inspection of the registration studies without consideration of the countries in which they were conducted would support the conclusion that vortioxetine is effective across a range of doses (5–20 mg/day)(see Table 2). Visual inspection of mean drug versus placebo differences likewise suggests that the therapeutic effects of vortioxetine are dose-dependent, although the FDA concluded that there was only sufficient evidence to conclude that the 20 mg/day dose was effective in the US. The FDA recognized that the 5 mg/day dose performed better in the studies conducted outside the US, but did not speculate on the reason. However, the FDA reviewers did note that, with respect to signal detection and assay sensitivity, duloxetine 60 mg/day also had a smaller effect size in the US studies than in the studies conducted outside of the US.[28]

4.2.2. Efficacy in late-life depression
One 8-week, placebo-controlled RCT evaluated the efficacy of the 5 mg dose of vortioxetine in adults aged 65 and older (mean age: 70.6 years).[31] The study included duloxetine (60 mg/day) as an active comparator and employed a standardized cognitive assessment battery in addition to symptomatic outcomes. At 8 weeks, both active medications were significantly more effective than the placebo; remission rates (final 24-item Hamilton Depression Rating Scale score ≤7) were 19.3%, 29.2%, and 34.7% for placebo, vortioxetine and duloxetine, respectively. Withdrawals due to adverse events were as follows: placebo, 3%; vortioxetine, 6%; and duloxetine, 10%.

With respect to effects on cognition, subjects’ cognition was evaluated with the Rey Auditory Verbal Learning Test (RAVLT) and the Digit Symbol Substitution Test (DSST). Path analysis was performed to differentiate between direct effects of the drug and indirect effects due to symptomatic improvement. Both duloxetine and vortioxetine showed significantly greater improvements than placebo on the RAVLT, with effect sizes of about 0.3 for the active therapies. Vortioxetine, but not duloxetine, also showed a significant improvement on the DSST.

4.3. Safety and tolerability of vortioxetine
A total of 2616 depressed adult patients took at least one dose of vortioxetine 5–20 mg/day in the short-term placebo-controlled trials of MDD that were reviewed by the FDA.[28] In this pooled data set, the attrition rates due to side effects in the active vortioxetine arms were as follows: 5 mg/day = 5%, 10 mg/day = 6%, 15 mg/day = 8%, and 20 mg/day = 8%, as compared to 4% in the placebo groups. The most common adverse event that led to attrition was nausea, which was the reason that about 1% of patients treated with vortioxetine prematurely discontinued therapy. Using the FDA convention to consider an adverse event to be common if it occurs with an incidence of at least 5% and occurs with an incidence that is at least twice that of placebo, vortioxetine therapy is associated with only three common side effects: nausea, vomiting, and constipation (see Table 3). All three of these side effects occurred at lower rates in the groups treated with 5–10 mg/day than in the groups treated with 15–20 mg/day doses. Moreover, in the studies that included duloxetine as the active comparator, the incidence of nausea, vomiting, and con-

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Table 3. Side effects reported by at least 5% of subjects taking vortioxetine and at an incidence of at least twice that of placebo in short-term RCTs reviewed by the FDA.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Placebo n = 1621</th>
<th>5 mg n = 1013</th>
<th>10 mg n = 699</th>
<th>15 mg n = 449</th>
<th>20 mg n = 455</th>
<th>Duloxetine n = 753</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>21%</td>
<td>26%</td>
<td>32%</td>
<td>32%</td>
<td>36%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1%</td>
<td>3%</td>
<td>5%</td>
<td>7%</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Constipation</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
<td>6%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Adapted from: Zhang et al., 2015 [28].
stipation was lower in the groups treated with 5–10 mg/day than documented in the patients receiving 60 mg/day of duloxetine (see Table 3). By contrast, the incidence of nausea and vomiting in the groups that received 15–20 mg/day vortioxetine was comparable to that observed in the duloxetine arms.

The manufacturer of vortioxetine was optimistic that the receptor profile of this drug would lower the risk of treatment-emergent sexual side effects. Several of the Phase 3 studies included prospective assessment of sexual function with standardized scales, and there did appear to be a low incidence of orgasmic dysfunction in men and women treated with lower doses of vortioxetine (i.e. 5–10 mg/day). However, as this potential advantage was not clearly evident in patients receiving 20 mg/day of vortioxetine, the FDA concluded that the drug did not have a definite advantage compared to existing standards.[28] Since then a randomized, double-blind trial of vortioxetine versus escitalopram found that vortioxetine was associated with significantly higher scores on the Changes in Sexual Functioning Questionnaire, Short Form (CSFQ-14; vortioxetine 8.8 vs. escitalopram 6.6 P = 0.013), suggesting a lower propensity for sexual side effects.[42]

Short-term efficacy studies found no significant changes in laboratory parameters, vital signs, or weight.[28]

