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REVIEW

Levomilnacipran and vortioxetine: Review of new pharmacotherapies for major depressive disorder

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Abstract

Major depressive disorder (MDD) is a common psychiatric disorder with an estimated lifetime prevalence rate in the range of 13% to 16% in the United States population. Patients with MDD often have symptoms such as depressed mood, loss of interest or pleasure in usual activities, changes in eating or sleeping patterns, fatigue, difficulty concentrating and thoughts of suicide. Although many pharmacotherapy treatment options are available for MDD, antidepressants can often cause adverse effects that could affect adherence to the medication. Additionally, it is estimated that MDD is unremitting in 15% of patients and 35% can have recurrent episodes. Given the high rate of recurrence and the adverse effects associated with existing medications, new treatment options for depression are needed. Both levomilnacipran and vortioxetine are new antidepressants that were approved by the food and drug administration in 2013 for the treatment of MDD in adults. Levomilnacipran is a serotonin norepinephrine reuptake inhibitor that was effective in several short term studies and sustained efficacy and tolerability was demonstrated in a 48-wk extension study. Vortioxetine is a multi-modal antidepressant and it is thought to work *via* inhibition of the serotonin (5-HT) transporter, 5-HT$_{3A}$, 5-HT$_{7}$ and 5-HT$_{1D}$ antagonist, a 5-HT$_{1B}$ partial agonist, and a 5-HT$_{1A}$ agonist. Vortioxetine was effective in the treatment of MDD in both short-term trials as well as in the prevention of relapse in a 24-36 wk trial. Sustained efficacy and tolerability was demonstrated in several long-term open-label trials. Further studies comparing levomilnacipran and vortioxetine to other currently available antidepressants are needed to establish its place in therapy.

Key words: Levomilnacipran; Vortioxetine; Adult; Major depressive disorder; Antidepressive agents

Core tip: Levomilnacipran and vortioxetine are the two newest antidepressant medications to join the armamentarium of treatment choices for major depressive disorder. Levomilnacipran, a serotonin norepinephrine reuptake inhibitor, is an enantiomer of the previously approved fibromyalgia agent milnacipran. Vortioxetine is a multimodal antidepressant with a unique mechanism of action, affecting several serotonin receptors as well as inhibiting serotonin reuptake. This review summarizes the clinical trial data as well as pharmacokinetic, dosing and

safety concerns with these two new agents.

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INTRODUCTION

Major depressive disorder (MDD) is a common psychiatric disorder with an estimated lifetime prevalence rate in the range of 13% to 16% in the United States population[1]. Patients with MDD often have symptoms such as depressed mood, loss of interest or pleasure in usual activities, changes in eating or sleeping patterns, fatigue, difficulty concentrating and thoughts of suicide. These symptoms persist over a period of at least 2 wk and are not attributable to other disorders such as substance-induced or general medical conditions[1].

Many pharmacotherapy treatment options are available for MDD. They include selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), miscellaneous antidepressants such as bupropion and mirtazapine and antipsychotics such as quetiapine and aripiprazole. Despite the wide variety of antidepressants available, antidepressants can often cause adverse effects such as weight gain, sexual dysfunction, anxiety, headache, nausea, and sleep disturbances which could affect adherence to the medication. Additionally, it is estimated that MDD is unremitting in 15% of patients and 35% can have recurrent episodes[1]. If no prophylactic maintenance treatment is provided, the risk of recurrence approaches 100% in patients with three or more lifetime depressive episodes[1]. Given the high rate of recurrence and the adverse effects associated with existing medications, new treatment options for depression are needed.

The objective of this article is to provide an overview of the two newest antidepressants, levomilnacipran and vortioxetine, and review the safety and efficacy data on these two medications.

LEVOMILNACIPRAN

Levomilnacipran (1S, 2R-milnacipran) was initially approved by the Food and Drug Administration (FDA) on July 26, 2013 for the treatment of MDD in adults (Table 1). Although levomilnacipran is the L-isomer in racemate milnacipran (Savella®) and it is reported to be the more active form of the two isomers, levomilnacipran is not approved for fibromyalgia and efficacy and safety of levomilnacipran for the management of fibromyalgia have not been established[2]. Interconversion between levomilnacipran and its stereoisomer does not occur in humans[3].

Pharmacology

Levomilnacipran is categorized as a SNRI antidepressant because it is thought to increase serotonin and norepinephrine (NE) in the central nervous system through inhibition of reuptake at serotonin (5-HT) and norepinephrine transporters. Levomilnacipran lacks significant affinity to other receptors such as adrenergic, muscarinic, or histaminergic receptors[3]. Levomilnacipran has 2-fold greater potency for inhibition of NE relative to serotonin reuptake[2]. Compared to other SNRIs such as duloxetine and venlafaxine, which preferentially inhibit 5-HT relative to NE reuptake, levomilnacipran has more than 10-fold higher selectivity for NE relative to serotonin reuptake inhibition[2]. Antidepressants with noradrenergic mechanisms of action may be effective in improving depression symptoms related to social functioning such as decreased concentration and loss of energy[4].

Pharmacokinetics

The concentration of levomilnacipran at steady state is proportional to the dose when administered within the range of 25 to 300 mg once daily. It reaches maximum plasma concentration within 6 to 8 h and terminal elimination half-life is approximately 12 h. The relative bioavailability of levomilnacipran is 92% compared to oral solution and its concentration is not significantly affected when administered with food. Levomilnacipran is metabolized primarily by cytochrome P450 (CYP) 3A4 with minor contribution by CYP2C8, 2C19, 2D6, and 2J2. Levomilnacipran and its inactive metabolites are eliminated primarily by renal excretion (Table 2)[3].

Clinical trials

Levomilnacipran has been studied in over 2600 patients with MDD in 7 clinical trials including: 5 short-term (10-11 wk) acute MDD trials, one long-term (≥ 24 wk) relapse prevention trial and one long-term (48 wk) extension study. Four of the short-term trials with results published to date have demonstrated positive efficacy for levomilnacipran for the acute treatment of MDD[5,6], the remaining study is not yet published. One of the studies was a 10-wk Phase Ⅱ study conducted outside of the United States and the other three studies were 10-11 wk Phase Ⅲ studies that included United States sites[7-11]. Two of the studies were fixed dose and two were flexible dose studies (Table 3).

Short-term trials: In the three published Phase Ⅲ short-term studies, patients were included if they were adult out-patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision (DSM-Ⅳ-TR) criteria for MDD with an ongoing episode of at least 4 to 8 wk duration and a minimum Montgomery-Asberg Depression Rating Scale (MADRS) score ranging from 26-30 at baseline indicating depression symptoms of moderate severity[12,13]. Patients

Table 1 Basic drug information for levomilnacipran and vortioxetine[3,20]

	Levomilnacipran	Vortioxetine
Brand names	Fetzima	Brintellix
Mechanism of action	Serotonin-norepinephrine reuptake inhibitor	Serotonin receptor reuptake inhibitor, serotonin-3 receptor antagonist and serotonin-1A receptor agonist
FDA approval date	July 26, 2013	September 30, 2013
Recommended dosing range	40 mg to 120 mg once daily with or without food	10 mg to 20 mg once daily
Dosage form	Extended-release capsules in 20 mg, 40 mg, 80 mg and 120 mg	Immediate release tablets in 5 mg, 10 mg, 15 mg and 20 mg

FDA: Food and Drug Administration.

