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To cite this article: William James Deardorff & George T Grossberg MD (2014) A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine, Expert Opinion on Pharmacotherapy, 15:17, 2525-2542, DOI: 10.1517/14656566.2014.960842

To link to this article: http://dx.doi.org/10.1517/14656566.2014.960842

Published online: 16 Sep 2014.
A review of the clinical efficacy, safety and tolerability of the antidepressants vilazodone, levomilnacipran and vortioxetine

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Introduction: As a leading cause of disability, major depressive disorder (MDD) is characterized by reduced quality of life and altered functioning. Current pharmaceutical treatment options are limited in their success by modest effects and adverse events that often lead to discontinuation. One current trend in antidepressant development is to combine inhibition of the serotonin transporter with other pharmacological targets, including the norepinephrine transporter or different serotonin receptors.

Areas covered: In a span of < 3 years, the FDA approved three new antidepressants for the treatment of MDD: vilazodone in January 2011, levomilnacipran in July 2013 and vortioxetine in September 2013. This article reviews the efficacy, safety and tolerability of these three drugs mainly from the Phase III trial data.

Expert opinion: All three drugs are effective in the treatment of MDD, but data comparing them to other antidepressants is currently lacking. Vilazodone was proposed to produce a more rapid onset and have fewer sexual side effects but neither effect has been conclusively shown. Levomilnacipran appears to be effective in improving functional impairment, including both social and work functioning. Vortioxetine is currently the only drug of the three with proven efficacy in elderly patients. It also appears to have cognitive enhancing properties which are largely independent of improved depressive symptoms. Overall, these drugs represent a promising step forward in antidepressant drug development.

Keywords: antidepressant, levomilnacipran, major depressive disorder, vilazodone, vortioxetine

1. Introduction

Major depressive disorder (MDD) is one of the leading causes of disability and is predicted to be the second-leading cause of burden of disease worldwide by 2030 [1,2]. Although antidepressants play an important role in treating MDD, the first decade of the twenty-first century saw a slowing in the development of novel antidepressants. A select sample of the FDA’s approvals shows that many were for repackaged drugs: an enantiomer of the racemic selective serotonin reuptake inhibitor (SSRI) citalopram (escitalopram), a transdermal patch of the monoamine oxidase inhibitor selegiline, a major metabolite of venlafaxine (desvenlafaxine), a different formulation of bupropion (bupropion hydrobromide) and an extended-release version of trazodone [3]. Some reasons that might account for the shortcomings of antidepressant drug discovery include inadequate dosing in clinical trials, limited time period of medications under patent protection and the financial risk of drugs with novel mechanisms [4]. The second decade appears more promising thus far with the FDA’s approval of vilazodone in January 2011, levomilnacipran...
in July 2013 and vortioxetine in September 2013. Vortioxetine was also approved by the European Medicines Agency in December 2013. The approval of three new antidepressants within a period of < 3 years is an exciting development in the treatment of a disorder with an estimated lifetime prevalence within a period of < 3 years is an exciting development in the treatment of a disorder with an estimated lifetime prevalence of 16% of the US population [5]. This review will analyze the clinical efficacy, safety and tolerability of these three drugs, primarily using data from select Phase III trials, and will emphasize their unique properties.

2. New generation of antidepressants

The second generation of antidepressants includes SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs) and drugs that exhibit multiple receptor profiles [6]. The second-generation antidepressants likely do not differ much from each other in terms of efficacy, meaning that expected side effects and cost play a large role in treatment selection [7,8]. A general trend in the development of newer drugs has been to target multiple receptors in addition to the serotonin transporter (SERT). This type of ‘intramolecular polypharmacy’ affects multiple neurotransmitter pathways, potentially leading to greater efficacy on a broader range of symptoms [6]. Another trend is the exploration of drugs affecting systems other than the aminergic system, such as different glutamate modulators and agomelatine, a melatonergic MT1/MT2 agonist and serotonin (5-hydroxytryptamine) (5-HT)2C antagonist licensed in Europe.

3. Mechanisms of action

Figure 1 reviews the mechanisms of action of the three antidepressants. Vilazodone acts as a partial 5-HT1A receptor agonist and serotonin reuptake inhibitor [9]. Vilazodone inhibits serotonin reuptake with an IC50 of 1.6 nM and binds to the human 5-HT1A binding sites with an IC50 of 2.1 nM [10]. Since the release of serotonin is regulated by presynaptic 5-HT1A autoreceptors, vilazodone was proposed to augment the effect of SERT inhibition [11]. Data from preclinical studies were hopeful that vilazodone could produce a rapid onset of action by increasing 5-HT output either through inhibiting or rapidly desensitizing 5-HT1A autoreceptors [12]. Early studies showed a greater elevation of extracellular 5-HT levels in the rat brain frontal cortex compared to SSRIs and a 30-fold greater potency at inhibiting serotonin reuptake compared to fluoxetine [13-15]. Rapid onset would be advantageous because of the delayed onset of antidepressants, which is generally attributed to the need for long-term adaptations such as receptor desensitization and signaling pathway alterations [16].

Levomilnacipran is an SNRI and the more active enantiomer of milnacipran, currently used in the USA for treating fibromyalgia and neuropathic pain and available in Europe for treating depression. Although levomilnacipran is not a novel antidepressant, its selectivity is slightly different compared to other SNRIs. The SNRIs duloxetine, venlafaxine and desvenlafaxine all preferentially inhibit 5-HT reuptake compared to norepinephrine (NE) reuptake. However, levomilnacipran shows an approximately twofold greater potency at inhibiting NE relative to 5-HT reuptake and a NE:5-HT transporter selectivity ratio of 27 and 17 times that of duloxetine and venlafaxine, respectively [17]. The IC50 values of levomilnacipran at human NE transporter and SERT receptors stably expressed in Chinese hamster ovary cells were 10.5 and 19.0 nM, respectively [17]. This is potentially advantageous because the noradrenergic system might be involved in mental and physical slowing, decreased concentration, social functioning and loss of energy [18]. In fact, treatment with milnacipran appears to enhance social functioning throughout a variety of studies [18].

