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ADIS DRUG EVALUATION

Vortioxetine: A Review of Its Use in Major Depressive Disorder

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Abstract Vortioxetine (Brintellix®) is a serotonin (5-HT) transporter inhibitor that also acts on several 5-HT receptors, such as the 5-HT_3 and 5-HT_{1A} receptors. It is approved in the US and the EU for the treatment of adult patients with major depressive disorder (MDD); this article reviews the pharmacological properties of oral vortioxetine and its clinical efficacy and tolerability in these patients. Vortioxetine is generally efficacious in patients with MDD in acute treatment trials (including elderly patients), in a relapse-prevention trial, and in open-label extension trials. It is associated with improved cognitive function in patients with MDD; this does not occur solely via improvement in depressive symptom severity. It is well tolerated, but is associated with significantly increased sexual dysfunction at the highest dosage; however, vortioxetine was shown to improve previous-treatment-emergent sexual dysfunction in patients with well-treated MDD to a greater degree than escitalopram. Vortioxetine extends the available treatment options for patients with MDD, and further investigation into its comparative efficacy versus other antidepressants will allow for more accurate placement among these treatment options.

Vortioxetine in Major Depressive Disorder: A Summary
One of very few novel antidepressants filed or approved in the last few years
Generally efficacious in acute-treatment, placebo-controlled trials with regard to change from baseline in depression scale scores
More efficacious than agomelatine at improving depression scale scores in an acute-treatment trial in patients with disease that had not adequately responded to selective serotonin reuptake inhibitor or serotonin/norepinephrine reuptake inhibitor monotherapy
Non-inferior to venlafaxine in improving depression scale scores in an acute-treatment trial in Asian patients with MDD
Efficacious at preventing relapse in a 6-month placebo-controlled trial, and demonstrated continued effectiveness as maintenance treatment in 52-week, open-label extension trials
Well tolerated; most adverse events are mild to moderate and transient in nature, and do not lead to treatment discontinuation. Nausea is the most common adverse event

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1 Introduction

Antidepressant treatment is one of the recommended treatment options for patients with major depressive disorder (MDD) [1]. There is a wide range of pharmacotherapy treatment options, and effectiveness is generally comparable between and within medication classes; the initial selection of drug is, as a result, generally based on anticipated adverse events (individualized to the patient), the pharmacological properties of the drug, and any past experiences the patient has had with antidepressant medications [1].

Current guidelines suggest initial treatment with a selective serotonin (5-HT) reuptake inhibitor (SSRI), a serotonin norepinephrine reuptake inhibitor (SNRI), mirtazapine, or bupropion [1]. However, only approximately one-half to three-quarters of patients respond to treatment with the first trial of antidepressant medication [2]; for example, data from the STAR*D study showed a 47 % response rate with up to 14 weeks' treatment with citalopram [3]. Guideline recommendations in the case of non-response (after drug dosage optimization) include changing to another first-line drug, or augmentation with another first-line drug, generally one from a different pharmacological class [1].

Antidepressant combinations with different mechanisms of action may allow for greater efficacy; however, a major difficulty with this is the potential for a greater number of adverse events [2]. Single agents interacting with multiple neurotransmitter systems have potential advantages over single agents that interact with a single system or combination-drug treatments. For instance, numerous biological pathways have been implicated in the development of MDD, and the tolerability of a single drug is likely to be better than that of drug combinations; moreover, patients with MDD also often have a wide range of related disorders, such as anxiety and cognitive dysfunction, which drugs with several mechanisms of action may be able to target to a greater extent [2].

Vortioxetine (Brintellix®) is a serotonin (5-HT) transporter inhibitor that also acts on several 5-HT receptors, such as the 5-HT_3 and 5-HT_{1A} receptors [4, 5]. It is approved in the US [4] and the EU [5] for the treatment of adults with MDD. This article reviews the pharmacological properties of oral vortioxetine and its clinical efficacy and tolerability in these patients.

2 Pharmacodynamic Properties

While vortioxetine's mechanism of action is not fully understood, it is believed to be related to the enhancement of CNS serotonergic activity via the inhibition of serotonin reuptake by the serotonin transporter (SERT) [4, 5]. Other actions include 5-HT_3, 5-HT_7 and 5-HT_{1D} receptor antagonism, 5-HT_{1A} receptor agonism and 5-HT_{1B} receptor partial agonism [4, 5]; this leads to modulation of neurotransmission in several systems, predominantly the serotonin system, but also the norepinephrine, dopamine, histamine, acetylcholine, GABA and glutamate systems [5]. This activity across several systems may be responsible for the antidepressant- and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed in animal studies [5]. However, it is yet to be established whether these actions contribute to these effects in humans, and, if they do, how they contribute [4, 5].

Vortioxetine binds to human SERT with high affinity (Ki = 1.6 nM) and potently and selectively inhibits serotonin reuptake (half maximal inhibitory concentration 5.4 nM) [4, 6]; it has a much lower affinity to the human norepinephrine (Ki = 113 nM) and dopamine (Ki > 1,000 nM) transporters [4]. It binds as an agonist to the human 5-HT_{1A} receptor with a Ki of 15 nM, as a partial agonist to the human 5-HT_{1B} receptor with a Ki of 33 nM, and as an antagonist to the human 5-HT_3, 5-HT_7 and 5-HT_{1D} receptors with Kis of 3.7, 19 and 54 nM, respectively [4, 6]. In positron emission tomography studies in healthy volunteers, vortioxetine 5, 10 and 20 mg/day demonstrated SERT occupancy rates in the brain of ≈50 [4, 5, 7], 53–65 [4, 5, 7, 8] and ≥80 % [4, 5, 7], respectively.

Table 1 summarizes the pharmacodynamic effects of vortioxetine observed in preclinical studies. Differences observed between vortioxetine and SSRIs/SNRIs (fluoxetine, duloxetine and escitalopram) in progesterone-withdrawal rodent models of depression (vortioxetine has an antidepressant effect; the SSRIs/SNRIs do not) suggest that it uses mechanisms beyond SERT inhibition to exert its effect [9–11].

Vortioxetine appears to have a different clinical pharmacological profile from that of SSRIs, according to results from a sleep study in healthy volunteers [12]. While both vortioxetine and paroxetine were associated with a significantly ($p < 0.0001$) increased latency in REM onset and decreased time in REM sleep versus placebo, REM sleep was affected to a significantly lesser degree with vortioxetine than with paroxetine, at the same SERT occupancy.

A randomized, double-blind, placebo- and moxifloxacin-controlled, 14-day trial found that vortioxetine 10 (therapeutic) or 40 mg/day (supratherapeutic) is unlikely to affect cardiac repolarization in healthy volunteers [13]. Study investigators raised no concerns with regard to difference between vortioxetine and placebo in baseline-adjusted, individual-corrected QT (QTc) interval [13]. Moreover, no clinically significant effects on ECG

Table 1 Preclinical pharmacodynamic effects associated with vortioxetine

Neurochemical and electrophysiological effects
Increases extracellular levels of serotonin [6, 15–17], dopamine [15–17], noradrenaline [15–17], acetylcholine [17, 18] and histamine [18] in regions of the brain implicated in depression
Increases mRNA levels of proteins involved in neuroplasticity in the PFC [19]
May modulate GABA and glutamate neurotransmission [20]; increases discharge rate of PFC pyramidal neurons [21]
Blocks 5-HT-induced spontaneous inhibitory post-synaptic currents in PFC pyramidal neurons and enhanced theta-burst LTP in hippocampal slices, in vitro [22]
Faster recovery of 5-HT neuronal firing in dorsal raphe nucleus than with fluoxetine [9, 23]
May not affect dopamine neuronal firing in the ventral tegmentum 0.5(significa)-9.9(v572 0 TD(9)Tj0 0 0 scn.4954 0 TD(,)Tj0 0.1 scn 5824 0 TD(15)Tj0 0 0 scn 1.0042 0 TD[(])-329.8(o)rhe)-331.1(noradrenaline)-

parameters (QT, QTc, PR and QRS intervals) have been observed in patients with MDD [5].

Vortioxetine 20 mg had no significant impact on gastric emptying time in healthy volunteers; however, a small but significant reduction in small intestinal transit time and subsequent colon arrival was observed [14].

2.1 Effects on Cognition in Clinical Trials

Vortioxetine does not adversely affect cognitive performance [29]. A randomized, double-blind, crossover, placebo- and mirtazapine 30 mg-controlled trial in 24 healthy volunteers found that single or repeated administration of vortioxetine 10 mg was not associated with impaired cognitive or psychomotor function or driving ability, whereas mirtazapine was transiently associated with impairments in these functions [29].

In elderly patients with MDD, cognitive performance was improved to a significantly ($p < 0.05$) greater extent in vortioxetine 5 mg/day ($n = 156$) than in placebo ($n = 145$) recipients, according to a randomized, double-blind, phase III trial (see Sect. 4.1.4 for further trial details) [30]. The treatment differences for the mean change from baseline to week 8 were +2.79 in DSST (number of correct symbols) score, +1.14 in RAVLT acquisition time score, and +0.47 in RAVLT delayed recall score. Duloxetine improved scores on the RAVLT scale, but not the other endpoints.