Table 2 Pharmacokinetic parameters for levomilnacipran and vortioxetine[3,20,21,24]

	Levomilnacipran	Vortioxetine
Bioavailability	92%	75% ± 9%
T_{max}	6-8 h	3-16 h
Volume of distribution	387-473 L	2400 L
Metabolism	Oxidation (primarily through CYP3A4), glucuronidation	Oxidation (primarily through CYP2D6), glucuronidation
Elimination	58% urine	50% urine, 26% feces
Clearance	21-29 L/h	38 L/h
Half-life	12 h	57-66 h
Protein binding	22%	98%-99%

CYP: Cytochrome P450; T_{max}: Time to maximum plasma concentration.

Table 3 Randomized controlled trials of levomilnacipran for major depressive disorder[3,5,7-11]

Ref.	*n*	Duration	Key inclusion criteria	Doses	Primary outcome
Montgomery *et al*[7] Phase Ⅱ	563	10 wk	Age 18-70 yr HAMD-17 > 22	Levomilnacipran 75-100 mg/d Placebo	Positive Change from baseline in MADRS Placebo: -14.5 Levomilnacipran: -18.7 ($P < 0.001$)
Greenberg[5] Phase Ⅲ	362	11 wk	Age 18-80 yr Clinician-rated MADRS ≥ 30 Self-rated MADRS ≥ 26	Levomilnacipran 40-120 mg/d Placebo	Negative Change from baseline in MADRS Placebo: -14.2 Levomilnacipran: -15.7 ($P = 0.249$)
Asnis *et al*[8] Phase Ⅲ	724	11 wk	Age 18-65 yr MADRS ≥ 30	Levomilnacipran 40 mg/d Levomilnacipran 80 mg/d Levomilnacipran 120 mg/d Placebo	Positive Change from baseline in MADRS Placebo: -11.6 40 mg: -14.8 ($P < 0.05$) 80 mg: -15.6 ($P < 0.01$) 120 mg: -16.5 ($P < 0.001$)
Bakish *et al*[9] Phase Ⅲ	568	10 wk	Age 18-75 yr MADRS ≥ 26	Levomilnacipran 40 mg/d Levomilnacipran 80 mg/d Placebo	Positive Change from baseline in MADRS Placebo: -11.3 40 mg: -14.6 ($P < 0.003$) 80 mg: -14.4 ($P < 0.004$)
Sambunaris *et al*[10] Phase Ⅲ	442	11 wk	Age 18-80 yr Clinician-rated MADRS ≥ 30 Self-rated MADRS ≥ 26	Levomilnacipran 40-120 mg/d Placebo	Positive Change from baseline in MADRS Placebo: -12.2 Levomilnacipran: -15.3 ($P < 0.01$)
Shiovitz *et al*[11] Phase Ⅲ	734	24 wk	Age 18-65 yr MADRS ≥ 22	Levomilnacipran 40 mg/d Levomilnacipran 80 mg/d Levomilnacipran 120 mg/d Placebo	Failed Percent of patient relapse Placebo: 13.91% Levomilnacipran: 20.54% ($P = 0.1651$)

HAMD: Hamilton Rating Scale for Depression; MADRS: Montgomery-Asberg Depression Rating Scale.

were required to have normal physical examination and clinical laboratory results and electrocardiogram findings. Patients were excluded if they had other comorbid DSM-Ⅳ-TR Axis Ⅰ disorders within the last 6 mo, history of nonresponse to adequate treatment with 2 or more antidepressants, medical conditions that may have interfered with the study, if they were pregnant or had significant risk of suicide. Patients

taking concomitant psychotropic medications (with the exception of eszopiclone, zolpidem, or zaleplon) were also excluded[8-10].

In the fixed-dose study by Bakish *et al*[9], the average age of participants ranged from 42.3-43.1 years, 62.2%-66% were female, and 72.6%-77.5% were Caucasian. Patients had an average of 3.5 depressive episodes and the duration of illness ranged from 12.8-14.7 years. The mean MADRS score at baseline ranged from 30.8-31.2 indicating moderate depression. Baseline demographics were similar between the treatment groups. The primary outcome for this study was change from baseline to end of study on the MADRS total score. Secondary outcomes included improvement in the Sheehan Disability Scale (SDS), response (≥ 50% improvement in MADRS score) and remission (MADRS score ≤ 10 at study endpoint). This study found statistically significant differences in change of MADRS total score between both levomilnacipran groups (40 mg and 80 mg) compared to placebo [40 mg: -3.3 (95%CI: -5.5 to -1.1), P = 0.003; and 80 mg: -3.1 (95%CI: -5.3 to -1.0), P = 0.004)][9]. A treatment effect is considered clinically significant if there is at least a 2-point difference between the active drug and the placebo group[7]. Levomilnacipran also demonstrated superiority over placebo in change in SDS total score [40 mg: -1.8 (95%CI: -3.6 to 0) P = 0.046; 80 mg: -2.7 (95%CI: -4.5 to -0.9) P = 0.003]. Response rates were found to be statistically significantly higher than placebo in both 40 mg (49%) and 80 mg (47%) groups (placebo 34%, P < 0.01). Remission rates were statistically significantly higher than placebo in the 40 mg and 80 mg groups, at 18% *vs* 30% and 32%, respectively (P < 0.01). Significantly more patients in the levomilnacipran 40 mg/d (P = 0.032) and 80 mg/d (P < 0.001) groups than the placebo group prematurely discontinued the study due to adverse events. Adverse effects were generally considered mild to moderate, with the most frequent and statistically significant adverse effects being nausea, dry mouth, constipation, increase heart rate, dizziness, hyperhidrosis, urinary hesitation and erectile dysfunction[9].

In another fixed-dose study of levomilnacipran 40 mg, 80 mg or 120 mg *vs* placebo, the average age of participants in ranged from 40.3-41.3 years, 58.9%-68.5% were female and 72.2%-76.1% were Caucasian. The average number of depressive episodes experienced per patient ranged from 5.3-9.7 and the duration of illness ranged from 10.2-12.6 years. The mean MADRS score at baseline ranged from 35.6-36.1, indicating severe depression. Baseline demographics were similar between the treatment groups. The primary outcome for this study was change from baseline to end of study on the MADRS total score. Secondary outcomes included improvement in SDS total score, response and remission rates as defined above. This study found statistically significant differences in change of MADRS total score between all 3 levomilnacipran groups compared to placebo [40 mg: -3.23 (P = 0.0186), 80 mg: -3.99 (P = 0.0038), and 120 mg: -4.86 (P = 0.0005)]. Levomilnacipran demonstrated superiority over placebo in change in SDS total score in the 80 mg and 120 mg groups only (-2.51 and -2.57, respectively, P < 0.05). Response rates were found to be statistically significantly higher than placebo only in the 120 mg group with a rate of 41.5% compared to 29.1% with placebo (P = 0.0107). Remission rates were found to be similar between the groups. Significantly more levomilnacipran than placebo patients discontinued due to adverse events. The most common adverse effects that led to discontinuation were nausea, vomiting and palpitations[8].