Vortioxetine functions as a SERT inhibitor (Ki = 1.6 nM, IC50 = 5.4 nM), 5-HT1A receptor agonist (Ki = 15 nM), 5-HT3 receptor antagonist (Ki = 3.7 nM), 5-HT7 receptor antagonist (Ki = 19 nM), 5-HT1D receptor antagonist (Ki = 54 nM) and 5-HT1B receptor partial agonist (Ki = 33 nM) [19,20]. This mechanism is thought to be advantageous for several reasons. 5-HT1A receptor agonists could desensitize somatodendritic and activate postsynaptic 5-HT1A receptors to elevate serotonin. 5-HT3 and 5-HT7 antagonists have been shown to regulate various neurotransmitter systems, although the mechanism is not fully understood [21,22].
Vortioxetine does appear to modulate glutamate and GABA transmission based on preclinical data involving serotonin depleted and progesterone-withdrawal studies in rats [23]. This could be attributed to its 5-HT3 antagonism given that 5-HT3 antagonists have been shown to enhance glutamate transmission via reductions in GABA-mediated inhibition [24]. In rat microdialysis studies, vortioxetine showed significant increases in 5-HT, dopamine and noradrenaline levels in the ventral hippocampus and medial prefrontal cortex [19,25]. Vortioxetine increased extracellular levels of 5-HT in the rat ventral hippocampus more than SSRIs and SNRIs [26]. Combined, the preclinical data show that vortioxetine’s multiple receptor targets are important for its antidepressant activity, indicating a novel mechanism distinct from SSRIs and SNRIs [27].

4. Clinical efficacy

The following is a selective review of published and non-published results from clinical trials that were obtained through online searches of http://www.ncbi.nlm.nih.gov/pubmed, http://www.clinicaltrials.gov, and http://www.fda.gov. Additional data reviewed by the FDA were obtained through http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Poster presentations at conferences such as the American Psychiatric Association and American Society of Clinical Psychopharmacology were also reviewed.

Several measures are commonly used to evaluate the clinical efficacy of antidepressants. Based on a primary efficacy measure, such as the Montgomery-Åsberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D/HDRS), 2-point differences from placebo at end point are generally considered clinically relevant [28]. Differences > 10% in response rate between placebo and treatment and a number needed to treat (NNT) < 10 are also considered clinically advantageous. Based on Cohen’s d effect size, values of 0.2 and 0.5 are considered small and medium, respectively [29]. Most antidepressants show effect sizes between 0.2 and 0.5 [30].

4.1 Vilazodone

A total of five 8-week Phase II trials involving vilazodone were performed with two using fixed doses (5, 10 and 20 mg/day) and three using a flexible titration design [31]. None of these
five trials showed a statistically significant difference from placebo on the HAM-D. Three of the five trials used an active comparator (fluoxetine or citalopram), which also did not show significant differences from placebo. A review of vilazodone cites flaws in methodology, use of low doses, a large number of investigative sites and use of the HAM-D as opposed to the MADRS as potential reasons for the failed studies [32]. The second Phase III trial involved patients aged 18 to 70 with MDD [35]. Doses of vilazodone were increased from 10 to 40 mg over a course of 2 weeks, with patients able to receive 20 mg if they could not tolerate the 40 mg dose. Vilazodone showed a statistically significant difference from placebo at week 8, with a least-squares mean difference (LSMD) of -3.2 points on the MADRS total score (d = 0.30) [34]. Significant difference from placebo occurred at week 1 for patients on vilazodone (LSMD = -1.7, p = 0.0002).

The second Phase III trial involved patients aged 18 to 70 with MDD [35]. Doses of vilazodone were increased from 10 to 40 mg over 2 weeks. Reducing the dose to 20 mg was not allowed. The mean difference on MADRS total score at week 8 was -2.5 between vilazodone and placebo (d = 0.23) [34]. Significant difference from placebo occurred starting at week 6 on vilazodone, which is considerably later than the previous trial.

Both trials showed >10% difference in response rates (≥50% decrease in MADRS total score from baseline) between vilazodone and placebo, which is considered clinically meaningful [28]. MADRS response rates were 40.4% for vilazodone and 28.1% for placebo in one trial and 43.7% for vilazodone and 30.3% for placebo in the other [34]. This is similar to a meta-analysis of five trials involving escitalopram, which showed response rates of 52.9% after 8 weeks on the MADRS for escitalopram and 37.3% for placebo [36]. The NNT for response and remission on MADRS with vilazodone was 8 and 12 in the pooled data, respectively [37]. Whereas both Phase III trials did not show significant differences in remission, data from a recent Phase IV trial using 40 mg/day vilazodone showed a significant difference after 8 weeks in remission rates (MADRS ≤ 10) from placebo (34 vs 22%, NNT = 9) [38,39]. In the Phase IV trial, the LSMD for vilazodone 40 mg versus placebo was -5.1 on MADRS total score, with categorical improvements across all 10 MADRS items [40].

Given that the anxiolytic drug buspirone and vilazodone act at the 5-HT1A receptor, vilazodone was hypothesized to help patients with MDD and high levels of anxiety [11]. In a post hoc analysis of both Phase III trials, a subgroup of patients classified as anxious based on HAM-D17 anxiety/somatization subscale scores showed significant difference from placebo on the MADRS (LSMD = -3.6) and the Hamilton Anxiety Scale (HAM-A) total score (LSMD = -1.82, d = 0.25) [41]. This is important clinically, given the poorer treatment outcomes and lower rates of remission in patients with anxious depression [42]. However, the authors explain that the retrospective nature limits the results since neither trial was designed to compare patients with anxious versus non-anxious depression.

A recent unpublished multicenter, randomized, double-blind, 10-week trial compared 20 mg vilazodone (n = 288) and 40 mg vilazodone (n = 287) with placebo (n = 281). The SSRI citalopram was used for assay sensitivity (40 mg, n = 282) [43]. The results showed a significant difference on MADRS total score (primary efficacy outcome) at week 10 for all groups compared to placebo. The LSMDs from placebo were -2.57 for vilazodone 20 mg, -2.82 for vilazodone 40 mg and -2.74 for citalopram 40 mg.

### 4.2 Levomilnacipran

Five short-term trials ranging from 8 to 10 weeks and one 24-week long-term maintenance trial were evaluated by the
FDA, prior to approval [44]. In all these studies, levomilnacipran was used on adult outpatients with MDD at a range of 40–120 mg/day. Two fixed-dose studies and two flexible-dose studies were considered supportive. One flexible-dose study and a long-term maintenance study did not achieve statistically significant results. The LSMD on the MADRS total score from baseline to the end of trial ranged from -3.1 to -4.9 for the four positive studies, compared to placebo, with statistically significant difference from placebo occurring during week 3 or week 4. Efficacy data for the five short-term trials are displayed in Table 2.

In a 10-week, Phase II non-US study, patients receiving flexible doses (75–100 mg/day) saw significant improvements in MADRS total score compared to placebo starting from week 3 onward, with a LSMD of -4.2 at week 10 [45]. In a post-hoc analysis of this trial, the authors noted that every item on the MADRS achieved statistically significant differences, indicating improvement across a broad range of symptoms [46].

A Phase III, USA, 8-week outpatient study compared three fixed doses of levomilnacipran (40, 80 and 120 mg/day) with placebo [47]. Significant improvements in MADRS total score were seen for all three doses compared to placebo, with the 80 and 120 mg groups achieving statistical significance at week 4. The authors concluded that dosing up to 120 mg was effective without decreased tolerability.