The tolerability profile during longer courses of therapy is documented by a number of long-term extension trials. The first report, which describes the results of a 52-week open-label extension protocol for patients who completed shorter-term double-blind RCTs, enrolled 535 patients who had obtained an adequate response to vortioxetine 2.5–10 mg/day.[43] A total of 61.3% (n = 328) of the patients completed the study; 83% of the completers were in remission, as defined by a final MADRS score of 10 or less, at the end of 1 year of preventive therapy. The most common side effects observed during longer-term treatment were nausea, headache, and nasopharyngitis, which occurred in more than 10% of patients. Six patients (2%) reported various complaints of sexual dysfunction as new side effects during ongoing therapy. This appears to be a very low incidence of sexual side effects, although in the absence of both a placebo control condition and a systematic assessment, it is difficult to calibrate the significance of these side effects. There were no clinically significant safety findings with respect to mean changes of vital signs, weight, ECG parameters, or clinical laboratory values.

In a second study, 834 outpatients with MDD who completed therapy in one of two double-blind RCTs were offered up to 52 weeks of ongoing therapy with flexibly adjusted (2.5–10 mg/day) vortioxetine therapy.[44] Across the year of extended vortioxetine therapy, the authors reported that no new safety signals were identified. Across all doses, the most common side effects were: nausea (15.2%), headache (12.4%), nasopharyngitis (9.8%), diarrhea (7.2%), and dizziness (6.8%). Again, there were few reports of new-onset sexual dysfunction. Neither weight gain nor changes in laboratory values, vital signs, or ECGs were noteworthy.

A third large trial, NCT01152996 enrolled 1075 subjects who completed a number of Phase 3 short-term trials [35–37] for a 52-week extension. Adverse events seen in more than 5% of the population included nausea, vomiting, diarrhea, constipation, upper respiratory infection, headache, weight gain, and insomnia. Withdrawal due to adverse events was 10.9%, and 29 serious adverse events were recorded. Serious adverse events were mainly single instances and likely unrelated to the study medication, though four subjects experienced disorders of the gallbladder and three attempted suicide.

NCT01323478, an open-label extension study of one of the Phase 3 efficacy trials, [34] followed up 71 trial completers for an additional 52 weeks, and found only one serious adverse event (cholelithiasis) and a 9.9% rate of withdrawal due to adverse events of any kind. Adverse effects were again most commonly nausea, headache, dizziness, and nasopharyngitis.

NCT00761306, another open-label extension study of one of the Phase 3 efficacy trials, [27] followed up 74 trial completers for an additional 52 weeks, and found only one serious adverse event (thyroiditis) and a 6.8% rate of withdrawal due to adverse events of any kind. Adverse effects were again most commonly nausea, headache, dizziness, and nasopharyngitis; 18.6% of subjects also experienced weight gain.

### 5. Post-marketing studies of vortioxetine

#### 5.1. Impact of cognitive function

The possibility that the receptor-mediated effects of vortioxetine may exert beneficial effects on cognition over and above those attributable to its antidepressant activity was suggested by both preclinical studies [45–47] and the findings of Katona and colleagues [31] in their RCT of older, depressed patients. If such effects could be confirmed prospectively in depressed patients, it would represent an important point of differentiation in clinical pharmacology vis-à-vis the SSRIs or SNRIs. A second study of the impact of vortioxetine therapy on cognition in depressed patients therefore was undertaken. [48] In this RCT of adults aged 18–65 years and suffering from MDD, patients were randomized to 8 weeks of double-blind treatment with placebo or either 10 or 20 mg/day of vortioxetine. The primary
outcome measure was improvement in a composite score derived from the DSST and RAVLT scores. Path analysis was also conducted to ascertain if improvement in cognition was attributable to reductions in depressive symptoms. Results indicated that both doses of vortioxetine were significantly better than placebo on the composite cognition score. Both doses of vortioxetine also resulted in a statistically significant improvement in depressive symptoms, and the path analysis indicated that the beneficial effect on cognition was not simply an epiphenomenon of symptomatic improvement.

5.2. Relative efficacy
None of the Phase 2 or Phase 3 studies reviewed by the FDA found significant effects favoring vortioxetine over the standard comparators, venlafaxine (1 study) and duloxetine (5 studies). Direct [49] and indirect [50] comparisons of efficacy confirm this conclusion.

5.3. Switching from other therapies
Like other newer antidepressants, vortioxetine is most commonly positioned as a second- or third-line therapy for patients who have not responded to or who had tolerability problems with an SSRI or SNRI. To date, only one study has evaluated vortioxetine therapy in this clinical context.[49] In this trial, 495 outpatients with MDD who had not responded to a course of SSRI/SNRI therapy in the current episode were switched to vortioxetine (10–20 mg/day) or agomelatine (25–50 mg/day) (1:1, blinded) for 12 weeks. Although not available in the US, agomelatine is one of the newer alternatives to SSRI/SNRI therapy in Europe and, as such, is a relevant comparator to vortioxetine. The first aim of the study was to test non-inferiority (i.e. the efficacy of vortioxetine was not inferior to that of agomelatine with a narrow, pre-defined range). Secondarily, conventional tests of superiority and tolerability also were performed. The primary analysis confirmed that vortioxetine (n = 252) was not inferior to agomelatine (n = 241). Moreover, the advantage in symptom improvement in the vortioxetine group (2.2 MADRS points) was statistically significantly greater than the improvement observed in the agomelatine group.