In the flexible-dose study by Sambunaris *et al*[10] (with a dose range 40 mg to 120 mg/d of levomilnacipran) the average age of participants was 45 years and 65% were female. The mean MADRS score at baseline was 35 indicating that the patients had at least moderate to severe depression. Baseline demographics were similar between the treatment groups. The primary and secondary outcomes for this study were the same as the above described trials. This study found statistically significant differences in change of MADRS total score and SDS total score between the levomilnacipran group compared to placebo [-3.095 (-5.256 to -0.935); P = 0.0051 and -2.632 (-4.193 to -1.070); P = 0.0010, respectively]. Response rates were found to be statistically significantly higher than placebo with a rate of 41.9% in the levomilnacipran compared to 29.4% in the placebo group (P = 0.0083). Remission rates were found to similar between the groups. The incidence of premature discontinuation due to adverse events was higher for levomilnacipran (7.8%) than placebo (3.2%) but the difference was not statistically significant (P = 0.0567)[10].

Long-term trials: One randomized, double-blind, placebo-controlled, relapse prevention study over ≥ 24 wk was conducted in 348 patients age 18 to 65 years with MDD in 36 sites in the United States and Canada[11]. Patients were included in the study if they met the DSM-Ⅳ-TR criteria for MDD with an ongoing episode of at least 4 wk duration, the diagnosis was confirmed by the Mini International Neuropsychiatric Interview and if they had a MADRS score ≥ 22 indicating moderate severity[12,13]. Patients were required to have normal physical examination and clinical laboratory results and electrocardiogram findings. Patients were excluded if they had other comorbid DSM-Ⅳ-TR Axis Ⅰ disorder within the last 6 mo, history of nonresponse to 2 or more adequate trials with antidepressants, medical conditions that may interfere with the study, if they were pregnant or if they had significant risk of suicide. Eligible patients were treated first with 12 wk of open-label, flexible-dose levomilnacipran 40-120 mg/d. Patients who met criteria for response (MADRS score ≤ 12) and had

a Clinical Global Impressions-Improvement (CGI-I) score ≤ 2 at both weeks 10 and 12, were randomized to receive either levomilnacipran or placebo once daily for 24 wk. Relapse was defined as MADRS score ≥ 22, CGI-I increase by ≥ 2 points or insufficient clinical response as judged by the investigators. The primary efficacy endpoint was the time to relapse within the first 24 wk of the double-blind period. Time to relapse was longer in the levomilnacipran group than the placebo group, but the difference was not statistically significant [HR = 0.68 (95%CI: 0.4-1.17, P = 0.165)]. The relapse rates observed in this study (placebo = 20.5%, levomilnacipran = 13.9%) were lower than the relapse rates anticipated in the statistical analysis (placebo = 38%, levomilnacipran = 20%), which compromised the projected statistical power. This study was underpowered and therefore it can be considered a failed study rather than a negative study[11].

One open-label extension study has been published so far[14]. It was a multicenter, open-label, flexible-dose study (40-120 mg/d) in adult patients with MDD who completed 1 of the 3 short-term studies. The study was 52 wk in duration and consisted of a 48-wk open-label period followed by a down-taper period of up to 4 wk. The median duration of treatment was 280 d and the final daily dose was 40 mg/d for 27%, 80 mg/d for 26% and 120 mg/d for 47% of patients. A mean decrease in MADRS total score of -23.6 was seen from baseline to the end of the 48-wk period. Rates of withdrawal due to adverse effects or insufficient therapeutic response were 13% and 8.1%, respectively The most common that were considered severe were nausea and headache[14].

Dosage recommendations

The recommended dose range of levomilnacipran is 40 mg to 120 mg once daily. The dose should be starting at 20 mg once daily for 2 d, and then increased to 40 mg once daily. The dose can be further increased by 40 mg at intervals of every 2 or more days. The maximum recommended dose is 120 mg once daily. The dose of levomilnacipran should not exceed 80 mg once daily when use concomitantly with strong CYP3A4 inhibitors. Levomilnacipran should be swallowed whole due to the extended-release formulation and it can be taken with or without food[3].

No dose adjustment is required in patients with mild renal impairment [creatinine clearance (CrCl) of 60-89 mL/min]. The maximum recommended dose is 80 mg once daily or 40 mg once daily for patients with moderate renal impairment (CrCl of 30-59 mL/min) or patients with severe renal impairment (CrCl of 15-29 mL/min), respectively. Levomilnacipran is not recommended for patients with end stage renal disease[3].

Drug interactions

Levomilnacipran appears to have a low potential to cause any clinically relevant inhibitory or inducing effects on the CYP450 system. Dose adjustment is recommended when co-administered with strong CYP3A4 inhibitors such as ketoconazole. MAOIs should be discontinued for at least 14 d prior to starting levomilnacipran. Levomilnacipran should be discontinued for at least 7 d prior to starting MAOI. Alcohol can cause a more rapid release of drug into the blood stream and it is not recommended to take levomilnacipran with alcohol[3].

Adverse effects

The most common adverse effects (≥ 5%) seen in both short and long-term trials of levomilnacipran were headache, nausea, dizziness, constipation, dry mouth, increased heart rate, tachycardia, erectile dysfunction, urinary hesitation, insomnia, vomiting, and hyperhidrosis[7-11,14]. Most adverse reactions were considered mild or moderate in intensity and 9% of patients in the short-term placebo-controlled trials discontinued treatment due to an adverse event. The most common adverse reaction leading to discontinuation in at least 1% of patients was nausea. Only urinary hesitation and erectile dysfunction appear to be dose-related[3,6].

Levomilnacipran had a mean increase in systolic blood pressure (SBP) of 3 mmHg and diastolic blood pressure (DBP) of 3.2 mmHg in the short-term, placebo-controlled studies. Mean increase in SBP was 3.9 mmHg and DBP was 3.3 mmHg in the long-term, 48-wk extension study[3,14]. Levomilnacipran had a mean increase in heart rate of 7.4 beats per minute (bpm) compared to a mean decrease of 0.3 bpm in placebo group. Orthostatic hypotension was observed in 11.6% of patients in the levomilnacipran group compared to 9.7% in the placebo group[3]. Mean increase in corrected QT interval (QTc) by Bazett's formula (QTcB) was 9.5 ms in levomilnacipran compared to 0.1 ms in the placebo group in the short-term studies. However, changes in QTc by Fridericia's method (QTcF) were small between groups (-2.5 and -1.4 ms for levomilnacipran and placebo, respectively). No patients had QTcF interval greater than 500 ms in short-term or extension studies[6]. One patient has QTcB greater than 500 ms in the extension study[14]. Since patients with significant medical conditions such as cardiovascular disease were excluded from the clinical trials, clinicians should use caution in these patients, and should monitor blood pressure and heart rate periodically.