A Phase III, 8-week outpatient trial in the USA and Canada compared fixed doses of levomilnacipran (40 and 80 mg/day) with placebo [48]. This study was unique in that it only included patients with recurrent depression. There was a statistically significant difference in change in MADRS as early as week 4 for both treatment groups.

A Phase III, USA, 8-week trial compared flexible dose levomilnacipran (40–120 mg/day) with placebo [49]. There was a statistically significant difference in change in MADRS as early as week 4. The Motivation and Energy Inventory Short Form (MEI-SF) was used to evaluate patient motivation and energy. The levomilnacipran group showed a statistically

### Table 2. Summary of MADRS and SDS total score data for levomilnacipran from five short-term, placebo-controlled trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Levomilnacipran dose (daily)</th>
<th>Measure</th>
<th>Baseline mean</th>
<th>LSM change, end point</th>
<th>LSMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo</td>
<td>Levomilnacipran</td>
<td>Placebo</td>
<td>Levomilnacipran</td>
</tr>
<tr>
<td>Montgomery et al. (2013) [45] 10-week, positive, Phase II study</td>
<td>75 – 100 mg</td>
<td>MADRS</td>
<td>30.5</td>
<td>30.9</td>
<td>-14.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>20.8</td>
<td>21.3</td>
<td>-7.7</td>
</tr>
<tr>
<td>Asnis et al. (2013) [47] 8-week, positive, Phase III study</td>
<td>40 mg</td>
<td>MADRS</td>
<td>35.6</td>
<td>36.0</td>
<td>-11.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>21.5</td>
<td>21.1</td>
<td>-7.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MADRS</td>
<td>35.6</td>
<td>36.1</td>
<td>-11.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>21.5</td>
<td>21.4</td>
<td>-7.2</td>
</tr>
<tr>
<td>Bakish et al. (2014) [48] 8-week, positive, Phase III study</td>
<td>40 mg</td>
<td>MADRS</td>
<td>31.0</td>
<td>30.8</td>
<td>-11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>16.4</td>
<td>16.7</td>
<td>-5.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MADRS</td>
<td>31.0</td>
<td>31.2</td>
<td>-11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>16.4</td>
<td>17.6</td>
<td>-5.4</td>
</tr>
<tr>
<td>Sambunaris et al. (2014) [49] 8-week, positive, Phase III study</td>
<td>40–120 mg</td>
<td>MADRS</td>
<td>35.2</td>
<td>35.0</td>
<td>-12.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>19.7</td>
<td>20.1</td>
<td>-5.4</td>
</tr>
<tr>
<td>Gommoll et al. (2014) [50] 8-week, negative, Phase III study</td>
<td>40–120 mg</td>
<td>MADRS</td>
<td>35.5</td>
<td>35.9</td>
<td>-14.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SDS</td>
<td>20.8</td>
<td>21.7</td>
<td>-8.2</td>
</tr>
<tr>
<td>Pooled population Montgomery et al. (2014) [51] 5 Phase II/III studies</td>
<td></td>
<td>MADRS</td>
<td>33.3</td>
<td>33.8</td>
<td>-12.9</td>
</tr>
<tr>
<td>Pooled population Sambunaris et al. (2014) [78] 5 Phase II/III studies</td>
<td></td>
<td>SDS</td>
<td>20.1</td>
<td>20.4</td>
<td>-2.2*</td>
</tr>
</tbody>
</table>

*Indicates statistically significant difference from placebo. Mixed model repeated measures was used for all calculations. LSMD: Least squares mean difference; MADRS: Montgomery-Åsberg depression rating scale; SDS: Sheehan Disability Scale.
significant difference from placebo on the MEI-SF total score and the cognitive and social subscales. This was promising given that deficits in the noradrenergic symptom cluster are thought to involve lack of energy.

The failed short-term Phase III trial was an 8-week outpatient study comparing flexible doses of levomilnacipran (40 – 120 mg/day) with placebo [50]. Although a numerically greater improvement in MADRS in the levomilnacipran groups compared to placebo (LSMD = -3.0) [51], the results were not statistically significant. The authors explain that one reason for the lack of statistical significance was that the placebo response was 2 – 3 points greater than in other comparable studies. The reason for this was unknown given the similarities to other trials.

A post-hoc pooled analysis of all five short-term trials showed a significantly greater improvement in MADRS in the levomilnacipran groups compared to placebo (LSMD = -3.0) [51]. All subgroups, except those with MDD duration of < 2 years and current episode duration of > 12 months, showed statistically significant improvements. The authors noted that patients with current episodes of > 12 months are more likely to have refractory MDD which might not respond to therapy. The group with MDD of < 2 years was relatively small and had a high response to placebo. The highest differences in response rates from placebo occurred in patients ≥ 60 years of age (17.9% difference), having ≥ 5 prior depressive episodes (14.6% difference) and having baseline MADRS total score of < 30 (14.1%). The subgroup with the smallest NNT for response (NNT = 6) and highest LSMD from placebo in MADRS total score (LSMD = -4.4) occurred in patients aged > 60. This is interesting given the small and inconsistent effect sizes seen in trials involving elderly patients [52]. However, the group size for patients ≥ 60 years was relatively small compared to the other subgroups. The overall pooled NNT for response and remission was 10 and 17, respectively.

4.3 Vortioxetine

Ten short-term trials and one relapse prevention trial were evaluated by the FDA to assess vortioxetine’s efficacy [53]. Of the 10 short-term trials, 6 and the relapse prevention trial were positive. One study was considered failure since the active comparator did not statistically differ from placebo. The final three were negative. Unlike studies with levomilnacipran, many of the studies included an active comparator (duloxetine or venlafaxine). Also unique to vortioxetine was that a trial on elderly patients was performed [62]. Finding antidepressants that are suitable for the elderly is important given the small effect sizes seen in controlled trials involving elderly patients [52]. In this 8-week USA and non-USA study, vortioxetine 5 mg was compared with placebo in patients with a mean age of 71 years. Vortioxetine 5 mg significantly separated from placebo at week 6, with a mean difference on the HAM-D24 (primary efficacy measure) of -3.32 at week 8. Duloxetine showed a mean difference of -5.48 at week 8 on the HAM-D24. When analyzed by country, the
US subgroup (n = 171) showed a LSMD of -0.7 for vortioxetine and -2.8 for duloxetine (both not significant) compared to placebo [53]. The non-US subgroup (n = 277) showed significant differences from placebo of -4.9 and -7.1 for vortioxetine and duloxetine, respectively.