Vortioxetine 10 ($n = 193$) and 20 mg/day ($n = 204$) were both more efficacious than placebo ($n = 194$) at improving cognitive function in patients with recurrent MDD, after 8 weeks' treatment in a randomized, double-blind study [31]. Vortioxetine 10 and 20 mg/day were associated with a significantly superior composite z-score [the weighted sum of the z-scores in the digit symbol substitution test (DSST) and the rey auditory verbal learning test (RAVLT); primary endpoint] versus placebo (mean difference from placebo of 0.36 and 0.33, respectively, both $p < 0.0001$). Moreover, vortioxetine 10 mg/day was associated with significant ($p < 0.05$) improvements versus placebo with regard to DSST and RAVLT separately (including the subscales), as well as scores on the trail making test (TMT) A and B, the choice reaction time task (CRT), the Stroop test, and the simple reaction time task. Vortioxetine 20 mg/day was also associated with significant ($p < 0.05$) improvements versus placebo in all cognitive tests except RAVLT (acquisition time) and CRT.

A further randomized, double-blind study, in patients with MDD and self-reported cognitive dysfunction, demonstrated that vortioxetine 10–20 mg/day ($n = 198$) was associated with a significantly greater change from baseline than placebo ($n = 194$) in DSST score (primary endpoint) [$p < 0.05$], perceived deficits questionnaire (PDQ) score ($p < 0.01$) and University of San Diego performance-based skills assessment (UPSA) score ($p < 0.001$) at week 8 of treatment [32]. The study included a duloxetine treatment arm ($n = 210$) as an active reference for depression outcomes; duloxetine did not significantly differ from placebo in change in DSST or UPSA score, but did significantly differ in change in PDQ score.

These improvements in cognitive function were shown to be not solely dependent on improvements in depression measures [30–32].

3 Pharmacokinetic Properties

Vortioxetine has a linear, dose-proportional pharmacokinetic profile following once daily administration of 2.5 to 60 mg doses [4, 5]. Steady state plasma concentrations are typically reached within 2 weeks [4, 5], and vortioxetine has an accumulation index of 5 to 6 [5]. Steady-state mean maximum plasma concentrations for vortioxetine 5, 10 and 20 mg/day were 9, 18 and 33 ng/mL, and were reached within 7–11 h of administration [4, 5]. Absolute

bioavailability was 75 % [4, 5, 33]. Food had no effect on the pharmacokinetics of vortioxetine [4, 5, 34].

Vortioxetine is extensively distributed into the extravascular compartment; it has a volume of distribution of ≈2,600 L [4, 5]. It is also highly plasma protein-bound (≥98 %), independent of plasma concentrations [4, 5].

Vortioxetine undergoes extensive metabolization in the liver, mainly via oxidation by several cytochrome P450 (CYP) enzymes, including CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 [4, 5, 35], followed by glucuronic acid conjugation [4, 5]. The major, pharmacologically inactive, carboxylic acid metabolite is formed via CYP2D6 oxidation; this means that poor metabolizers of CYP2D6 have a vortioxetine plasma concentration that is approximately twice that of extensive metabolizers, and these patients may require a lower dosage (Sect. 6) [4, 5].

Approximately 59 and 26 % of a single oral dose of [^{14}C]-labelled vortioxetine were recovered as metabolites in the urine and faeces, respectively [4]. Negligible amounts of unchanged drug were found in the urine for up to 48 h [4] and in the faeces [5]. The mean terminal elimination half-life of vortioxetine is ≈66 h [4, 5] and the mean oral clearance is 33 L/h [5].

The pharmacokinetics of vortioxetine are not affected in a clinically meaningful way by sex [4, 36], race [4, 36], renal impairment (mild, moderate, severe or end-stage renal disease) [4, 5] or mild or moderate hepatic impairment [4, 5, 37]. No dosage adjustment on the basis of age is recommended in the US [4]; however, the EU summary of product characteristics recommends initiating treatment at 5 mg/day (and advises caution when using dosages higher than 10 mg/day) in elderly patients, as the exposure to vortioxetine increased by up to 27 % in healthy volunteers aged ≥65 years versus those aged ≤45 years, receiving multiple doses of 10 mg/day [5]. Vortioxetine treatment is not recommended [4] (or caution should be exercised [5]) in patients with severe hepatic impairment, as it has not been studied in this population.

Exposure to vortioxetine is increased when a strong CYP2D6 inhibitor (e.g. bupropion, fluoxetine, paroxetine or quinidine) is administered concomitantly and decreased when a strong CYP inducer (e.g. rifampicin, carbamazepine, phenytoin) is administered concomitantly; dosage should be decreased if coadministered with a strong CYP inhibitor and may need to be increased if coadministered with an strong CYP inducer, if coadministration with these drugs is deemed necessary [4, 5, 38]. Ethanol and aspirin have no effect on vortioxetine pharmacokinetics [4, 5]. No vortioxetine dosage adjustment is necessary when coadministered with CYP3A4 (e.g. ketoconazole) or CYP2C9 (e.g. fluconazole) inhibitors [5, 38].

No dosage adjustment is necessary for the comedications when vortioxetine is coadministered with a CYP1A2 (e.g. duloxetine), CYP2A6, CYP2B6 (e.g. bupropion), CYP2C8 (e.g. repaglinide), CYP2C9 (e.g. S-warfarin), CYP2C19 (e.g. diazepam), CYP2D6 (e.g. venlafaxine), CYP3A4/5 (e.g. budesonide), or P-glycoprotein (e.g. digoxin) substrate, and no dosage adjustment for lithium, aspirin or warfarin are necessary [4, 5]; however, caution is occasionally advised [5]. The pharmacology of these drugs exhibited negligible change when coadministered with vortioxetine [4, 5, 39–41]. Coadministration of vortioxetine with warfarin did not result in any significant change in international normalized ratio (INR), despite vortioxetine being highly plasma protein-bound [4, 5]. Vortioxetine had no significant effects on the pharmacokinetics of a combined oral contraceptive (ethinyl estradiol/levonorgestrel) [5, 38].

In vitro data indicate that vortioxetine is not likely to inhibit or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or P-glycoprotein [4, 5]; no clinically relevant interactions with drugs metabolized by these enzymes are expected [4].

A population pharmacokinetic-pharmacodynamic meta-analysis showed that there is a dosage-response relationship, well described by an E_{max} (non-linear) model (E_{max} is defined as the maximum effect attributable to the drug), for vortioxetine in patients with MDD, with higher average plasma concentrations of vortioxetine at steady-state associated with a greater change in Montgomery–Åsberg Depression Rating Scale (MADRS) total score [42].

4 Therapeutic Efficacy

Table 2 shows definitions of scales, abbreviations and other endpoint terms used in the trials in this section.

4.1 Acute Treatment versus Placebo

Data on the efficacy of vortioxetine versus placebo as acute treatment for MDD are available from one randomized, double-blind, multicentre, phase II trial [43], one randomized, double-blind, multicentre, phase II/III trial [44], and eight randomized, double-blind, multicentre, phase III trials [45–52]. Additional data are available from a randomized, double-blind, placebo-controlled, multicentre phase III trial in elderly patients with MDD [30].

4.1.1 Phase II and II/III Trials

In the phase II trial, patients aged 18–65 years with MDD with a current major depressive episode and a MADRS total score of ≥30 were randomized to 6 weeks' treatment

Table 2 Definitions of scales, abbreviations and other efficacy endpoint terms used in phase II and III clinical trials, where provided