All clinical trials had a down-taper period range from 1 to 4 wk[7-11,14]. Patients should be monitored for symptoms of discontinuation syndrome when discontinuing levomilnacipran and reduce the dose gradually[3]. No clinically significant effects on body weight or laboratory tests were reported in the short-term studies but five patients experienced potentially clinically significant high transaminase values (≥ 3x upper limits of normal of aspartate aminotransferase and alanine aminotransferase levels) in the 48-wk extension study[6,14].

Levomilnacipran is contraindicated in patients with hypersensitivity to levomilnacipran, milnacipran, or any excipients in the formulation. Patients with uncontrolled narrow-angle glaucoma should not use levomilnacipran since it is associated with an increased risk of mydriasis. Similar to other antidepressants, levomilnacipran is contraindicated to use with MAOI, methylene blue, or linezolid concurrently due to the increased risk of serotonin syndrome. Levomilnacipran should be used with caution in patients with controlled narrow-angle glaucoma and patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma should be monitored. Patients being started on any antidepressant medication should be screened for bipolar disorder and monitored closely for clinical worsening, suicidality and behavior changes. Serotonin syndrome, abnormal bleeding, activation of mania/hypomania and hyponatremia are all class warnings of the SSRI and SNRI antidepressants that also apply to levomilnacipran[3].

Levomilnacipran is listed as pregnancy category C. No teratogenic effects have been seen in the offspring of rats and rabbits exposed to levomilnacipran at doses up to 8 to 16 times the maximum recommended human dose (MRHD). An increase in early post natal rat pup mortality was seen at a dose equivalent to 5 times the MRHD given during pregnancy and lactation[3]. Pregnancy was reported in three patients during the 48-wk open-label extension study conducted by Mago *et al*[14]. Two of the three patients prematurely discontinued from the study and all three pregnancies resulted in live births with no complications. Levomilnacipran has been detected in the milk of lactating rats, but no data is available for nursing women[3].

VORTIOXETINE

Vortioxetine was initially approved by the FDA on September 30, 2013 and became available on the United States market in early 2014[15,16]. Like levomilnacipran it is currently approved for use in MDD. Trials supporting its use in generalized anxiety disorder have also been completed; however, they are beyond the scope of this review.

Pharmacology

Vortioxetine is categorized as a "multi-modal" antidepressant because it is thought to work *via* two complementary mechanisms of action[17,18]. In addition to being an inhibitor of the 5-HT transporter [serotonin transporter (SERT)], vortioxetine also functions as a 5-HT receptor modulator, acting as a 5-HT_{3A}, 5-HT_{7} and 5-HT_{1D} antagonist, a 5-HT_{1B} partial agonist, and a 5-HT_{1A} agonist[17,19,20]. It is unclear exactly which of these activities contributes to its antidepressant efficacy though it is likely a combination of these receptor modulatory effects coupled with the SERT blockade[19,20].

Most selective SSRI antidepressants, which are so named because they are thought to work exclusively through their inhibition of SERT, require approximately 80% SERT occupancy to exert therapeutic efficacy. Vortioxetine exhibits approximately 50% SERT occupancy at 5 mg/d, 65% at 10 mg/d and 80% at 20 mg/d[20]. Given its demonstrated efficacy in clinical trials at doses as low as 5 mg/d, it can be postulated that other mechanisms are actively involved[19,21-23].

Pharmacokinetics

Vortioxetine exhibits linear and dose-dependent pharmacokinetics with a terminal half-life of approximately 57-66 h[20,24]. The absolute bioavailability has been established to be approximately 75% after a single administration of 20 mg, and its absorption does not appear to be effected by the presence or absence of food. It is a lipophilic compound with a high affinity for peripheral tissue, causing it to have a large volume of distribution. It is also highly protein bound (98%-99%)[24]. Vortioxetine is extensively metabolized *via* oxidation *via* the cytochrome P450 system, followed by glucuronidation, primarily to a metabolite that is likely pharmacologically inactive due to its inability to cross the blood brain barrier[20,24]. Vortioxetine is metabolized primarily by CYP2D6 and poor metabolizers of this enzyme have approximately twice the vortioxetine plasma concentration of extensive metabolizers[20]. Approximately 59% of vortioxetine metabolites are eliminated through the urine and 26% through the feces. Negligible amounts of unchanged vortioxetine are excreted in the urine[20]. The presence of renal impairment or mild-moderate hepatic impairment does not seem to affect the clearance of vortioxetine[20].

Clinical trials

Vortioxetine has been studied in over 9000 patients with MDD in 25 clinical trials including: 14 short-term (6-12 wk) acute MDD trials, one long-term ($\geqslant$ 24 wk) maintenance of remission study, 6 long-term (52 wk) extension studies, 3 short-term (2-8 wk) studies focused on cognition and one short-term (8 wk) trial focused on sexual dysfunction[25,26]. Seven of the 12 short-term trials with results published to date have demonstrated positive efficacy for at least one dose of vortioxetine for the acute treatment of MDD (Table 4)[25-27]. One of these trials demonstrated efficacy in the elderly and another in patients who had an inadequate response to previous antidepressant treatment[25]. The only dose to show clinical efficacy in a United States population is the 20 mg/d.

Short-term trials: The first of the short-term trials was a multinational (excluding the United States) phase Ⅱ trial conducted by Alvarez and colleagues in 429 patients with moderate to severe MDD over 6 wk[21]. Patients were randomized equally to a fixed dose of vortioxetine 5 or 10 mg, venlafaxine XR 225 mg, or placebo for 6 wk[21,25]. Patients who had failed

Table 4 Randomized controlled trials of vortioxetine for major depressive disorder[21-23,27,29,31-36]