One recent 12-week non-US trial not included in the FDA’s review randomized patients to vortioxetine (10–20 mg) or agomelatine (25–50 mg) after inadequate response to SSRI/SNRI monotherapy [63]. Eligibility criteria included patients with inadequate response for at least 6 weeks to an SSRI (citalopram, escitalopram, paroxetine and sertraline) or SNRI (duloxetine and venlafaxine). Vortioxetine was statistically superior to agomelatine on the MADRS starting at week 4, with a difference at week 8 of 2.2 points. Vortioxetine was also significantly superior in response and remission rates. At week 12, response rates were 69.8% for vortioxetine and 56.0% for agomelatine, and remission rates were 55.2% for vortioxetine and 39.4% for agomelatine. Switching to vortioxetine from either an SSRI or SNRI was numerically superior to switching to agomelatine. The differences between vortioxetine and agomelatine on MADRS total score was -2.6 (p < 0.01) for patients switching from an SSRI (n = 377) and -1.8 (not significant) for patients switching from an SNRI (n = 114) [64].

The one failed study was an 8-week non-US trial involving patients randomly assigned to 2.5, 5 or 10 mg vortioxetine, placebo or 60 mg duloxetine [65]. All groups did not statistically significantly differ from placebo at 8 weeks using a last-observation-carried-forward approach. However, the use of the mixed model repeated measures (MMRM) approach yielded significant difference from placebo for the 5 and 10 mg vortioxetine and duloxetine groups. Mean differences on MADRS total score from placebo using the MMRM approach were -2.5 for 5 mg vortioxetine, -2.6 for 10 mg vortioxetine and -3.0 for duloxetine.

The three negative studies were all performed in the USA [66-68]. They included a 6-week study using 5 mg, 8-week study using 10 and 15 mg and 8-week study using 2.5 and 5 mg vortioxetine. In one study, the authors describe that a potential reason for the negative result was that duloxetine had higher levels of adverse events (AEs), leading patients to believe that they were on active drug [68]. Since the rates of AEs for placebo and vortioxetine were similar, patients may have thought that they were not on active

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment dose (daily)</th>
<th>Measure</th>
<th>Baseline mean</th>
<th>LSM change, end point</th>
<th>LSMD</th>
</tr>
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<td>Placebo</td>
<td>Treatment</td>
<td>Placebo</td>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>Alvarez et al. (2012) [56]</td>
<td>Vortioxetine 5 mg</td>
<td>MADRS</td>
<td>33.9</td>
<td>34.1</td>
<td>-14.5</td>
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<tr>
<td>6-week, non-US Phase II; LOCF</td>
<td>Vortioxetine 10 mg</td>
<td>MADRS</td>
<td>33.9</td>
<td>34.0</td>
<td>-14.5</td>
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<tr>
<td>Venlafaxine 225 mg</td>
<td>MADRS</td>
<td>33.9</td>
<td>34.2</td>
<td>-14.5</td>
<td>-20.9</td>
</tr>
<tr>
<td>Boulenger et al. (2014) [58]</td>
<td>Vortioxetine 15 mg</td>
<td>MADRS</td>
<td>31.5</td>
<td>31.8</td>
<td>-11.7</td>
</tr>
<tr>
<td>8-week, non-US Phase III; MMRM</td>
<td>Vortioxetine 20 mg</td>
<td>MADRS</td>
<td>31.5</td>
<td>31.2</td>
<td>-11.7</td>
</tr>
<tr>
<td>Duloxetine 60 mg</td>
<td>MADRS</td>
<td>31.5</td>
<td>31.2</td>
<td>-11.7</td>
<td>-21.2</td>
</tr>
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<td>Mahableshwarkar et al. (2013) [61] 8-week, US Phase III; MMRM</td>
<td>Vortioxetine 15 mg</td>
<td>MADRS</td>
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<td>31.9</td>
<td>-12.8</td>
</tr>
<tr>
<td>Vortioxetine 20 mg</td>
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<td>32.8</td>
<td>-12.8</td>
<td>-16.9</td>
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<td>Jacobsen et al. (2013) [60] 8-week, US Phase III; MMRM</td>
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<td>HAM-D24</td>
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<td>32.5</td>
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<td>Vortioxetine 5 mg</td>
<td>HAM-D24</td>
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<tr>
<td>Vortioxetine 10 mg</td>
<td>HAM-D24</td>
<td>32.7</td>
<td>33.1</td>
<td>-11.3</td>
<td>-16.2</td>
</tr>
<tr>
<td>Katona et al. (2012) [62] 8-week, US and non-US Phase III study in elderly patients; LOCF</td>
<td>Vortioxetine 5 mg</td>
<td>HAM-D24</td>
<td>29.4</td>
<td>29.2</td>
<td>-10.3</td>
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<tr>
<td>8-week, US and non-US Dulexetine 60 mg</td>
<td>HAM-D24</td>
<td>29.4</td>
<td>28.5</td>
<td>-10.3</td>
<td>-15.8</td>
</tr>
<tr>
<td>Pooled data Thase et al. (2014) [54]</td>
<td>Vortioxetine 5 mg</td>
<td>MADRS</td>
<td>-2.6*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine 10 mg</td>
<td>MADRS</td>
<td>-3.5*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vortioxetine 20 mg</td>
<td>MADRS</td>
<td>-4.5*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Indicates statistically significant difference from placebo.

HAM-D24: Hamilton depression rating scale 24 item; LOCF: Last-observation-carried-forward; LSMD: Least squares mean difference; MADRS: Montgomery-Åsberg depression rating scale; MMRM: Mixed model repeated measures.
drug. One consistent point mentioned was that many trials involving MDD will not yield successful results, with one analysis reporting that 53% of MDD trials yield successful results and treatment effect has declined over time [69].

One observation seen throughout the trials was the smaller treatment effect sizes in USA compared to non-US patients. The FDA reviewers speculated that body mass index differences may explain the regional difference [53]. However, the results were not supported. A second observation was that vortioxetine may be equally effective in patients with higher anxiety symptoms. A recent meta-analysis from nine short-term studies found that patients with a baseline HAM-A score ≥ 20, indicating higher anxiety, had similar improvements in MADRS total score compared to the total population [70]. This is clinically meaningful given the lower response rates in patients with anxious depression [42]. Several trials for vortioxetine in the treatment of generalized anxiety disorder (GAD) have been performed, but the results thus far have been inconsistent [71].