Term	Definition
CGI-I	Clinical Global Impression-Improvement Scale. A seven-point change-in-mental-illness rating scale; scores range from 1 (very much improved), through 4 (no change) to 7 (very much worse)
CGI-S	Clinical Global Impression-Severity Scale. A seven-point mental-illness rating scale; scores range from 1 (normal) to 7 (extremely ill)
DFFS	Depression and Family Functioning Scale. A 15-item HR-QOL scale assessing two domains: partner and family interactions, and quality of relationships. Each item has a five-point ordinal response scale
EQ-5D	EuroQol. An HR-QOL scale that incorporates five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a self-rated VAS score indicating the patient's general health
HAMA	Hamilton Anxiety Rating Scale. A 14-item scale. Scores for each item range from 0 to 4, yielding an overall score of 0–56. A higher score indicates more severe anxiety
HAMD	Hamilton Depression Rating Scale. A 17- ($HAMD_{17}$) or 24-item ($HAMD_{24}$) scale. Scores for each item range from 0 to 2, 3 or 4, yielding an overall score of 0–52 ($HAMD_{17}$) or 0–76 ($HAMD_{24}$). A higher score indicates more severe depression
MADRS	Montgomery–Åsberg Depression Rating Scale. A ten-item scale. Scores for each item range from 0 to 6, yielding an overall score of 0–60. A higher score indicates more severe depression
Q-LES-Q-SF	Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form. A patient-reported, 16-item HR-QOL scale. Scores for each item range from 1 (very poor) to 5 (very good); however, the final two items are stand-alone and are not included in the total score, which ranges from 14 to 70
Remission	Defined as a MADRS total score $\leq$10 [30, 43–54], a $HAMD_{17}$ score $\leq$7 [30, 43, 45, 47] or a CGI-S score $\leq$2 [30, 43, 45, 46, 54]. Some studies [30, 43, 45–47] used several scales to define remission
Response	Defined as a $\geq$50 % decrease from baseline in MADRS total score [30, 43–48, 51, 52, 54] or $HAMD_{24}$ total score [30, 43, 47, 49, 50], or a CGI-I score $\leq$2 [30, 43, 45, 46, 54]. Some studies [30, 43, 45–47] used several scales to define response
SDS	Sheehan Disability Scale. An HR-QOL scale for assessing functional impairment. Comprises three domains (work, social life, and family life), each rated on a 10-point VAS, ranging from 0 (unimpaired) to 10 (highly impaired)
SF-36	Medical Outcomes Study Short-Form health survey-36. A patient-reported survey of HR-QOL. Comprises eight items, each rated from 0 (maximum disability) to 100 (no disability)
WLQ	Work Limitation Questionnaire. A 25-item HR-QOL scale that comprises four domains (time management, physical demands, mental/interpersonal and output demands). Scale scores range from 0 (limited none of the time) to 100 (limited all of the time)

HR-QOL health-related quality of life, *VAS* visual analogue scale

with vortioxetine 5 ($n = 109$) or 10 mg/day ($n = 101$), venlafaxine extended-release 225 mg/day (titrated from 75 mg/day during the first week) as an active reference ($n = 114$), or placebo ($n = 105$) [43].

The primary endpoint was the change from baseline in MADRS total score at week 6, in the modified intent-to-treat (mITT) population, using last-observation-carried-forward (LOCF) analysis of covariance (ANCOVA) imputation [43].

Recipients of vortioxetine 5 and 10 mg/day experienced a significantly ($p < 0.0001$) greater improvement in MADRS total score than placebo recipients from baseline to 6 weeks [difference from placebo in change from baseline −5.9 (vortioxetine 5 mg/day) and −5.7 (vortioxetine 10 mg/day)] [43]. Recipients of the active reference, venlafaxine, also demonstrated a significantly greater change in MADRS total score than placebo (−6.4; $p < 0.0001$). Significant differences from placebo were observed from week 2 (vortioxetine 10 mg/day) and week 3 (vortioxetine 5 mg/day and venlafaxine).

Furthermore, vortioxetine 5 and 10 mg/day recipients had significantly ($p < 0.01$) greater improvement than placebo recipients in secondary endpoints [Hamilton Depression Rating Scale ($HAMD_{24}$), Hamilton Anxiety Rating Scale (HAMA), Clinical Global Impression-Severity Scale (CGI-S) and Clinical Global Impression-Improvement Scale (CGI-I) scores] as well as significantly ($p < 0.01$) greater response and remission rates [43].

Patients in the phase II/III placebo-controlled trial were randomized to 8 weeks' treatment with oral vortioxetine 5 ($n = 142$), 10 ($n = 147$) or 20 ($n = 149$) mg/day or placebo ($n = 150$) [44]. Eligible patients were aged 20–64 years, and had a primary diagnosis of MDD, a current major depressive episode of $\geq$3 months' duration, a MADRS total score $\geq$26, and a CGI-S score of $\geq$4.

The primary endpoint was the change from baseline in MADRS total score at week 8 [44]. Primary assessments were carried out in the mITT population using LOCF ANCOVA imputation. At baseline, the mean MADRS total score was 31.7.

After 8 weeks, the mean change from baseline in MADRS total score (primary endpoint) did not differ significantly between any of the vortioxetine dosages and placebo recipients (difference from placebo of −0.6, −1.7 and −1.8 for vortioxetine 5, 10 and 20 mg/day, respectively) [44]. No statistical analyses were provided for

vortioxetine 5, 10 and 20 mg/day versus placebo in response rate (49, 54 and 51 vs. 39 %, respectively), remission rate (25, 29 and 31 vs. 27 %), CGI-I score or change in SDS score.

4.1.2 Phase III Trials

Patients in the phase III placebo-controlled trials were randomized to treatment with oral vortioxetine 1 [47], 2.5 [45, 50], 5 [45, 47, 49, 50], 10 [45, 47, 48, 52], 15 [46, 51, 52] or 20 [46, 48, 51] mg/day, oral duloxetine 60 mg/day as an active reference [45, 46, 50, 51], or placebo [45–52]. As vortioxetine 1 and 2.5 mg/day are not in the approved dosage range [4, 5], data from these treatment groups are not further discussed. Treatment lasted 6 [49] or 8 weeks [45–48, 50–52].

Eligible patients were aged 18–75 years [45–47, 49, 50, 55–57], and had a primary diagnosis of (recurrent [46]) MDD [45–52]. They were also required to have a current major depressive episode of ≥3 months' duration [45–47, 49, 50, 55, 57], a MADRS total score ≥22 [50], ≥26 [45–47, 55–57] or ≥30 [49], and a CGI-S score of ≥4 [46, 55–57].

Exclusion criteria included current or certain past psychiatric disorders other than MDD, a history of neurological disorders, serious risk of suicide [45–47, 49, 50, 55–57], formal psychological treatment [45, 46, 55], current depressive symptoms resistant to two antidepressant treatment regimens (each of ≥6 weeks' duration) [45–47, 49, 50, 55, 57], failure to respond or hypersensitivity to duloxetine treatment [45, 46], or taking certain concomitant medication [45, 46, 49, 50, 55–57].

The primary endpoints were the change from baseline in MADRS total score at week 8 [45, 46, 48, 51, 52] or in $HAMD_{24}$ total score at week 6 [49] or 8 [47, 50]. Primary assessments were carried out in the mITT population [45–47, 49, 50, 55–57], using LOCF ANCOVA [45, 49, 50] or a mixed model for repeated measurements (MMRM) [46–48, 55, 57] imputation.

There were generally no clinically relevant differences between treatment groups in patient characteristics at baseline [45–47, 49–51]. The mean age was 42–47 years [45–47, 49, 50], and approximately two-thirds of patients were women [45–47, 49, 50]. At baseline, the mean MADRS total score was 29.4–34.1 (moderate to severe depression) [45–47, 49, 50], the mean CGI-S score was 4.5–4.8 [45, 46, 50], the mean $HAMD_{24}$ score was 28.7–33.1 [45, 47, 49, 50], the mean HAMA score was 17.4–23.0 [45, 46, 50], and the current major depressive episode had started about 6–9 months before trial enrolment [45, 46]. The median duration of the current episode was 22–28 weeks [46, 50].

4.1.2.1 Depressive Symptoms, Response and Remission Vortioxetine was generally more efficacious than placebo at higher dosages (15 or 20 mg/day) and was either more efficacious or did not significantly differ from placebo at lower dosages (5 or 10 mg/day) with regard to the primary endpoints of improving MADRS [45, 46, 48, 51, 52] and $HAMD_{24}$ [47, 49, 50] total scores in patients with MDD, after 6 [49] or 8 [45–48, 50–52] weeks of treatment.

After 6 or 8 weeks, the mean change from baseline in MADRS total score (primary endpoint in five studies [45, 46, 48, 51, 52]) differed significantly ($p < 0.05$) between vortioxetine 5 mg/day and placebo recipients in one [47] of three [45, 47, 49] phase III trials; between vortioxetine 10 mg/day and placebo recipients in one [47] of four [45, 47, 48, 52] phase III trials; between vortioxetine 15 mg/day and placebo recipients in one [46] of three [46, 51, 52] phase III trials; and between vortioxetine 20 mg/day and placebo recipients in three of three [46, 48, 51] phase III trials (Table 3).

In one trial [45], there was no significant difference between active-reference and placebo recipients in the primary endpoint of change from baseline in MADRS total score (Table 3), in addition to the lack of a difference between recipients of vortioxetine 5 or 10 mg/day and those receiving placebo. As a result, this study was classified by the authors as 'failed'. However, when analysed using MMRM as a sensitivity analysis, vortioxetine 5 and 10 mg/day and duloxetine were all significantly more efficacious than placebo with regard to change from baseline in MADRS total score ($p < 0.05$); thus, this study was ultimately considered to have supportive data [45]. One other trial reported a sensitivity analysis using a MMRM, but this trial found similar results to the main analysis: no significant difference between vortioxetine 5 mg/day and placebo in change from baseline in $HAMD_{24}$ total score [50].

The mean change from baseline in $HAMD_{24}$ total score (primary endpoint in three studies [47, 49, 50]) after 6 or 8 weeks differed significantly ($p < 0.05$) between vortioxetine 5 mg/day and placebo recipients in one [47] of four [45, 47, 49, 50] phase III trials and between vortioxetine 10 mg/day and placebo recipients in one [47] of two [45, 47] phase III trials (Table 3).