Ref.	*n*	Duration	Key inclusion criteria	Doses	Primary outcome
Alvarez *et al*[21] Phase Ⅱ	429	6 wk	Age 18-65 yr MADRS ⩾ 30	Vortioxetine 5 mg/d Vortioxetine 10 mg/d Placebo Venlafaxine XR 225 mg/d	Positive Change from baseline in MADRS Placebo: -14.5 5 mg: -20.4 (P < 0.001) 10 mg: -20.2 (P < 0.001) Venlafaxine: -20.9 (P < 0.001)
Baldwin *et al*[29] Phase Ⅲ	776	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 2.5 mg/d Vortioxetine 5 mg/d Vortioxetine 10 mg/d Placebo Duloxetine 60 mg/d	Failed Change from baseline in MADRS Placebo: -14.8 2.5 mg: -16.2 (P = 0.219) 5 mg: -16.5 (P = 0.132) 10 mg: -16.3 (P = 0.185) Duloxetine: -16.8 (P = 0.074)
Jain *et al*[32] Phase Ⅲ	600	6 wk	Age 18-75 yr MADRS ⩾ 30	Vortioxetine 5 mg/d Placebo	Negative/failed Change from baseline in HAM-D$_{24}$ Placebo: -13.87 5 mg: -14.61 (P = 0.407)
Mahableshwarkar *et al*[33] Phase Ⅲ	611	8 wk	Age 18-75 yr MADRS ⩾ 22	Vortioxetine 2.5 mg/d Vortioxetine 5 mg/d Placebo Duloxetine 60 mg/d	Negative Change from baseline in HAM-D$_{24}$ Placebo: -10.5 2.5 mg: -12.05 (P = 0.138) 5 mg: -11.08 (P = 0.577) Duloxetine: -13.47 (P = 0.005)
Henigsberg[23] Phase Ⅲ	560	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 1 mg/d Vortioxetine 5 mg/d Vortioxetine 10 mg/d Placebo	Positive Change from baseline in HAM-D$_{24}$ Placebo: -11.3 1 mg: -14.82 (P < 0.001) 5 mg: -15.42 (P < 0.001) 10 mg: -16.23 (P < 0.001)
Boulenger *et al*[31] Phase Ⅲ	608	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 15 mg/d Vortioxetine 20 mg/d Placebo Duloxetine 60 mg/d	Positive Change from baseline in MADRS Placebo: -11.7 15 mg: -17.2 (P < 0.0001) 20 mg: -18.8 (P < 0.0001) Duloxetine: -21.2 (P < 0.0001)
NCT01153009[34] Phase Ⅲ	614	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 15 mg/d Vortioxetine 20 mg/d Placebo Duloxetine 60 mg/d	Positive Change from baseline in MADRS Placebo: -12.83 15 mg: -14.3 (NS) 20 mg: -15.57 (P < 0.05) Duloxetine: -16.9 (P < 0.001)
NCT01163266[36] Phase Ⅲ	462	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 10 mg/d Vortioxetine 20 mg/d Placebo	Positive Change from baseline in MADRS Placebo: -10.8 10 mg: -13.0 (NS) 20 mg: -14.4 (P < 0.01)
NCT01179516[35] Phase Ⅲ	469	8 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 10 mg/d Vortioxetine 15 mg/d Placebo	Negative/failed Change from baseline in MADRS Placebo: -12.87 10 mg: -13.66 (P = 0.597) 15 mg: -13.36 (P = 0.745)
NCT01255787[27] (unpublished) Phase Ⅲ	600	8 wk	Age 20-64 yr MADRS ⩾ 26	Vortioxetine 5 mg/d Vortioxetine 10 mg/d Vortioxetine 20 mg/d Placebo	Negative Change from baseline in MADRS Placebo: -13.99 5 mg: -14.61 (P = 0.907) 10 mg: -15.68 (P = 0.301) 20 mg: -15.82 (P = 0.240)
Boulenger *et al*[22] Phase Ⅲ	400	24-64 wk	Age 18-75 yr MADRS ⩾ 26	Vortioxetine 5-10 mg/d Placebo	Positive Time to relapse-vortioxetine *vs* placebo HR = 2.01 (95%CI: 1.26-3.21) (P = 0.0035)

NCT: National clinical trial; MADRS: Montgomery-Asberg Depression Rating Scale; HAM-D$_{24}$: Hamilton Rating Scale for Depression (24-items).

adequate trials of two or more antidepressants, who were receiving formal behavioral or psychotherapy, or who had significant suicidal thoughts were excluded[21]. Of the 426 patients who were treated in the trial, the average age was 43.3, 62.7% were women and 92% were Caucasian. The mean baseline MADRS score was 34, indicating a severe level of depression[12,13,25]. There were no statistically significant differences between treatment groups at baseline[21]. Both doses of vortioxetine were statistically significantly superior to placebo on the primary endpoint of mean change from baseline in MADRS total score at week 6. The mean difference from placebo was 5.9 points for 5 mg, 5.7 points for 10 mg, and 6.4 points for venlafaxine, translating to medium effect sizes of 0.56 for 5 mg and 0.54 for 10 mg of vortioxetine ($P < 0.001$ for each)[28]. A statistically significant difference compared to placebo was seen from week 2 onwards in the venlafaxine and vortioxetine 5 mg group and week 3 onwards in the vortioxetine 10 mg group. Response and remission rates (as defined in the description of the levomilnacipran trials above) were also statistically significantly higher for all of the active treatment arms when compared to placebo, ranging from 67%-73% response and 45%-49% remission in the vortioxetine 5 mg arm, 68%-76% response and 45%-50% remission in the vortioxetine 10 mg arm, and 72%-77% response and 46%-55% remission in the venlafaxine arm as compared to 40%-49% response rates and 26%-28% remission rates in the placebo arm depending on how response or remission was defined. The study was not powered to be able to detect statistical differences between vortioxetine and venlafaxine. Adverse effects were generally considered mild to moderate, with the most frequent and statistically significant adverse effects being nausea, hyperhidrosis and vomiting. Venlafaxine patients also experienced significantly more dry mouth, constipation and sexual dysfunction, particularly anorgasmia, than placebo-treated patients. Only the venlafaxine group had more patients withdraw from the trial due to adverse effects (14%) than placebo group (4%) ($P = 0.009$)[21].

A similar study conducted by Baldwin *et al*[29] in 776 patients with moderate to severe MDD, which was also conducted in several countries outside of the United States. Patients also had to be in a current major depressive episode (MDE) for at least 3 mo. Other inclusion and exclusion criteria were similar to the Alvarez trial. Patients were randomized to either a fixed dose of vortioxetine 2.5, 5 or 10 mg, duloxetine 60 mg or placebo for 8 wk[29]. The mean baseline MADRS score was 31.9 indicating moderate to severe MDD and the mean Hamilton Rating Scale for Anxiety (HAM-A) score was 23.0, indicating at least a mild to moderate level of anxiety[30]. The average age of trial participants was 45 years, approximately two-thirds were women, and the majority (78%) were Caucasian, with a significant minority being Asian (21%). As none of the active treatment arms separated from placebo on the primary endpoint, mean change in MADRS score at week 8, using a last observation carried forward analysis approach, this was considered a failed trial. However, when using the mixed model method of analysis with repeated measures, the vortioxetine 5 and 10 mg and duloxetine groups were statistically significant when compared to placebo on the primary and most secondary outcomes, including mean change from baseline in the Hamilton Rating Scale for Depression (24-items) (HAM-D_{24}), HAM-A, and CGI-I scores. The clinical significance of these outcomes, however, is questionable, as the difference from placebo on the MADRS scores were only 1.6, 2.5, 2.6 and 3.0 points for vortioxetine 2.5, 5, 10 mg and duloxetine, respectively. This study was also not powered to be able to detect a difference between vortioxetine and the active control, duloxetine. In terms of adverse effects of vortioxetine, only the incidence of nausea was statistically significantly greater than placebo, while patients in the duloxetine arm experienced significantly more nausea, dizziness, hyperhidrosis and decreased appetite than placebo-treated patients. The rates of withdrawal from the study were comparable between each of the treatment arms[29].