5. Onset of action

Onset of action is an important issue given that early improvement predicts a more stable response to treatment and greater rates of remission [72,73]. Vilazodone’s partial 5-HT1A agonist properties were hypothesized to translate to a rapid onset of action by preventing the 5-HT1A receptor’s role in decreasing serotonin release through negative feedback [74]. Significant differences from placebo occurred at week 1 and week 6 in the two Phase III trials. In the pooled data, a statistically significant difference from placebo occurred with vilazodone at week 1 on MADRS total score and on 7 of 10 MADRS single items at week 1 or 2 [75]. It should be noted that the Phase III studies used a titration design, meaning that subtherapeutic doses of 10 mg were used at week 1. The FDA reviewers concluded that vilazodone’s potential rapid onset of action was not conclusively shown in the Phase III data [31]. They felt that the effect seen at week 1 was not determined to be clinically meaningful. Pooled data from the two Phase III trials found that patients treated with vilazodone were significantly more likely to achieve early sustained response (9 vs 4%, odds ratio = 2.29) compared with placebo, defined as ≥ 50% change in MADRS score at week 1 or 2 and last two treatment visits [76]. Another analysis of a Phase IV trial found that significantly more patients had early improvement at 2 weeks with vilazodone (49%) compared to placebo (35%, p = 0.003) [77]. These early responders showed greater improvements in MADRS and higher remission and response rates compared to patients without early improvement. Although this provides further evidence suggesting that early response is indicative of better outcomes, future studies are still needed that include a fixed-dose design with an active comparator to see if vilazodone truly has a faster onset.

Levomilnacipran and vortioxetine typically achieved separation from placebo between weeks 2 and 4 in the successful clinical trials.

6. Functional impairment in MDD

The authors of studies involving levomilnacipran consistently emphasized the need to address the social and occupational functioning aspect of MDD. For this reason, an important secondary measurement was the Sheehan Disability Scale (SDS), which is used in assessing functional impairment in work/school, social and family life settings. A Phase II study showed a statistically significant difference for all three subscales of the SDS, with a LSMD on SDS total score of -3.4 from placebo [45]. Most other studies seemed to confirm these results, although not to the same extent (Table 2). One result worth mentioning is that even patients with high functional impairment (SDS > 17) at baseline showed significant changes versus placebo in MADRS at week 8 with 80 mg levomilnacipran (LSMD = -4.5) [48].

A post-hoc analysis that pooled five short-term trials found significant differences across all three functional domains of the SDS compared to placebo and a significant mean change in SDS scores (LSMD = -2.2) [78]. The NNT for combined response and remission, which incorporates both MADRS and SDS scores, was 10.2 and 15.2, respectively. When stratified by age, sex and baseline MADRS, the levomilnacipran groups all showed significantly greater improvements in SDS total score than placebo. Levomilnacipran also showed greater improvement in patients who had higher levels of functional impairment (LSMD of -2.5 and -1.8 for patients with SDS total score of ≥ 21 and < 21, respectively). A more recent post-hoc analysis showed that a significant number of patients shifted from higher levels of baseline impairment to lower levels at end of treatment across all three functional domains [79].

Levomilnacipran’s ability to significantly reduce SDS total score and MADRS concurrently in short-term trials is important since a pooled analysis of short-term trials involving duloxetine showed that functional improvement occurred later than symptomatic improvement [80]. Although resolution of symptoms may be an early sign of response, functional improvement may indicate more meaningful change [81]. Patient surveys have indicated that positive aspects of mental health, such as self-confidence, optimism and a return to normal functioning, may be a better indication of remission [82]. Thus, levomilnacipran’s improvement in functional impairment is promising and clinically relevant given that improvement in symptoms and psychosocial functioning is associated with a higher chance of long-term effects [83].

The SDS was used in some studies for vortioxetine, with one showing significant difference from placebo on the SDS for the 15 mg (d = 0.47) and 20 mg (d = 0.55) groups [58]. In another study, 20 mg but not 10 mg vortioxetine achieved significant results (LSMD = -2.4 for the 20 mg group) [53,60].
Since the results were mixed, the FDA reviewers did not feel that there was sufficient evidence to include functional impairment in the product labeling [53]. In the trial comparing vortioxetine with agomelatine after inadequate response to an SSRI/SNRI, vortioxetine was significantly superior to agomelatine on SDS total score (LSMD = -2.2) and all three subscales at week 8 [63]. The SDS was not used in trials involving vilazodone.

7. Cognitive dysfunction in MDD

As one of the core symptoms of MDD, cognitive dysfunction is an important mediator of psychosocial and functional impairment, most notably workforce performance [84,85]. A growing body of evidence seems to support the role of vortioxetine in enhancing cognition. In rat studies involving contextual fear conditioning and novel object recognition tests, vortioxetine enhanced contextual and episodic memory [86]. Vortioxetine also increased cell proliferation in the hippocampus and accelerated maturation of immature neurons [87]. Vortioxetine reversed cognitive deficits induced by 5-HT depletion, improving both recognition and spatial working memory in rats [88]. The SSRI escitalopram and SNRI duloxetine were unable to reverse memory impairments induced by 5-HT depletion, showing that vortioxetine’s effect on serotonin receptors is likely essential [89].

In a clinical trial of vortioxetine in elderly patients, the Rey Auditory Verbal Learning Test (RAVLT) and Digit Symbol Substitution Test (DSST) were used to assess cognitive performance [62]. These tests were chosen because they are clinically sensitive, address cognitive domains known to be impaired in patients with depression and widely used in clinical psychopharmacology [90]. Although vortioxetine and duloxetine showed significant improvements in the RAVLT, only vortioxetine showed significant difference from placebo on the DSST. Path analysis showed an 83% direct effect on the DSST for vortioxetine, indicating improved cognition that is largely independent of improved depressive symptoms. Thus, vortioxetine not only improved verbal learning and memory like duloxetine but also improved processing speed, executive functioning and attention. These results are consistent with a previous study in elderly patients using the same cognitive tests where duloxetine improved verbal learning and memory but did not show a difference from placebo in focused attention and executive functioning [90].

A more recent trial was the first large placebo-controlled study to demonstrate improved cognitive performance as a primary measure in patients aged ≤ 65 with recurrent MDD [91]. The primary efficacy measure was a change in a composite z-score (sum of the z-scores in the DSST and RAVLT) from baseline to week 8. Both 10 and 20 mg doses of vortioxetine showed significant improvements on both primary and secondary measures, indicating improved memory, executive function, speed of processing and attention [92]. The effect sizes on the DSST were d = 0.51 and d = 0.52 for 10 and 20 mg vortioxetine, respectively. Path analysis showed that cognitive improvements were largely a direct effect, independent of depressive symptom improvement. Cognitive performance improved even in patients who were nonresponders or non-remitters as measured by the MADRS. Vortioxetine also improved subjective measures of cognition, such as attention, prospective memory and planning. As a secondary efficacy outcome, the mean differences from placebo at week 8 in MADRS total score were significant, with values of -4.7 for vortioxetine 10 mg and -6.7 for vortioxetine 20 mg [93].

There is not much mention of the cognitive properties of levomilnacipran or vilazodone. In one levomilnacipran trial, a battery of cognitive tests was performed, showing a significant difference on the continuity of attention composite score [49]. However, many other areas of cognition did not reach significance.

8. Long-term treatment studies

Long-term treatment is an important part of antidepressant therapy. A systematic review of 31 randomized trials found that continued treatment with antidepressants approximately halved the absolute risk of relapse [94]. Since symptomatic improvement often occurs before the pathophysiology is resolved, long-term studies are needed to demonstrate a drug’s ability to treat the underlying cause of depression.