In two trials (one investigating higher dosages of vortioxetine 15 and 20 mg/day [46], the other investigating lower dosages of 5 and 10 mg/day [47]), vortioxetine (all dosages) was associated with a significantly ($p < 0.001$) higher response rate than placebo at week 8 [46, 47]. In the higher-dosage study, response rates were 57.0 or 63.1 % (MADRS and CGI-I response, respectively) in vortioxetine 15 mg/day, 61.6 or 70.2 % in vortioxetine 20 mg/day, and 32.3 or 38.0 % in placebo recipients [46]. In the lower-dosage study, response rates were 45.3 or 43.9 %

Table 3 Efficacy of vortioxetine versus placebo in 6- to 8-week, randomized, double-blind, multicentre phase III trials

References (treatment duration)	Treatment (mg/day)	No. of pts (mITT)	Mean change from baseline[a,b]				Response[c] rate (% pts)	Remission[c] rate (% pts)
			MADRS total score		$HAMD_{24}$ total score			
			Absolute change [baseline]	Difference from PL	Absolute change [baseline]	Difference from PL		
Baldwin et al. [45, 58][d,e,f] (8 weeks)	VOR 5	155	−16.5 [32.7]	−1.7	−15.0 [31.3]	−1.8	56	36
	VOR 10	151	−16.3 [31.8]	−1.5	−14.9 [30.4]	−1.6	58	36
	DUL 60[g]	149	−16.8 [31.4]	−2.0	−15.7 [29.9]	−2.5*	57	35
	PL	145	−14.8 [31.7]		−13.3 [29.8]		47	34
Boulenger et al. [46, 59][f] (8 weeks)	VOR 15	149	−17.2*** [31.8]	−5.5***			57***	35**
	VOR 20	151	−18.8*** [31.2]	–7.1***			62***	38***
	DUL 60[g]	146	−21.2*** [31.2]	−9.5			74***	54***
	PL	158	−11.7 [31.5]				32	19
Henigsberg et al. [47][d] (8 weeks)	VOR 5	129	−15.1*** [30.6]	−4.2***	−15.4*** [32.1]	−4.1***	45***	25**
	VOR 10	122	−15.7*** [31.6]	−4.8***	−16.2*** [33.1]	−4.9***	50***	24**
	PL	128	−10.9 [30.6]		−11.3 [32.7]		23	12
Jacobsen et al. [48, 56][f] (8 weeks)	VOR 10	155	−13.0 [32.3]	−2.2			34	21
	VOR 20	150	−14.4** [32.4]	−3.6**			39*	22
	PL	157	−10.8 [32.0]				28	14
Jain et al. [49] (6 weeks)	VOR 5	300	−15.8 [34.1]	−0.32	−14.6 [32.7]	−0.74	46	29
	PL	300	−15.5 [34.0]		−13.9 [32.2]		46	32
Mahableshwarkar et al. [50][d] (8 weeks)	VOR 5	153			−11.1 [29.8]		38	27
	DUL 60[g]	152			−13.5** [28.7]		51***	46
	PL	153			−10.5 [29.5]		32	28
Mahableshwarkar et al. [51, 57][f] (8 weeks)	VOR 15	147	−14.3 [31.9]	−1.5			44	27
	VOR 20	154	−15.6* [32.0]	−2.8*			44	29
	DUL 60[g]	152	−16.9*** [32.9]	−4.1***			55**	26
	PL	161	−12.8 [31.6]				39	27
Mahableshwarkar et al. [52, 55][f] (8 weeks)	VOR 10	157	−13.7 [34.1]				38	27
	VOR 15	152	−13.4 [33.7]				37	24
	PL	160	−12.9 [33.4]				33	22

ANCOVA analysis of covariance, *DUL* duloxetine, *HAMD* Hamilton Depression Rating Scale, *LOCF* last observation carried forward, *MADRS* Montgomery–Asberg Depression Rating Scale, *mITT* modified intent-to-treat population, *MMRM* mixed model repeated measures, *PL* placebo, *pts* patients, *VOR* vortioxetine

* $p < 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ vs. PL

[a] The primary endpoint was the change from baseline in MADRS [45, 46, 48, 51, 52] or $HAMD_{24}$ [47, 49, 50] total score

[b] Imputation for change in MADRS and $HAMD_{24}$ total score was done using LOCF ANCOVA [45, 49, 50] or MMRM [46–48, 51, 52]

[c] Response was defined as a ≥50 % reduction in MADRS [45, 46, 48, 51, 52] or $HAMD_{24}$ [47, 49, 50] total score. Remission was defined as a MADRS total score of ≤10 [45, 46, 48, 49, 51, 52] or <10 [50] or a $HAMD_{17}$ total score of ≤7 [47]. In studies where more than one definition of response or remission was used [45–47], the definitions selected for presentation here were those most closely associated with the primary endpoint

[d] These trials also had a treatment arm where patients received VOR 1 mg/day ($n = 140$ [47]) or 2.5 mg/day ($n = 155$ [45] and 153 [50]). However, as these are not approved dosages [4, 5], results from these arms are not discussed

[e] This trial was classified as a 'failed trial', as there was no significant difference between the active reference and PL in the primary endpoint

[f] (Additional[58, 59]) data were taken from an abstract [48, 51, 52] and/or http://www.ClinicalTrials.gov [55–59]

[g] Active reference; the study was not powered for comparison between this drug and VOR

($HAMD_{24}$ and MADRS response, respectively) in vortioxetine 5 mg/day, 49.6 or 48.9 % in vortioxetine 10 mg/day, and 23.0 or 24.5 % in placebo recipients [47]. A further trial demonstrated a significant difference ($p < 0.05$) between vortioxetine 20 mg/day, but not vortioxetine 10 mg/day, and placebo in MADRS response rate

(39 and 34 vs. 28 %, respectively) [56]. In all other studies, there was no significant difference between vortioxetine and placebo in this outcome [45, 49–52]. See Table 3 for further details.

Additionally, in two trials, vortioxetine (all dosages) was associated with a significantly ($p < 0.05$) higher remission rate than placebo at week 8 [46, 47]. In the higher-dosage study, remission rates were 34.9 or 40.9 % (MADRS and CGI-I remission, respectively) in vortioxetine 15 mg/day, 38.4 or 45.0 % in vortioxetine 20 mg/day, and 19.0 or 21.5 % in placebo recipients [46]. In the lower-dosage study, remission rates were 24.5 or 28.8 % ($HAMD_{24}$ and MADRS remission, respectively) in vortioxetine 5 mg/day, 23.7 or 26.6 % in vortioxetine 10 mg/day, and 11.5 or 16.5 % in placebo recipients [47]. In the other studies [45, 49–52], there was no significant difference between vortioxetine and placebo in this measure. See Table 3 for further details.

In the studies that investigated depression endpoints in patients with high baseline anxiety (HAMA baseline score ≥20 [45–47, 49, 50, 56]), vortioxetine was generally associated with a greater change from baseline to week 6 [49] or 8 [46, 47, 56] than placebo in MADRS [46, 56] or $HAMD_{24}$ [47, 49] total score. Vortioxetine 15 and 20 mg/day recipients had significantly ($p < 0.001$) greater improvements in MADRS total score than placebo recipients (−17.4 and −18.6 vs. −12.2, respectively) in one study [46], as did vortioxetine 10 and 20 mg/day versus placebo recipients (−14.55 and −17.52 vs. −10.26; $p < 0.05$ and $p < 0.001$, respectively) in another study [56]. Moreover, the $HAMD_{24}$ total score was improved to a significantly greater extent in patients receiving vortioxetine 5 mg/day (−15.50 [47] and −16.18 [49]; $p < 0.05$) than in placebo recipients (−11.02 [47] and −13.41 [49]) in two [47, 49] of four [47, 49, 50, 58] studies and in one [47] of two [47, 58] studies in patients receiving vortioxetine 10 mg/day (−15.61 [vs. −11.02 with placebo]; $p = 0.001$ [47]).

4.1.2.2 Global Improvement At week 8, vortioxetine 15 and 20 mg/day were both associated with a significantly ($p < 0.001$) lower mean CGI-I score than placebo (2.18 and 1.92 vs. 2.86, respectively) [46]. A further study found that vortioxetine 20 mg/day but not 10 mg/day was associated with a significantly ($p < 0.05$) lower CGI-I score at week 8 than placebo (2.69 and 2.59 vs. 2.89 for vortioxetine 10 and 20 mg/day vs. placebo) [48, 56]. At the lower dosages of vortioxetine 5 and 10 mg/day, the CGI-I score was also significantly lower with vortioxetine than placebo after 8 weeks (2.37 and 2.29 vs. 2.84; both $p < 0.001$) [47]. All other trials reported no significant difference between vortioxetine and placebo in CGI-I score at endpoint [45, 49–52].