Two similar trials demonstrated efficacy for vortioxetine in a multinational population, excluding the United States. In these trials, patients were treated for 8 wk with vortioxetine 1, 5, 10 mg or placebo once daily in the trial conducted by Henigsberg *et al*[23] and vortioxetine 15 or 20 mg, duloxetine 60 mg or placebo in the study by Henigsberg *et al*[23] and Boulenger *et al*[31]. Other inclusion and exclusion criteria were similar to the above described trials. The average age of patients in these trials was approximately 47 years, the great majority were Caucasian and roughly two-thirds were female[23,31]. All doses of vortioxetine, as well as duloxetine, showed a statistically significant improvement on the primary outcome, change from baseline HAM-D_{24} in the Henigsberg trial, and change in MADRS in the Boulenger trial (Table 4). In the Henigsberg trial, these differences translated to moderate effect sizes of 0.37, 0.41 and 0.54 for vortioxetine 1, 5 and 10 mg, respectively[23]. MADRS and HAM-D_{24} scores began to separate from placebo at week 2 for most doses, and week 4 for the vortioxetine 15 mg/d arm. Statistically significant differences were seen for many of the secondary outcomes as well, with the exception of the change in the SDS, which did not show a difference from placebo with any dose of vortioxetine in the Henigsberg trial, but did show improvement in the Boulenger trial[23,31]. Such positive secondary outcomes included change in MADRS score, change in HAM-D_{24} in patients with a baseline HAM-A score $\geqslant$ 20, and response and remission rates based on both the HAM-D_{24} and the MADRS[23,31]. Response rates ranged from 46.8%-61.6% and remission rates from 20.9%-38.4% for vortioxetine as compared to 74.0% response and 54.1% remission

in the duloxetine group and 23.0%-32.3% response and 11.5%-19.0% remission for placebo. Adverse effects occurring in ⩾ 5% of subjects in any of the vortioxetine treatment groups included nausea, headache, nasopharyngitis, and dizziness. One incidence of pancreatitis with vortioxetine 10 mg/d was judged by the investigator to be possibly related to the medication[23]. No statistically significant changes in the Arizona Sexual Experiences (ASEX) scale were seen in any of the treatment arms in the Boulenger trial, even when stratified according to sex or baseline sexual function status. However, the most frequent primary reason for withdrawing from the study was adverse events and the percentage of patients in the vortioxetine 20 mg arm that discontinued due to adverse events was significantly higher than placebo [11.3% *vs* 4.4%, respectively (*P* value not reported)]. Nausea and dry mouth occurred statistically more often with duloxetine than with placebo ($P < 0.001$)[31].

In patients being switched from vortioxetine 15 or 20 mg to placebo at the end of 8 wk, only the 20 mg group experienced a statistically significantly higher score on the Discontinuation Emergent Signs and Symptoms Scale (DESS). This difference was seen in week 9 ($P = 0.0297$), but was not statistically significant at week 10 ($P = 0.1690$), indicating short-lived discontinuation symptoms. Increased dreaming or nightmares was the most reported new or worsening symptom in the vortioxetine-treated patients. Patients in the duloxetine arm were tapered down to 30 mg/d for one week and then switched to placebo. Duloxetine-treated patients also scored higher on the DESS during the taper period with patients reporting new or worsening dizziness/lightheadedness, trouble sleeping, insomnia, irritability, fatigue/tiredness, anxiety, tearfulness, headache, agitation, and mood swings[31].

The first United States short-term trial was published by Jain and colleagues and enrolled 600 patients age 18-75 years with moderate to severe MDD. Patients had to have a MADRS score ⩾ 30 at baseline and were excluded if they had significant risk of suicide or history of non-response to 2 or more antidepressants[32]. Patients were required to be in a current MDE for at least 3 mo. Patients were randomized to vortioxetine 5 mg once daily or placebo for 6 wk. Vortioxetine did not separate from placebo in the primary outcome, change in HAM-D_{24} total score at week 6 (Table 4), nor most of the secondary outcomes such as response and remission. Vortioxetine did, however, statistically significantly decrease HAM-D_{24} scores (-13.4 points) in individuals with a baseline HAM-A score > 19 (indicating moderate anxiety) ($P = 0.049$). The effect size in this subgroup was small (0.21), indicating a low level of clinical significance[28,32]. The most common adverse effects seen in the vortioxetine-treated group were nausea (19%), headache (17.1%), diarrhea (11.4%), dry mouth (8.4%) and dizziness (6.4%). The rates of nausea and diarrhea appeared much higher than with placebo (9.4% and 7.0%, respectively). There were no differences between the groups in the number of patients who withdrew from the study due to adverse effects. Additionally, no significant discontinuation effects were seen after stopping vortioxetine during the 2-wk follow up period[32].

A series of three 8-wk trials were conducted in the United States by Mahableshwarkar *et al*[33]. Each of these trials included patients aged 18-75 years with similar inclusion and exclusion criteria as the above described trials, with the exception of the cutoff requirements on the MADRS at baseline. One trial had a relatively modest cutoff of ⩾ 22 and the other two trials required a score of ⩾ 26. Two of the trials used duloxetine 60 mg/d as an active reference. The first trial included vortioxetine 2.5 mg, 5 mg, placebo or duloxetine, the other trial to include a duloxetine arm also studied vortioxetine 15 or 20 mg/d. The trial without an active reference included vortioxetine 10 or 15 mg/d. The average age of participants in these trials ranged from 42.7-45.1 years, 63.5%-73.8% were female, 74.2%-76.5% were Caucasian, and a significant minority (17.3%-22.7%) were Black. The mean MADRS score at baseline ranged from 29.8-33.7[33-35]. Baseline demographics were similar between the treatment groups, however there was a significant difference in baseline body mass index (BMI) in one trial, with patients in the vortioxetine 5 mg group having a slightly higher mean BMI (31.38 kg/m^2) than the vortioxetine 2.5 mg, duloxetine or placebo treatment arms (29.48-30.14 kg/m^2) (*P* value not reported)[25,33]. Only the 20 mg/d arm in any of the vortioxetine arms showed statistically significant improvement in the primary outcome, in this case change in MADRS from baseline (Table 4). Duloxetine, however, did show a significantly greater improvement in the primary outcome in both trials to include it, and was significant in many of the secondary outcomes in these trials as well[33,34].

Nausea, dry mouth and headache were the most frequently reported adverse effects with vortioxetine in these trials and nausea was also the most common adverse events leading to discontinuation. Sexual side effect rates, as measured by the ASEX scale, were similar to that of duloxetine in one trial (51.0% with vortioxetine 2.5 mg, 37.5% with 5 mg, 46.9% with duloxetine, as compared to 33.3% with placebo)[18,33]. In the trials that examined higher doses of vortioxetine, rates of sexual dysfunction as measured by the ASEX were generally similar to what was seen in placebo-treated patients[25,26]. No significant differences in DESS scores were seen in the vortioxetine groups as compared to placebo in the higher dose vortioxetine trial, despite abrupt discontinuation from 15 or 20 mg/d[25].