Levomilnacipran currently has one long-term maintenance study [95]. Patients who responded to a 12-week treatment period completed a 24-week double-blind treatment period comparing fixed doses of levomilnacipran (n = 235) to placebo (n = 113). Although time to relapse was greater with levomilnacipran than with placebo, the result was not statistically significant. The absolute difference in relapse rate was 6.6% (placebo = 20.5%, levomilnacipran = 13.9%). The authors concluded that this was more of a failed study rather than a negative study. The low relapse rate in the placebo group meant that the sample size was not large enough to provide adequate power. The low relapse rate for placebo was surprising given that a relapse rate of 41% for patients on placebo was reported in a review of pooled relapse prevention studies [94]. Thus, levomilnacipran’s efficacy has not currently been demonstrated beyond 8 weeks.

Vortioxetine has been studied more thoroughly in long-term trials. A relapse prevention study enrolled non-US patients who were in remission (MADRS ≤ 10) after they finished a 12-week, open-label study involving 5 or 10 mg vortioxetine [96]. Vortioxetine showed a statistically significant difference in time to relapse compared to placebo in the first 24 weeks. The hazard ratio was 2.01, meaning that patients on placebo had a twofold higher risk of relapse than patients on vortioxetine. Patients on vortioxetine had a relapse rate of 13% compared to 26% for placebo. A pool of seven relapse-prevention trials with designs of 1 – 2 months open-label antidepressant treatment and 6-month relass-
prevention period reported a similar relapse rate of 15% for active drug and 34% for placebo [94].

In one vortioxetine study measuring long-term safety and tolerability, the mean MADRS total score decreased from 16.2 at open-label baseline to 5.0 at week 52 [97]. In another study, HAM-D24 total score decreased from 17.6 at open-label baseline to 8.2 at week 52 [98]. In a third study, MADRS total score decreased from 13.5 at open-label baseline to 5.5 at week 52, with a response rate of 84.3%, remission rate of 71.2% and relapse rate of 9.7% [99]. Nearly 90% of patients in this study who responded to acute treatment and completed all 12 months of vortioxetine treatment achieved remission. This long-term trial was almost as large as a maintenance study involving escitalopram [100]. Although the completion rate with vortioxetine (61%) was lower than escitalopram (74%), the rate of withdrawal due to AEs was slightly lower than escitalopram (7.9 vs 8.8%). In the escitalopram study, the remission rate (defined as MADRS ≤ 12, which is less stringent than the vortioxetine study) was 79.4% at week 52. A more recent open-label study showed decreases in MADRS total score from 19.9 at baseline to 11.9 after 52 weeks [101].

The only long-term trial involving vilazodone lacked a placebo group and assessed efficacy as a secondary objective. In this 52-week study, MADRS scores declined from 29.9 at baseline to 11.4 at week 8 and 7.1 at 1 year [102].

9. Safety and tolerability

9.1 Vilazodone
The overall safety and tolerability data for vilazodone was similar to the SSRIs. In the two Phase III trials, discontinuations due to AEs were 7% for vilazodone and 3% for placebo [10]. The most frequent AEs were gastrointestinal in nature, typically occurring early in treatment. Vilazodone was not associated with significant weight gain compared to placebo. AEs that occurred with vilazodone at a rate of ≥ 5% and twice the frequency of placebo were diarrhea (28%), nausea (23%), vomiting (5%), sexual dysfunction (9%) and insomnia (6%) (Table 4). The 52-week study of vilazodone found that frequent AEs included diarrhea (35.7%), nausea (31.6%) and headache (20.0%) [102]. Severe gastrointestinal AEs occurred in 3.5% of patients (n = 21) in this study. The median time to onset of diarrhea and nausea was 4 and 5 days, respectively. Among all placebo-controlled trials, suicidal behavior was identified in four subjects on placebo and two subjects on vilazodone [10]. A recent small study showed that vilazodone was well tolerated and not associated with significant discontinuation emergent symptoms in patients immediately switched from an SSRI/SNRI [103]. There were no clear drug-related changes in laboratory parameters or vital signs among all placebo-controlled trials [10].

Since the prevalence of sexual dysfunction associated with SSRI treatment is estimated to be around 30 – 40%, the authors of the clinical trials were hopeful that vilazodone could provide a more favorable option in regard to sexual functioning [104]. Sexual AEs with a ≥ 1% incidence in the 52-week study included decreased libido (4.2%), anorgasmia including abnormal orgasm (2.3%), erectile dysfunction (4.2%) and delayed ejaculation in males (3.1%) [102]. Sexual dysfunction was measured by the Arizona Sexual Experiences Scale (ASEX) in one short-term trial and the Changes in Sexual Functioning Questionnaire (CSFQ) in a short- and long-term trial [33,35,102]. Although slight improvements on the ASEX and CSFQ were seen, the FDA emphasized that no definitive conclusion can be drawn from this data since no active comparator was used [10]. A recent study that compared 20 and 40 mg vilazodone with placebo and the SSRI citalopram (40 mg) sought to address the FDA’s concerns [105]. Improvements were seen on the CSFQ across all groups (LSM increases of 2.5 for placebo, 2.6 for vilazodone 20 mg, 2.0 for vilazodone 40 mg and 1.5 for citalopram). For patients with normal baseline sexual functioning, 12% on placebo, 16% on vilazodone 20 mg, 15% on vilazodone 40 mg and 17% on citalopram met the criteria for sexual dysfunction at two consecutive visits.

9.2 Levomilnacipran
Among five short-term trials, roughly 9% of patients in the levomilnacipran groups discontinued due to AEs compared to 3% in the placebo groups [106]. AEs occurred in 77 and 61% of patients in the levomilnacipran and placebo groups, respectively. The most frequent AEs, with occurrence ≥ 5% and twice the rate of placebo, were nausea, constipation, hyperhidrosis, heart rate (HR) increase, erectile dysfunction, tachycardia, vomiting and palpitations (Table 4). Although most AEs did not appear to have a dose-dependent effect, urinary hesitancy and erectile dysfunction were reported at increased frequency with higher doses [44]. AEs were generally mild to moderate, with one trial reporting that 96% of AEs were mild or moderate in intensity [50]. Most cases of nausea were transient and occurred during week 1 or week 2. Suicidal ideation as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) was reported in 22% of placebo and 24% of levomilnacipran patients [106]. Suicidal behavior was reported in < 1% of both groups. There were no significant effects on body weight. In the long-term study, patients on levomilnacipran reported a mean decrease of about 0.5 kg [95].