The change in CGI-S score at week 8 was significantly ($p < 0.001$) greater with vortioxetine 15 and 20 mg/day than placebo (−2.1 and −2.4 vs. −1.3, respectively) [46]. However, at the lower dosage of 5 mg/day, vortioxetine had no significant effect on the change in CGI-S score when compared with placebo at week 6 (−1.46 vs. −1.46) [49]. Change in CGI-S score either did not differ significantly between groups [45] or was not investigated [47, 48, 50–52] in any of the other trials.

4.1.2.3 Anxiety Higher dosages of vortioxetine also appear to have a positive effect on anxiety symptoms [46, 48]. The change from baseline to week 8 in HAMA score was −9.6 and −11.1 versus −7.1 in vortioxetine 15 and 20 mg/day versus placebo recipients ($p < 0.01$) [46]. Moreover, vortioxetine 20 mg/day was associated with a significantly ($p < 0.05$) greater change in HAMA score from baseline to week 8 than placebo in another trial (neither the results for the 10 mg/day dosage nor the numerical data for either dosage were reported) [48]. Change in HAMA score did not differ significantly between groups [45], was not reported to be investigated [49–52], or significance was not reported [60] in any of the other trials.

4.1.2.4 Disability and Health-Related Quality of Life Vortioxetine was either more efficacious or did not significantly differ from placebo with regard to improvements in score on disability and health-related quality-of-life (HR-QOL) scales; treatment differences were particularly evident at higher dosages [46–52]. Changes from baseline to 8 weeks in Sheehan Disability Scale (SDS) total score were −7.7 and −8.4 versus −4.5 for vortioxetine 15 and 20 mg/day versus placebo (both $p < 0.01$) [baseline values 20.6, 20.7 and 19.8, respectively] [46]; a further study found that vortioxetine 20 mg/day, but not 10 mg/day, was associated with a significantly ($p < 0.05$) greater change in SDS total score at week 8 than placebo (−7.25 and −8.26 vs. −5.86 for vortioxetine 10 and 20 mg/day vs. placebo) [48, 56]. However, the difference in change from baseline in SDS total score was either not significant or significance was not reported for vortioxetine 5 mg/day versus placebo at 6 weeks [49] or vortioxetine 5 [45, 47, 50], 10 [45, 47, 52], 15 [51, 52] or 20 [51] mg/day versus placebo at 8 weeks in other studies. In addition, changes from baseline in Q-LES-Q-SF total score were +3.3 and +4.5 versus +5.2 for vortioxetine 15 and 20 mg/day versus placebo, respectively (both $p < 0.01$) [baseline values 33.2, 33.7 and 34.1] [46].

A meta-analysis of acute-treatment trials of vortioxetine in patients with MDD (four investigating SF-36 scores and seven investigating SDS scores; the number of studies reporting change in EQ-5D scores was not reported), with a

total of 2,155 vortioxetine (5, 10, 15 or 20 mg/day) and 1,316 placebo recipients, found that vortioxetine 5 and 20 mg/day were associated with a significantly greater improvement in SF-36 Mental Component Summary score than placebo [+2.6 ($n = 604$) and +4.8 ($n = 328$), respectively; both $p \leq 0.001$] [61]. Vortioxetine 10 mg/day was associated with a significantly greater improvement in EQ-5D Health State score than placebo (+7.5; $p < 0.05$; $n = 86$), and vortioxetine 10 and 20 mg/day were associated with significantly greater improvements than placebo in SDS total score [−1.7 ($n = 269$) and −2.4 ($n = 234$), respectively; both $p < 0.01$]. Placebo score improvement was not reported for any endpoint [61]. The analyses were in the mITT population and used MMRM.

4.1.3 Pooled Analyses of Depressive Symptoms

A meta-analysis of nine acute-treatment studies of vortioxetine 5, 10, 15, or 20 mg/day versus placebo ($n = 847$, 687, 436, 446 and 1215, respectively) in patients with MDD found that the mean difference from placebo in change in MADRS total score from baseline to week 6 or 8 was −2.6 ($p = 0.008$), −3.5 ($p < 0.001$), −2.6 (not significant), and −4.5 ($p < 0.001$) for vortioxetine 5, 10, 15 and 20, respectively [62]. Moreover, significant (p value not specified) differences from placebo were evident in response rate, remission rate, CGI-I score and CGI-S score for all four vortioxetine dosages.

Number-needed-to-treat analyses from a systematic review found that the number need to treat for response versus placebo was 7 and the number needed to treat for remission versus placebo was 11 [63].

4.1.4 In Elderly Patients

A randomized, double-blind, placebo- and active reference-controlled, multicentre, phase III study investigated the efficacy of vortioxetine in elderly patients with recurrent MDD [30]. Patients received vortioxetine 5 mg/day ($n = 156$), placebo ($n = 145$) or the active reference duloxetine 60 mg/day ($n = 151$) for 8 weeks of double-blind treatment.

Included patients were aged ≥65 years and had a primary diagnosis of MDD, whose current episode of MDD had lasted at least 4 weeks, and who had experienced at least one previous MDD episode before the age of 60 years [30]. They were also required to have a MADRS total score of ≥26. Exclusion criteria included a Mini-Mental State Examination score of <24; current psychiatric or mental disorders other than MDD; chronic liver disease; a myocardial infarction within the past 6 months; elevated intraocular pressure, clinically significant unstable illness; irregular thyroid-stimulating hormone values; and a recent history of cancer. The use of certain medications was not permitted; however, antiarrhythmics, certain antihypertensives, proton pump inhibitors and aspirin as antiplatelet treatment were permitted.

The primary endpoint was the change in $HAMD_{24}$ score from baseline to week 8, in the mITT population (using LOCF ANCOVA imputation) [30]. If applicable (following the pre-defined testing hierarchy), this was extended to weeks 6, 4, 2 and 1.

At baseline, the mean age was 71 years, approximately two-thirds of patients were women, the current MDD episode had lasted ≈33 weeks, ≈91 % of patients had concurrent disorders (most commonly osteoarthritis, type 2 diabetes, hypertension, drug hypersensitivity, back pain, benign prostatic hyperplasia and hypercholesterolaemia), 69–74 % of patients were taking concomitant medication (27–37 % initiated concomitant medication during the study) [most commonly simvastatin, aspirin, multivitamins and hydrochlorothiazide], and the mean rating scale scores were: MADRS total 30.3–30.7, $HAMD_{24}$ total 28.5–29.4, HAMA total 19.2–19.9, and CGI-S 4.7–4.8 [30]. No significant differences between groups were found at baseline with regard to patient characteristics.

Vortioxetine 5 mg/day was significantly more efficacious than placebo with regard to the primary endpoint of change in $HAMD_{24}$ score from baseline at week 8 (treatment difference −3.3; $p = 0.0011$) and week 6 (−2.1; $p = 0.0240$), but not at week 4 [30]. Duloxetine was also significantly more efficacious than placebo at weeks 8 and 6 ($p < 0.001$ at both time points), with a treatment difference of −5.5 at week 8.

Vortioxetine was also significantly ($p < 0.01$) more efficacious than placebo with regard to the mean change from baseline to week 8 in MADRS score (treatment difference −4.29), HAMA score (−2.35), and CGI-S score (−0.60), as well as with regard to mean CGI-I score at week 8 (treatment difference −0.56) [30]. Remission and response were also significantly higher in vortioxetine than in placebo recipients, with remission rates of 29.2–33.8 % (depending on the definition of remission) in vortioxetine recipients versus 19.3–20.7 % in placebo recipients ($p < 0.05$), and response rates of 53.2–61.7 versus 35.2–38.0 %, respectively ($p < 0.01$).

4.2 Acute Treatment versus Agomelatine

The efficacy of vortioxetine 10–20 mg/day [$n = 252$ (mITT population)] versus agomelatine 25–50 mg/day [$n = 241$ (mITT population)] in adult patients with MDD that had not adequately responded to SSRI/SNRI monotherapy was investigated in a randomized, double-blind, multicentre, flexible-dosage, phase III study, with a 12-week treatment period [54]. Eligible patients were aged

18–75 years and had a diagnosis of single-episode or recurrent MDD, a MADRS total score ≥22 [and a MADRS item 1 (apparent sadness) score ≥3], a current major depressive episode of <12 months' duration, and an inadequate response (symptoms considered non-responsive or partially responsive) during the current major depressive episode to a single treatment course of an adequate dosage of SSRI/SNRI monotherapy, for an adequate duration period. Exclusion criteria included a history of a lack of response to agomelatine or previous exposure to vortioxetine; current or certain past psychiatric disorders other than MDD, generalized anxiety disorder or social anxiety disorder; a history of neurological disorders; serious risk of suicide; formal psychological treatment; or taking certain concomitant medication.

Patients received vortioxetine 10 mg/day for the first week or agomelatine 25 mg/day for the first 2 weeks; at the end of weeks 1 (vortioxetine recipients) 2, 3 or 4 (vortioxetine and agomelatine recipients), dosage could be increased to vortioxetine 20 mg/day or agomelatine 50 mg/day [54]. The investigator could decrease the dosage to vortioxetine 10 mg/day or agomelatine 25 mg/day if tolerability issues occurred. After week 4, the dosage was fixed. At the start of week 5, a total of 65 % of vortioxetine and 72 % of agomelatine recipients were receiving the highest dosage (20 and 50 mg/day, respectively).