The second study to show efficacy for vortioxetine in a United States population was conducted by Jacobsen and colleagues in 462 patients randomized

to vortioxetine 10 mg, vortioxetine 20 mg or placebo once daily. Inclusion and exclusion criteria where the same as the above studies by Mahableshwarkar *et al*[33] and Boulenger *et al*[22,31]. The average age of patients in this trial was 42.8 years, 69.9% were Caucasian, 27.9% were Black, and 72.5% were female[25]. The mean MADRS score at baseline was 32.2[36]. Vortioxetine 20 mg/d separated from placebo on the primary outcome, change from baseline in MADRS total score, with a mean difference of 14.41 points (P = 0.002), while vortioxetine 10 mg/d did not, with a mean difference of 12.96 as compared to placebo, with a mean difference of 10.77 (P = 0.058)[36].

The most recently completed short-term placebo-controlled trial was a combined phase Ⅱ and Ⅲ trial conducted in 600 patients, age 20 to 64 years, in Europe and Asia. Patients in this trial were treated with vortioxetine 5, 10, or 20 mg or placebo. Average age of included participants was 44.4 years, 62.5% were female and 69% were Caucasian, with the remaining 31% being Asian. The mean MADRS score at baseline was 31.7. None of the treatment arms separated from placebo on the primary endpoint, change in MADRS (Table 4). Statistical analysis was not performed for any of the secondary outcomes. Nausea was the most commonly reported adverse effect and the rate was the highest in the 20 mg vortioxetine group (24.7%)[27].

The only short-term trial to include an active comparator was a trial of 501 patients with moderate to severe MDD who had a documented inadequate response to SSRI or SNRI monotherapy. This trial was conducted in Europe and compared flexibly-dosed vortioxetine 10-20 mg/d to flexibly dosed agomelatine 25-50 mg/d. Agomelatine works as a NE and dopamine disinhibitor and is marketed in Europe as an antidepressant. Average age of participants in this trial was 46.3 years, 74.7% were female, and almost 100% of patients were Caucasian. The mean baseline MADRS score at baseline was 28.9[25,37]. At weeks 8 and 12, vortioxetine provided significantly greater improvement in the MADRS as compared to agomelatine, with a between group difference of 2.2 points at week 8 (P = 0.018) and 2.0 points at week 12 (P = 0.0054)[25,37]. Change from baseline in HAM-A score, response and remission rates, and all other secondary outcomes were also significantly superior in vortioxetine-treated patients as compared to agomelatine-treated patients[37]. Fewer patients in the vortioxetine group discontinued due to adverse effects than the agomelatine group and the most commonly reported adverse effects with both treatments were nausea, headache, dizziness and somnolence. Numerically more patients in the agomelatine group reported headache, dizziness and somnolence and more patients in the vortioxetine group reported nausea[25].

The efficacy of vortioxetine in an elderly population (≥ 65 years) was established in an 8-wk trial conducted by Katona *et al*[38] in 453 patients randomized to vortioxetine 5 mg/d, duloxetine 60 mg/d or placebo. The mean age of patients in this trial was 71 years, approximately two-thirds were women, and 95% were Caucasian. Mean baseline MADRS score was approximately 30. Approximately 91% of patients had concurrent medical, psychiatric or neurologic disorders and the mean baseline HAM-A score was 19. Both vortioxetine and duloxetine were statistically significant when compared to placebo on the primary outcome, change in HAM-D_{24} at week 8. Vortioxetine had a 3.3 point difference from placebo (P = 0.0011) and duloxetine had a 5.5 point difference (P < 0.0001). Response and remission rates were also significant for both drugs with rates of 53.2%-61.7% response and 29.2%-33.8% remission for vortioxetine, depending on the definition, 63.3%-72.1% response and 34.7%-46.9% remission with duloxetine and 35.2%-38.0% response and 19.3%-20.7% remission with placebo[38].

Secondary exploratory outcomes focused on cognition, which were measured with the Digit Symbol Substitution Test (DSST) and the Rey Auditory Verbal Learning Test (RAVLT) were statistically significantly superior to placebo for vortioxetine. Duloxetine had statistically significant improvement on the RAVLT but not the DSST. Effect sizes on these outcomes were generally small for vortioxetine (0.24-0.27) which calls into question the clinical significance of these findings[38]. The only adverse effect that occurred significantly more frequently in the vortioxetine group than placebo was nausea. Significantly more patients in the duloxetine group experienced nausea, fatigue, constipation, dry mouth, hyperhidrosis and somnolence[38] .

The final short-term trial in adult MDD patients examined sexual functioning in adults experiencing SSRI-related sexual dysfunction[39]. Preliminary results have recently been presented at a meeting of the American Society of Clinical Pharmacology and are currently available from the manufacturer's website[40]. In this trial, 447 patients with recent major depressive episodes that were currently being treated with an SSRI were discontinued from their current treatment and randomized to vortioxetine titrated to 20 mg once daily or escitalopram 20 mg once daily for 8 wk. Patients treated with vortioxetine experienced statistically significant improvement in sexual functioning as measured by the changes in sexual functioning questionnaire short-form-14 (P = 0.013).

Long-term trials: The only long-term trial to employ a double-blind, randomized, placebo-controlled design was a 24-64 wk relapse prevention study conducted in 404 patients, age 18-75 years with MDD in 17 countries in Europe, Asia and Africa. Inclusion and exclusion criteria were similar to the short-term phase Ⅱ trial conducted by Alvarez *et al*[21]. Eligible patients were treated first with 12 wk of open-label, flexible-

dose vortioxetine 5-10 mg/d. The study design was nearly identical to the relapse prevention study conducted for levomilnacipran. Patients who achieved remission (MADRS score ⩽ 10) at both weeks 10 and 12, were randomized to receive vortioxetine or placebo once daily for 24-64 wk. Patients were withdrawn from the study if at any time they suffered a relapse (MADRS score ⩾ 22) or an insufficient clinical response as judged by the investigator. The primary efficacy endpoint was the time to relapse within the first 24 wk of the double-blind period. There were no significant differences between the treatment groups at time of randomization. The mean MADRS score at the time of randomization was 4.8% and 65% of the vortioxetine-treated patients were on 10 mg/d, with the remaining 35% on 5 mg/d. Patients treated with vortioxetine were statistically significantly less likely to relapse with a hazard ratio of 2.01 (95%CI: 1.26-3.21, P = 0.035)[22].

The proportion of patients that relapsed on placebo was also statistically significantly higher in the placebo group (26%) than in the vortioxetine group (13%) (P = 0.013)[22]. Interestingly, there was a lower risk of relapse for Caucasian patients than for Asian patients, however the number of Asian patients enrolled in the study was small (17.7% of the placebo group and 15.7% of the vortioxetine group)[22]. Nausea and headache were the most common adverse effects in the open-label period (25.7% and 18.3% respectively). The only adverse effect that was statistically significantly higher in the vortioxetine group during the double-blind phase was nausea (8.8% *vs* 3.1% with placebo)[22].