Overall, a greater percentage of spontaneous reports of sexual dysfunction were seen in the levomilnacipran group compared to placebo [44]. The most common sexually related AEs in male patients included erectile dysfunction (5.9%; dose-dependent effect), ejaculation disorder (4.7%) and testicular pain (3.8%). The ASEX was used in one study, with both placebo and levomilnacipran groups reporting mean decreases in ASEX total score at week 8 [50]. However, these results are limited since no active comparator was used (such as an SSRI with known sexual side effects) [44].

Having noradrenergic effects, levomilnacipran did show statistically significant increases in HR, systolic blood pressure.
SBP), and diastolic blood pressure (DBP) \cite{107}. SBP and DBP increased on average by 3.0 and 3.2 mmHg for levomilnacipran, respectively, compared to a decrease of 0.4 mmHg in SBP and no change in DBP for placebo. Compared to a HR change of -0.3 beats per minute (bpm) for placebo, levomilnacipran showed a mean change of +7.4 bpm. For patients with normal BP or pre-hypertension at baseline, 10.4% of patients treated with levomilnacipran had a hypertensive reading after the treatment period compared to 7.1% of placebo patients \cite{44}. For this reason, blood pressure should be monitored during treatment. A dose-dependent increase in the QTcB interval was also seen in levomilnacipran patients compared to a decrease in placebo patients \cite{106}.

### 9.3 Vortioxetine

The FDA reviewers pooled short-term studies of MDD, studies involving vortioxetine and GAD and the open-label long-term studies, to analyze the safety of vortioxetine \cite{53}. Among this pool, the safety profile was fairly similar to the SSRIs. The most common AEs included nausea (22 – 32%), vomiting (3 – 7%) and constipation (3 – 6%) (Table 4). A dose-dependent relationship was seen for nausea, constipation and overall incidence of AEs. In the MDD short-term studies, the percentage of AEs leading to discontinuation was 6.2% for vortioxetine, 9.0% for duloxetine and 3.8% for placebo. More patients in the 20 mg (8.4%) compared to the 5 mg (5.2%) group discontinued due to AEs. In the long-term relapse study, AEs that occurred in > 10% of patients included nausea, headache and nasopharyngitis \cite{99}. About 92% of patients with AEs had AEs that were considered mild or moderate.

The most commonly reported AE was nausea, which was seen in 22 – 32% of vortioxetine patients compared to 9% of placebo patients \cite{53}. About 15 – 20% of patients experienced nausea in the first 2 days of treatment. Although most cases were mild and transient, ~10% of patients in the vortioxetine group had nausea that was persistent till the end of 8 weeks. Suicidal ideation as measured by the C-SSRS was reported in 11.2% of patients receiving vortioxetine compared to 12.5% of patients receiving placebo. Among all studies, no significant weight gain was seen in patients treated with vortioxetine. There were also no differences in vital signs, ECG and laboratory parameters.

Rates of spontaneously reported AEs related to sexual dysfunction were low, with one study reporting incidences of 0% for placebo, 2% for 2.5 mg vortioxetine, 4% for 5 and 10 mg vortioxetine and 14% for duloxetine \cite{65}. Since these rates are often low due to underreporting, a recent abstract analyzed ASEX data used in six short-term MDD trials and one GAD study \cite{108}. The incidence of developing treatment-emergent sexual dysfunction (TESD) in patients without baseline sexual dysfunction based on the ASEX was numerically higher for vortioxetine 5 – 20 mg (37.1%) and duloxetine (48.2%) compared to placebo (32.0%). TESD rates for the vortioxetine 5, 10, 15 and 20 mg groups were not statistically higher than placebo. TESD rates for duloxetine did significantly differ from placebo, which confirmed

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Vilazodone data</th>
<th>Levomilnacipran data</th>
<th>Vortioxetine data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vilazodone (n = 433)</td>
<td>Placebo (n = 436)</td>
<td>Levomilnacipran (n = 1583)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>84%</td>
<td>73%</td>
<td>77%</td>
</tr>
<tr>
<td>Nausea</td>
<td>23%</td>
<td>5%</td>
<td>17%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28%</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Headache</td>
<td>15%</td>
<td>14%</td>
<td>17%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>8%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Constipation</td>
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</tr>
<tr>
<td>Hyperhidrosis</td>
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<td></td>
<td>9%</td>
</tr>
<tr>
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<td>Increased</td>
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<td></td>
<td>2%</td>
</tr>
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</tr>
<tr>
<td>Tachycardia</td>
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<td></td>
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</tr>
<tr>
<td>Palpitations</td>
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<td></td>
<td>6%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>2%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Data for vilazodone was taken from the FDA medical review \cite{10}. Values for any TEAE for vilazodone were based on a database of all placebo-controlled trials, which included all Phase II and two Phase III trials (n = 977 for placebo and n = 1578 for vilazodone) \cite{10}. Data for levomilnacipran was taken from \cite{106} and FDA medical review Table 65 \cite{44}. Data for vortioxetine was based on the Major depressive disorder (MDD)/GAD short-term trial pool in the FDA medical review Table 115 \cite{53}. Incidences are for all doses combined.

AEs: Adverse events; GAD: Generalized anxiety disorder; TEAE: Treatment-emergent adverse event.
assay sensitivity. However, this analysis should be interpreted with caution. The FDA reviewers evaluated the same seven studies and included two TESD categories: one was defined as incidence at any visit and the second was incidence at two consecutive visits [53]. This second definition was considered more reliable and clinically meaningful. Using the second definition, TESD incidence for males was numerically higher with vortioxetine 20 mg (28.8%) than duloxetine 60 mg (26.3%) and placebo (13.6%). TESD incidence for females was also higher for 15 mg vortioxetine (33.3%) and 20 mg vortioxetine (34.3%) than duloxetine 60 mg (28.4%) and placebo (20.0%) (Tables 98 and 99 [53] FDA medical review). A recent study randomized patients to 8 weeks of vortioxetine or escitalopram treatment after they had responded to treatment with an SSRI and experienced TESD [109]. After 8 weeks, patients on flexible doses of vortioxetine showed a significant improvement in CSFQ-14 total score, with a mean change difference of 2.2 points from 20 mg escitalopram (p = 0.013).

Vortioxetine was also well tolerated in the study involving elderly patients. In the 8-week treatment period, 3% in the placebo group, 6% in the vortioxetine group and 10% in the duloxetine group withdrew due to AEs [62]. The only AE associated with vortioxetine with a significantly higher percentage than placebo was nausea.

10. Conclusion

Developing antidepressants that have greater efficacy and a favorable tolerability profile is a major goal of the pharmaceutical industry. This is important given that first-line therapies typically only achieve 20–40% remission; and adherence for the recommended length of time is less than half, due in part to unwanted side effects [7,110]. The approval of vilazodone, levomilnacipran and vortioxetine is an important achievement in a field that has seen some setbacks in the past decade.