The primary endpoint was the change from baseline to week 8 in MADRS total score, in the mITT population using MMRM [54]. The initial comparison was a non-inferiority analysis (non-inferiority was established if the upper bound of the two-sided 95 % CI of the difference between treatment groups in MADRS total score at week 8 did not exceed +2 points), followed by a superiority comparison.

No clinically relevant differences between treatment groups in baseline characteristics were found [54]. At baseline, the mean age was 46 years, approximately three-quarters of patients were women, the current depressive episode had started a mean of 19 weeks before trial entry and was the first episode for 28 % of patients (most patients had had two previous depressive episodes), and the mean MADRS total score was 29.1 in vortioxetine and 28.7 in agomelatine recipients. Corresponding scores on the HAMA, CGI-S and SDS scales were 21.6 and 21.4, 4.4 and 4.4, and 19.2 and 19.3, respectively. The SSRI or SNRIs taken before trial entry for the current episode were sertraline (24 %), escitalopram (19 %), citalopram (18 %), venlafaxine (17 %), paroxetine (15 %) and duloxetine (6 %).

Vortioxetine was non-inferior to and significantly more efficacious than agomelatine at decreasing MADRS total score [54]. The difference in change from baseline in MADRS total score between recipients of vortioxetine and those receiving agomelatine was −2.2 (95 % CI −3.5 to −0.8) at 8 weeks (change from baseline −16.5 and −14.4; $p = 0.0018$). This difference was significant from week 4 onwards ($p < 0.01$). At week 12, the treatment difference in change from baseline was −2.0 ($p < 0.01$).

Vortioxetine was also significantly more efficacious than agomelatine with regard to change from baseline in HAMA total score (treatment difference −1.9 for both weeks 8 and 12; both $p < 0.001$), change from baseline in CGI-S score (treatment difference −0.3 for both weeks 8 and 12; both $p < 0.01$), and CGI-I score (treatment difference −0.3 for both weeks 8 and 12; both $p < 0.01$); these were significant from week 4 onwards ($p < 0.05$) [54]. Moreover, vortioxetine was associated with a significantly greater MADRS response rate at weeks 8 (62 vs. 47 %; $p < 0.01$) and 12 (70 vs. 56 %; $p < 0.01$), as well as a significantly greater remission rate at weeks 8 (41 vs. 30 %; $p < 0.01$) and 12 (55 vs. 39 %; $p < 0.01$). CGI response and remission were also significantly greater among vortioxetine than agomelatine recipients at these time points (all $p < 0.05$).

Vortioxetine was associated with a greater change from baseline than agomelatine in SDS total score at weeks 8 (treatment difference −2.2; $p < 0.01$) and 12 (treatment difference −1.8; $p < 0.05$); the difference was significant from week 4 onwards [54]. Change in HR-QOL was also significantly ($p < 0.05$) greater in vortioxetine than agomelatine recipients in EQ-5D score from week 4 onwards, in DFFS score at weeks 8 and 12, and in WLQ score at week 8.

4.3 Acute Treatment versus Venlafaxine

The efficacy of vortioxetine 10 mg/day ($n = 211$) versus venlafaxine extended-release 150 mg/day ($n = 226$) in adult patients from Asia with MDD was investigated in a randomized, double-blind, phase III, non-inferiority study, with an 8-week treatment period [64]. Eligible patients were aged 18–65 years and had a diagnosis of MDD and an MADRS total score ≥22. Data from this trial were taken from an abstract.

The primary endpoint was change from baseline to week 8 in MADRS total score, analysed in the mITT population using LOCF ANCOVA. A non-inferiority test margin of ±2.5 points on the MADRS scale was used [64]. The baseline MADRS total score was 32.3 in both groups.

The non-inferiority of vortioxetine to venlafaxine in this acute-treatment trial was established, with a difference in change from baseline to week 8 in MADRS total score between vortioxetine and venlafaxine of −1.2 (95 % CI −3.0 to 0.6) [64]. The MADRS total score at week 8 was 13.6 in vortioxetine and 14.8 in venlafaxine recipients.

MADRS response rates at week 8 were 66.5 and 61.4 % in vortioxetine and venlafaxine recipients, respectively; MADRS remission rates were 43.1 and 41.4 % [64]. HAMA total, CGI, SDS total and Q-LES-Q scores also improved to a similar extent between treatments at week 8.

4.4 Relapse Prevention

The efficacy of vortioxetine with regard to the prevention of relapse in patients with MDD in remission after acute treatment was investigated in a randomized, placebo-controlled, multicentre, phase III trial [53]. The initial treatment period ($n = 639$) involved 12 weeks of open-label, flexible-dosage treatment with vortioxetine 5 or 10 mg/day (fixed dosage for weeks 8–12). Patients in remission (MADRS total score $\leq$10) at both weeks 10 and 12 of this period were then randomized into the double-blind treatment period ($n = 400$), and received either vortioxetine 5 or 10 mg/day (at the dosage they were receiving during the final 4 weeks of the initial treatment period; 25 and 75 % of patients, respectively) or placebo, for a minimum of 24 weeks (range 24–64 weeks).

Included patients were aged 18–75 years and had a primary diagnosis of MDD, with a major depressive episode of $\geq$4 weeks' duration and at least one prior major depressive episode, and a MADRS total score of $\geq$26 [53]. Exclusion criteria included current or certain past psychiatric disorders other than MDD, a history of neurological disorders, serious risk of suicide, a score $\geq$5 on MADRS item 10 (suicidal thoughts), formal psychological treatment, current depressive symptoms resistant to two antidepressant treatment regimens (each of $\geq$6 weeks' duration), or taking certain concomitant medication.

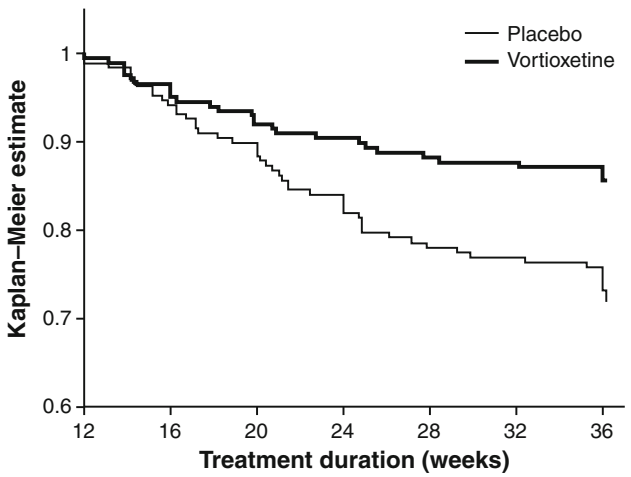

Fig. 1 Efficacy of vortioxetine 5 or 10 mg/day versus placebo in the prevention of relapse in patients with MDD in remission after acute treatment with vortioxetine [53]. Kaplan–Meier survival analysis of relapse over 24 weeks, following 12 weeks' initial treatment. $p = 0.0035$ vs. placebo. Adapted from Boulenger et al. [53], with permission

The primary endpoint was the time to MDD relapse [MADRS total score $\geq$22 or insufficient therapeutic response (as judged by the investigator)] within the first 24 weeks of the double-blind period, in the mITT population ($n = 396$) [53].

No significant differences between vortioxetine and placebo recipients were evident at baseline of the double-blind period. The mean age at baseline was 45 years, approximately two-thirds of patients were women, the mean time since the start of the current major depressive episode was 23 weeks (range 4 weeks to 4 years), and patients had had a mean of 2.1 previous major depressive episodes [53]. At the beginning of the double-blind period, the mean MADRS total, $HAMD_{17}$ total, HAMA total and CGI-S scores were, respectively, 4.9 and 4.7, 4.7 and 4.0, 5.1 and 4.6, and 1.6 and 1.5, for vortioxetine and placebo recipients, respectively.

Vortioxetine recipients had a significantly longer time to MDD relapse than placebo recipients within the first 24 weeks of the double-blind period (primary endpoint), with a hazard ratio (HR) of 2.01 (95 % CI 1.26–3.21; $p = 0.0035$; Fig. 1) [53].

A significantly lower proportion of vortioxetine than placebo recipients relapsed (13 vs. 26 %; $p = 0.0013$) [53]. The mean worsening from baseline of the relapse-prevention period to week 24 of the relapse-prevention period was significantly lower in vortioxetine than in placebo recipients (mITT; observed cases; ANCOVA) in MADRS total (-0.6 vs. 1.4; $p < 0.01$), $HAMD_{17}$ total (0.3 vs. 1.6; $p < 0.05$) and CGI-S (-0.1 vs. 0.2; $p < 0.001$) scores [53]. There was no significant difference between vortioxetine and placebo recipients in change in HAMA total score (-0.2 vs. 0.9).