Out of the six open-label extension trials that have been conducted for vortioxetine for the treatment of MDD, five of them currently have results available. Doses in these trials ranged from 2.5-20 mg/d. Three of these trials were performed outside of the United States, one exclusively in the United States and one in multiple countries including the United States. Depression scale scores continued to improve in all of the open-label extension studies, as did rates of response and remission in trials that measured this information. The most common adverse effects seen in the long-term trials were nausea and headache. Other commonly reported adverse effects reported in one or more of the trials included dizziness, nasopharyngitis and weight increase. Rates of withdrawal due to adverse effects were generally low and ranged from 5.9%-10.9%[25,41-43].

Dosage recommendations

Vortioxetine is available in dosage strengths of 5, 10, 15 and 20 mg immediate release tablets. The recommended starting dose of vortioxetine is 10 mg once daily with or without food. It is recommended that this be titrated to 20 mg once daily, as tolerated. No specific titration recommendations are outlined in the package insert, however, most clinical trials increased to 15 or 20 mg/d after one week at a dose of 10 mg/d. Patients who do not tolerate 10-20 mg/d can be decreased down to 5 mg/d[20].

The maximum recommended dose is 10 mg/d in patients who are known CYP2D6 poor metabolizers or who are on a strong CYP2D6 inhibitor (such as bupropion, paroxetine or fluoxetine). Patients who are taking concomitant CYP strong inducers (such as carbamazepine, phenytoin or phenobarbital) for more than 14 d may need a dose increase to maintain adequate plasma levels; however, it is not recommended to go above three times the original dose[20]. No dose adjustment is recommended based on age, race, gender, ethnicity or renal function. Patients with mild-end stage renal impairment or mild-moderate hepatic impairment can be administered vortioxetine safely without dose adjustment. Vortioxetine is not recommended in patients with severe hepatic impairment since it has not been studied in this population[20].

Drug interactions

Vortioxetine does not appear to have any clinically relevant inhibitory or inducing effects on the CYP450 system[24]. It is a substrate of several of the CYP450 enzymes and dose adjustments are recommended when used concomitantly with strong CYP2D6 inhibitors or strong CYP450 inducers. Because vortioxetine is highly protein bound, it is possible that coadministration with other highly protein bound drugs may increase the free concentrations of the other drug. Yet, in a study with coadministration of warfarin, a highly protein-bound drug, no significant change in international normalized ratio was seen[20].

Adverse effects

The most common adverse effects seen in both short and long-term trials of vortioxetine were nausea, constipation and vomiting. Nausea appears to be dose-related, with almost one-third of patients on 15 or 20 mg/d experiencing nausea. It also seems to be transient for most patients, with an average duration of 2 wk, however, as many as 10% of patients continued to experience nausea at the end of the 6- to 8-wk trials[20].

Spontaneously reported sexual adverse effects were low in the clinical trials for vortioxetine. In order to more accurately capture a side effect that is generally underreported, the ASEX was used in several of the clinical trials for vortioxetine. For patients without sexual dysfunction at baseline, rates of treatment emergent sexual dysfunction according to the ASEX were somewhat higher than placebo, with rates of 22%-34% in females and 16%-29% in males as compared to 20% and 14% with placebo, respectively. As with nausea, this adverse effect appears to be dose-dependent, with the highest rates occurring at 20 mg/d[20].

Most of the clinical trials employed a rapid dis-

continuation upon cessation of vortioxetine. Rates of discontinuation symptoms were low overall, with some patients reporting headache and muscle tension[20]. One of two trials that measured such symptoms *via* the DESS showed a statistically significant difference[25,31]. It is recommended that patients taking 15 or 20 mg/d of vortioxetine be tapered down to 10 mg/d for one week before completely discontinuing the medication[20].

Contraindications and warnings related to vortioxetine include hypersensitivity to vortioxetine or any excipients in the formulation as well as concomitant use of MAOIs, linezolid or methylene blue. Vortioxetine should be discontinued at least 21 d before starting one of these medications and usage of vortioxetine within 14 d of use of an MAOI is also contraindicated. Patients being started on any antidepressant medication should be screened for bipolar disorder and monitored closely for clinical worsening, suicidality and behavior changes. Serotonin syndrome, abnormal bleeding, activation of mania/hypomania and hyponatremia are all class warnings of the SSRI and SNRI antidepressants that also apply to vortioxetine. No abnormal laboratory (except sodium), weight or vital sign changes have been noted in clinical trials with vortioxetine. According to the product information, a clinical study has demonstrated that a single dose of vortioxetine 20 or 40 mg does not appear to increase the impairment of mental or motor skills due to alcohol consumption[20].

Vortioxetine is listed as pregnancy category C. Developmental delays, but no teratogenic effects have been seen in the offspring of rats and rabbits exposed to vortioxetine. The medication has been seen to enter the milk of lactating rats, but no data is available for nursing or pregnant women[20].

CONCLUSION

Both levomilnacipran and vortioxetine are new antidepressants that were approved by the FDA in 2013 for the treatment of MDD in adults. Levomilnacipran is a SNRI that was effective in several short term studies and sustained efficacy and tolerability was demonstrated in 1 long-term (48 wk) extension study. The most commonly observed adverse effects are headache, nausea, dizziness, constipation, dry mouth, increased heart rate, tachycardia, erectile dysfunction, urinary hesitation, insomnia, vomiting, and hyperhidrosis. Levomilnacipran seems to have a weight-neutral profile that was demonstrated in both short and long-term studies. Although most of the adverse effects are considered mild to moderate, this may limit its clinical utility, especially in patients with baseline cardiovascular disease. Additional long-term studies and studies comparing levomilnacipran to other antidepressants are needed to establish its place in therapy.

Vortioxetine was effective in the treatment of MDD in both short-term (6-8 wk) trials as well as in the prevention of relapse in a 24-36 wk trial. Sustained efficacy and tolerability was demonstrated in several long-term open-label trials. Its efficacy was also established in a trial of patients who had unsatisfactory response to an SSRI or SNRI. Some unique benefits of vortioxetine may include its ability to improve depressive symptoms in patients with high levels of baseline anxiety, its low-moderate risk for causing sexual dysfunction and its relatively low risk for sedation, weight gain, and discontinuation symptoms upon rapid withdrawal. Vortioxetine's drug interaction potential, high rates of nausea and cost may limit its clinical utility. Currently the only dose of vortioxetine that has been proven to be effective in a United States population is 20 mg/d, which is also the dose associated with the most adverse effects.

Several generic antidepressants are currently available at a modest cost. Compared to these medications, these brand-name products may be cost prohibitive. Further studies comparing levomilnacipran and vortioxetine to other currently available antidepressants may be needed to establish its place in therapy.

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