As a dual SSRI and partial 5-HT1A agonist, vilazodone showed greater increases in serotonin compared to SSRIs in preclinical studies [13]. Whereas all Phase II trials were unsuccessful, two Phase III trials proved vilazodone’s efficacy compared to placebo. Two recent trials with unpublished results seem to confirm the Phase III data, with one Phase IV study showing an efficacy similar to the SSRI citalopram [43]. The AEs related to treatment with vilazodone are mostly gastrointestinal, including diarrhea and nausea [10].

Levomilnacipran is an SNRI with a twofold greater potency at inhibiting NE over 5-HT reuptake [17]. Based on the clinical data, levomilnacipran showed significant improvements over placebo on the MADRS and SDS and was generally well tolerated. As an SNRI, levomilnacipran showed increases in HR and blood pressure [107]. AEs that were consistently seen in the trials included nausea, constipation and hyperhidrosis [106].

Vortioxetine acts as a SERT inhibitor, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and 5-HT3, 5-HT7 and 5-HT1D receptor antagonist [19]. In preclinical studies, vortioxetine treatment resulted in greater increases in many neurotransmitters compared to other antidepressants [25]. The Phase III trial data proved vortioxetine’s efficacy compared to placebo. Vortioxetine was well tolerated not only in elderly patients but also throughout all Phase III trials. The main AEs were gastrointestinal in nature, including nausea, constipation and vomiting [53].

11. Expert opinion

Due to its 5-HT1A partial agonism, vilazodone was predicted to have a rapid onset of action [11]. Although one trial provided evidence for this idea, it seems that vilazodone’s rapid onset was not conclusively shown in the Phase III data [31]. Based on post-hoc analyses that showed vilazodone to be effective in patients with MDD and secondary anxiety symptoms, vilazodone might function best in this patient population [41]. However, since these analyses are retrospective, future studies would be needed that explicitly compare vilazodone with other antidepressants in treating patients with anxious depression. Thus far, no long-term placebo-controlled trials have been performed with vilazodone. Results of a relapse study are expected early 2015 [111]. At this time, vilazodone’s role in treating MDD will likely be relegated to a potential second-line treatment.

Although levomilnacipran is now the fourth SNRI approved for MDD in the USA, it is unique in its twofold greater potency at inhibiting NE reuptake [17]. This was hypothesized to translate to a greater effect on the noradrenergic cluster of MDD symptoms, including alertness, arousal, energy and interest in life, all of which are important in social functioning [18]. The Phase III trial data does seem to back up this claim to a certain extent. Levomilnacipran significantly improved functional impairment as measured by the SDS even in short-term trials, which is impressive given that improvements in functioning typically lag behind symptomatic improvement [78,112]. Thus, patients who might benefit most from levomilnacipran include those with decreased energy, motivation and attention that impact their daily functioning. Unfortunately, levomilnacipran’s efficacy has not been proven in a long-term placebo-controlled trial.

Given its unique multimodal profile, vortioxetine was proposed to play a role in patients with inadequate response to monotherapy [20]. The only current evidence for this claim involves vortioxetine’s superiority to agomelatine when used in patients with inadequate response to an SNRI or SSRI [63]. Vortioxetine was superior on the primary measure and all secondary measures, including functional impairment and quality of life measures. Future studies involving currently approved FDA antidepressants would help in providing further support for the role of vortioxetine in patients with inadequate response. Vortioxetine’s efficacy in elderly patients is an important point given the modest effects of antidepressants in the elderly [62]. The cognitive enhancing properties of vortioxetine are also an exciting development, especially considering...
that improvements in cognition were largely independent of improved depressive symptoms [91]. This would suggest that vortioxetine may be especially helpful in patients with difficulty in functioning due to lack of attention or difficulties in processing information. Vortioxetine also showed significant long-term efficacy in regard to relapse and remission rates, which are comparable to other available antidepressants [96]. The diminished efficacy of vortioxetine in US patients compared to non-US patients is puzzling and remains unclear. The FDA reported that the results of inspections from two foreign sites were acceptable [53]. Since 20 mg/day achieved statistical significance in Phase III US trials, 20 mg/day should be the targeted dose, if tolerated, in US patients.

Tolerability plays an important role in patient compliance, with common reasons for noncompliance including weight gain and sexual dysfunction [113]. All three drugs appear to be weight neutral. Rates of spontaneously reported sexual dysfunction were fairly low for all three drugs, but these are known to be underreported. Only one trial involving levomilnacipran used the ASEX to measure sexual dysfunction, and the results could not be fully interpreted since no active control was used [50]. Sexual functioning was more extensively assessed for vortioxetine, but the results are mixed. Based on data from seven short-term studies using the ASEX and among patients without baseline sexual dysfunction, lower doses of vortioxetine appear to not show significant differences from placebo in rates of TESD [108]. However, the highest dose of vortioxetine (20 mg) displayed rates of TESD greater than duloxetine when TESD was defined as incidence at two consecutive visits [53]. This is potentially problematic given that 20 mg is the targeted dose for US patients. For vilazodone, the trial authors reported that the occurrence of sexual AEs in vilazodone-treated patients did not show a difference from placebo. However, the FDA was not convinced with this assessment mostly because an active control could not confirm assay sensitivity [31]. A recent post-hoc analysis of a Phase IV trial showed that the rates of sexual dysfunction were similar for patients treated with placebo, vilazodone and citalopram [105]. This does not seem to indicate that vilazodone has an advantage over SSRIs in regard to sexual functioning. Thus, a clear advantage over other antidepressants in regard to sexual functioning has not been consistently shown for any of these drugs. Although all three drugs were well tolerated within the clinical trials, none of them seem to offer a substantial advantage over currently available SSRIs/SNRIs in terms of tolerability.

Overall, these three new antidepressants represent a promising step forward in antidepressant drug development. With limited studies that compare their efficacy to other antidepressants, it might be difficult to recommend them over other antidepressants. The current lack of long-term studies involving the efficacy of vilazodone and levomilnacipran is a major concern given the long-term nature of depression and significant risk of relapse. Future trials will further clarify their role as possible first-line treatments for MDD, in maintenance therapy, and whether the extra cost of these non-generic medications is justifiable. Further studies are also needed to look at the efficacy and mania-inducing potentials of these drugs in bipolar depression. More geriatric studies need to be done, including a vortioxetine study in depressed patients with major neurocognitive disorders such as Alzheimer’s disease. Studies that recruit patients with MDD without baseline sexual dysfunction and use an active comparator such as an SSRI would also be necessary to determine effects on sexual functioning. Last, more data on risk of suicide and treatment of MDD with psychosis with these agents would be desirable.

**Declaration of interest**

GT Grossberg serves as a consultant to Forest Laboratories, Lundbeck, Takeda and Otsuka. GT Grossberg has received research support for his department from Lundbeck, Novartis, Takeda, Otsuka, Accera and Noven. 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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