4.5 Extension Studies

Data from four open-label, phase III extension studies [65–68] (each extending one or several of the phase III trials [45–48, 50–52]) and one extension study [69] of the phase II trial [43] are available. Patients received vortioxetine at lower (2.5–10 [65, 67] or 5–10 [69] mg/day) ($n = 74$–834) [65, 67, 69] or higher (15–20 mg/day) ($n = 71$ [66] and 1,075 [68]) [66, 68] dosages for 52 weeks. Response was defined as a decrease in MADRS total score of $\geq$50 % [65–67, 69] from the baseline of the lead-in study [65, 66] or the open-label extension study [67].

MADRS total scores decreased from 10.7 [69] and 13.5 [65] at the beginning of the extension study to 5.3 [69] and 5.5 [65] at 52 weeks in patients receiving lower dosages of vortioxetine and from 16.2 [66] and 19.9 [68] to 5.0 [66] and 11.9 [68] in patients receiving higher dosages

(observed cases). The proportions of MADRS responders increased from 76 % [69] and 63 % [65] to 93 % [69] and 94 % [65] in lower-dosage and from 48 to 94 % in higher-dosage recipients [66], and the proportions of MADRS remitters increased from 58 % [69] and 42 % [65] to 82 % [69] and 83 % [65] in lower-dosage and from 32 to 81 % in higher-dosage recipients [66] (observed cases).

In the study investigating HAMD endpoints (in patients receiving vortioxetine 2.5–10 mg/day), the $HAMD_{24}$ total score at week 52 was 8.2 (down from 17.6 at the beginning of the extension study), the $HAMD_{24}$ response rate was 60 %, and the $HAMD_{17}$ remission rate was 62 % (observed cases) [67].

In one study (in patients receiving vortioxetine 2.5–10 mg/day), 9.7 % of the 226 patients in remission at the start of the extension study relapsed (MADRS total score ≥22) [65].

5 Tolerability

Vortioxetine is well tolerated in patients with MDD [4, 5, 30, 43–54, 64–69]. In a pooled analysis of clinical trials, adverse events were mostly of mild to moderate severity, transient, did not lead to treatment discontinuation, and occurred within the first 2 weeks of treatment [5]. Overall, the most common adverse event was nausea (Fig. 2a), which was more common in women than in men [4, 5]. The incidence of nausea was dose related, it was usually of mild to moderate severity, and it occurred most commonly in the first week of treatment and lasted for a median of 2 weeks [4].

In acute-treatment studies, the proportions of patients with at least one adverse event were 56–71 % in vortioxetine 5 mg/day [45, 47, 49, 50], 42–74 % in vortioxetine 10 mg/day [45, 47, 48], 57 % in vortioxetine 15 mg/day [46], 66–69 % in vortioxetine 20 mg/day [46, 48] and 43–64 % in placebo [45–50] recipients.

Where statistical data were reported, nausea occurred in a significantly ($p < 0.05$) greater proportion of vortioxetine 10 mg/day (22 %) than placebo (9 %) recipients, and diarrhoea occurred in a significantly ($p < 0.05$) smaller proportion of vortioxetine 5 mg/day (2 %) than placebo (7 %) recipients in one study [45]. Another study also reported that significantly ($p < 0.001$) more vortioxetine 15 and 20 mg/day recipients had nausea than placebo recipients (27 and 32 vs. 10 %, respectively) [46].

Serious adverse events occurred in similar proportions across treatment groups, in low numbers (<2 %), in acute-treatment, placebo-controlled trials [45–47, 49, 50]. No deaths were considered to be related to study treatment [45–47, 49, 50].

The study investigating vortioxetine 10–20 mg/day versus agomelatine 25–50 mg/day found that a total of 54 and 53 % of patients had at least one treatment-emergent adverse event [54]. The most common adverse events included nausea (16 vs. 9 %), headache (10 vs. 13 %), dizziness (7 vs. 12 %) and somnolence (4 vs. 8 %); the incidence of discontinuation as a result of treatment-emergent adverse events was 6 versus 8 %, respectively. Sleep-related adverse events occurred in 11 % of both treatment groups, sexual dysfunction occurred in <1 % of vortioxetine and 0 % of agomelatine recipients, and self-harm occurred in 0 and <1 % of patients, respectively (no adverse events were related to suicidal behaviour). Patients in both treatment groups had a general improvement in scores on MADRS item 10 (suicidal thoughts); vortioxetine recipients had a significantly greater improvement in this measure from week 4 onwards ($p < 0.05$). Serious adverse events occurred in 1 % of vortioxetine and 2 % of agomelatine recipients; none were related to self-harm, and no deaths occurred.

Approximately half as many vortioxetine 10 mg/day recipients as venlafaxine extended-release 150 mg/day recipients discontinued treatment as a result of adverse events; the most common adverse events in this acute-treatment, non-inferiority trial included nausea, dizziness, dry mouth and decreased appetite [64].

A total of 5, 6, 8 and 8 % of vortioxetine 5, 10, 15 and 20 mg/day recipients, respectively, and 4 % of placebo recipients discontinued treatment as a result of adverse reactions, in a pooled analysis of 6- to 8-week placebo-controlled trials [4]. Nausea was the most common adverse event leading to discontinuation [4].

Following abrupt discontinuation of vortioxetine 15 or 20 mg/day, some patients experienced headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week [4]. However, there was no clinically relevant difference to placebo in the incidence or nature of discontinuation symptoms in the 6- to 12-week acute-treatment studies or the 24- to 64-week longer-term studies [5].

In the acute-treatment studies, number-needed-to-harm analyses found that the number need to harm for discontinuation as a result of adverse events versus placebo was 36, and the numbers needed to harm for nausea, constipation and vomiting versus placebo were 6, 64 and 28, respectively [63].

In elderly (aged ≥65 years) patients receiving vortioxetine ≥10 mg/day, the withdrawal rate was higher than that of younger patients [5]. Moreover, elderly patients receiving vortioxetine 20 mg/day had higher incidences of nausea and constipation (42 and 15 %) than younger patients (27 and 4 %) [5]. In the trial investigating the 8-week efficacy and tolerability of vortioxetine in only