5.4. Other post-marketing studies
A Phase 2/3 randomized placebo-controlled trial completed in Asia, Europe, and Oceania, NCT01255787, found no significant difference in MADRS total score versus placebo for doses of 5, 10, or 20 mg of vortioxetine in major depression (n = 600). NCT01355081, a Phase 3 randomized placebo-controlled trial completed in Japan, also failed to find a significant reduction in MADRS vs. placebo (n = 366).

6. Conclusion
Vortioxetine is a structurally and mechanistically novel antidepressant with a safety and efficacy profile that appears to be comparable to that of duloxetine. Classified by the FDA as an SSRI, the novelty of this drug is found in its therapeutic activities derived from multimodal activity at serotonin receptors. Specifically, this agent may have important clinical advantages by virtue of its cognition-enhancing effects. The drug also may have a lower incidence of sexual adverse effects, at least at lower therapeutic doses. If post-marketing data and clinical experience confirm such advantages, then vortioxetine will represent a valuable albeit incremental new option for patients.

7. Expert commentary
Although truly novel (i.e. non-monoaminergic) approaches to the pharmacotherapy of depression continue to be a major goal of antidepressant development, there is some cause for hope that vortioxetine, which is a monoaminergic drug with a novel array of effects on pre- and postsynaptic receptors, may offer a clinical profile that differentiates it from both the current first-line therapies and other newer antidepressants.

Launched throughout the US and Europe in late 2013 and early 2014, the efficacy of this drug was evident in an unusually extensive Phase 3 research program. As vortioxetine was compared a number of times to SNRIs, it was also established that this drug has an efficacy profile that is comparable to other effective treatments of MDD.

With respect to tolerability, early studies suggested that vortioxetine therapy at lower doses, especially 5 mg/day, may be associated with a lower overall side effect burden than the SNRIs. A lower incidence of treatment-emergent sexual side effects looked particularly promising. However, as the efficacy of the 5 mg/day dose could not be established in the US, it was necessary to develop the efficacy profile of higher doses, and ultimately only the 20 mg/day dose was consistently established as efficacious in the US. Although further studies are needed with direct head-to-head comparisons, at this time there, is no evidence that vortioxetine at 20 mg/day has a more favorable side effect profile than SNRIs.
A second and potentially unique clinical feature of vortioxetine pertains to its effects on memory and executive function. Recognition of such effects was not serendipitous: based on the pharmacology of this drug, preclinical studies were undertaken early on that suggested favorable effects on cognition. Although it can be said that all antidepressants have some beneficial effects on cognition when effective, two studies have now found that the effects of vortioxetine on memory and executive function appear to be largely independent of the magnitude of the antidepressant effect. If confirmed and particularly if shown in comparison to first-line antidepressants, it is conceivable that vortioxetine will become the preferred treatment for depression in later life or perhaps even for depressive episodes associated with significant complaints of cognitive dysfunction. A study of vortioxetine therapy in older, depressed patients with mild cognitive impairment is now greatly needed.

As with any drug that has been marketed for less than 1 year, more extensive post-marketing data are not yet available. The therapeutic landscape is littered with discarded claims of superiority for many recently introduced antidepressants. For this reason, we are cautiously optimistic regarding the potential of vortioxetine, rather than being as enthusiastic as we would be, were it a truly revolutionary treatment option. It also must be noted that long-term efficacy data is still lacking and so any sound appraisal of the longer-term use of this agent must await more data.

Declaration of interest

M E Thase has been an advisory/consultant for Alkermes, Allergan, AstraZeneca, Bristol-Myers Squibb Company, Cerecor, Inc., Eli Lilly & Co., Forest Laboratories, Gerson Lehrman Group, Fabre-Kramer Pharmaceuticals, Inc., GlaxoSmithKline, Guidepoint Global, H. Lundbeck A/S, MedAvante, Inc., Merck and Co. Inc. (formerly Schering Plough and Organon), Moksha8, Naurex, Inc., Neurontics, Inc., Novartis, Ortho-McNeil Pharmaceuticals (Johnson & Johnson; Janssen), Otsuka, Pamlab, L.L.C. (Nestle) Pfizer (formerly Wyeth Ayerst Pharmaceuticals), Shire US Inc., Sunovion Pharmaceuticals, Inc., Trius Therapeutic, Inc. and Takeda. He has received grant support from Agency for Healthcare Research and Quality, Alkermes, AssureRx, Avanir, Forest Pharmaceuticals, Janssen, National Institute of Mental Health and Otsuka Pharmaceuticals. M E Thase has equity holdings in MedAvante, Inc. and receives royalties from American Psychiatric Foundation, Guilford Publications, Herald House and W.W. Norton & Company, Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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