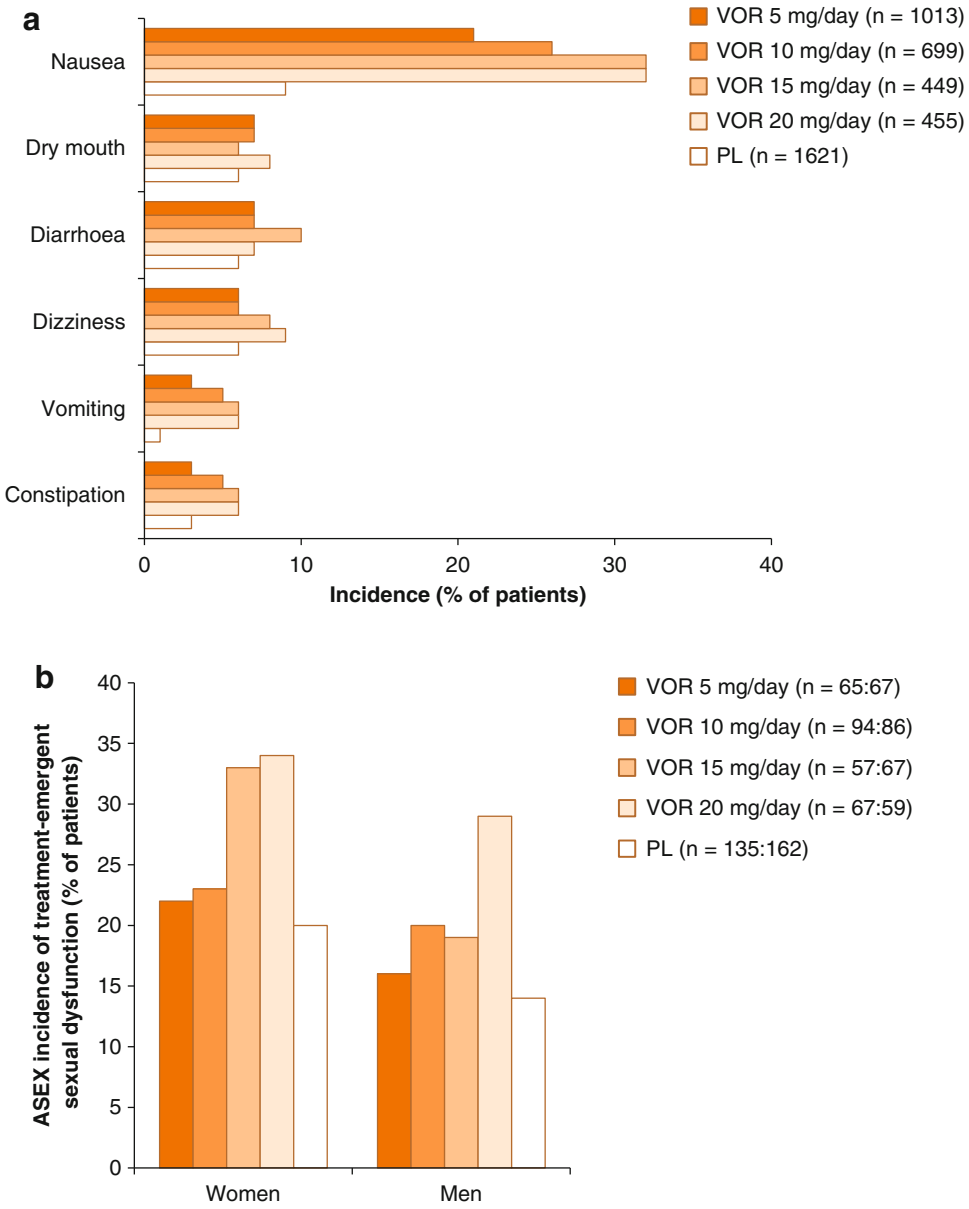

Fig. 2 Tolerability of vortioxetine 5–20 mg/day versus placebo in patients with major depressive disorder [4]. **a** Incidence of the most common adverse events (occurring in ≥5 % of patients in any vortioxetine dosage at an incidence of ≥2 % greater than that in placebo recipients) in a pooled analysis of trials covering 6–8 weeks' treatment. **b** Incidence of treatment-emergent sexual dysfunction in patients without sexual dysfunction at baseline (patients numbers are presented as women: men). Sexual dysfunction was defined as a total ASEX score ≥19, any single ASEX item score ≥5, or three or more ASEX item scores ≥4, at two concurrent visits during the study. *ASEX* Arizona Sexual Experiences Scale, *PL* placebo, *VOR* vortioxetine

elderly patients, a total of 62 % of vortioxetine 5 mg/day and 61 % of placebo recipients had at least one adverse event, serious adverse events occurred in similar proportions across treatment groups in low numbers, and there were no deaths [30]. In this study, significantly more vortioxetine 5 mg/day than placebo recipients had nausea (22 vs. 8 %) [30].

There is a boxed warning in the US prescribing information regarding an increased risk of suicidal thoughts and behaviour in children, adolescents and young adults receiving antidepressants in acute-treatment studies; patients over the age of 24 years did not have an increased risk in these studies, and there was a decreased risk in patients aged ≥65 years [4]. As a result of this class warning, close monitoring is required in patients receiving vortioxetine (as with all antidepressants) [4, 5], as is screening for the risk of bipolar disorder (symptoms of mania/hypomania have been reported in <1 % of vortioxetine recipients, in premarketing clinical trials) [4]. The incidence of suicide-related adverse events in acute-treatment vortioxetine trials was low and/or did not differ between vortioxetine and placebo recipients [45–47, 49, 50].

Sexual dysfunction is known to be a potential symptom of depression, as well as a potential adverse event linked with certain drugs. In a pooled analysis of 6- to 8-week trials, voluntarily reported sexual dysfunction adverse events occurred in 3, 4, 4 and 5 % versus 2 % of men, and

<1, 1, <1 and 2 % versus <1 % of women, receiving vortioxetine 5, 10, 15 and 20 mg/day versus placebo [4]. To allow for under-reporting of sexual-related adverse events, the Arizona Sexual Experiences Scale (ASEX) was used in addition to voluntary reporting, in a pooled analysis of seven trials [4]. Results from this analysis are shown in Fig. 2b [4]. While there was no clinically relevant difference between placebo and vortioxetine 5–15 mg/day in the incidence of treatment-emergent sexual dysfunction (using ASEX), there was a significant increase in sexual dysfunction in the vortioxetine 20 mg/day group versus the placebo group [incidence difference of 14.2 % (95 % CI 1.4–27.0)] [5].

However, vortioxetine 10–20 mg/day ($n = 225$) was associated with a significantly ($p = 0.013$) greater improvement than escitalopram 10–20 mg/day ($n = 222$) in Changes in Sexual Functioning Questionnaire Short-Form (CSFQ-14) total score (primary endpoint) after 8 weeks' treatment (mean between-group difference +2.2; 95 % CI 0.48–4.02), in a randomized, double-blind study in patients with well-controlled MDD who were experiencing treatment-emergent sexual dysfunction during treatment with prior medications (including citalopram, sertraline and paroxetine) [70]. Patients stopped treatment with their prior medication before initiating treatment with vortioxetine or escitalopram. A clinically meaningful response occurred at week 2. Baseline CSFQ scores were 36.4 in vortioxetine and 36.3 in escitalopram recipients.

Vortioxetine is not associated with clinically important changes in laboratory test results (serum chemistry [aside from sodium], haematology or urinalysis), body weight, or vital signs [4, 5]. Hyponatremia has been reported in patients receiving vortioxetine, and may be more common in elderly patients [4, 5].

There is an increased risk of the development of serotonin syndrome with serotonergic antidepressants, particularly when used concomitantly with other serotonergic drugs or drugs that impair serotonin metabolism [4, 5]. The use of vortioxetine concomitantly with monoamine oxidase inhibitors (MAOIs) is thus contraindicated [4, 5].

There is an increased risk of bleeding events with drugs that interfere with serotonin reuptake inhibition; this risk may be increased even more if the drug is used concomitantly with aspirin, non-steroidal anti-inflammatory drugs, warfarin or other anticoagulants [4, 5]. Seizures are also a potential risk with antidepressant use [5]. Vortioxetine had no effect on the incidence of insomnia or somnolence [5].

Overdosage of vortioxetine may lead to adverse events [4, 5]. A single dose of vortioxetine 40–75 mg was associated with increased rates of nausea, dizziness, diarrhoea, abdominal discomfort, generalized pruritus, somnolence and flushing [4, 5].

5.1 Longer-Term Tolerability

The five phase II [69] and III [65–68], 52-week, extension trials had tolerability data that were consistent with other studies [65–67, 69]. In these studies, 71–86 % of patients had adverse events [65–69], most of which were mild to moderate [65–67, 69]. The most common (≥10 % of patients) included nausea (15–24 % [65, 67, 68]) [65–69], headache (12–15 % [65, 67, 68]) [65–69], nasopharyngitis (11 % [65]) [65, 66] and dizziness [66]. There were 8 [65] or 18 [67] sexual dysfunction adverse events, 0–6 potentially suicide-related adverse events [65, 66, 69] (one study reported 10 % of patients experienced suicidal ideation [67]), and serious adverse events occurred in 3–4 % of patients [65, 67, 68]. A total of 6–11 % of patients withdrew from treatment as a result of adverse events [65–69], and there were either no deaths [66–69] or none considered related to treatment [65].

6 Dosage and Administration

Oral vortioxetine is indicated for the treatment of adult patients with MDD, in the US [4] and the EU [5]. The recommended starting dosage (for patients aged <65 years [5]) is 10 mg/day, taken once daily with or without food [4, 5]. The dosage may be increased to a maximum of 20 mg/day, as tolerated, and can be decreased to 5 mg/day if tolerability is an issue [4, 5]. Treatment should then continue for several months or longer (the EU recommends ≥6 months after resolution of symptoms [5]) of maintenance therapy [4, 5].

While the EU summary of product characteristics does not recommend a down-titration period for discontinuation of treatment [5], the US prescribing information recommends that higher dosages of vortioxetine (15 or 20 mg/day) be decreased to 10 mg/day for one week before full discontinuation of the drug, to avoid transient discontinuation adverse events, such as headache or muscle tension (see Sect. 5) [4].

The concomitant use of vortioxetine and MAOIs is contraindicated, as there is an increased risk of serotonin syndrome (see Sect. 5) [4, 5]. There should be a period of ≥14 [5] or ≥21 days [4] between stopping vortioxetine treatment and starting treatment with an (irreversible, non-selective [5]) MAOI, and a period of ≥14 days between stopping (irreversible, non-selective [5]) MAOI treatment and starting treatment with vortioxetine [4, 5].

The US prescribing information states that patients who are known CYP2D6 poor metabolizers should receive a maximum vortioxetine dosage of 10 mg/day, and the vortioxetine dosage should be halved when patients are receiving a concomitant CYP2D6 strong inhibitor (such as

bupropion) [4]; the EU summary of product characteristics recommends a lower dosage, depending on individual patient response [5]. When a strong CYP inducer (e.g. rifampin) is coadministered for >14 days, an increased dosage of vortioxetine may be required, according to the US prescribing information; the final dosage should not exceed three times the original dosage [4]. The EU summary of product characteristics recommends a dosage adjustment of vortioxetine, depending on patient response, in these patients [5].

No dosage adjustment for vortioxetine is recommended by the US prescribing information in elderly patients (aged ≥65 years) [4]; however, the EU summary of product characteristics states that the lowest possible dosage (5 mg/day) be used in these patients, and to use caution with dosages higher than 10 mg/day, as data for higher dosages in these patients are limited [5]. The US prescribing information recommends no dosage adjustment on the basis of race, sex, ethnicity, renal function or mild to moderate hepatic impairment [4]. The EU summary of product characteristics states that caution should be exercised when treating patients with severe renal impairment, as there are limited data in these patients [5]. Vortioxetine has not been studied in patients with severe hepatic impairment, and treatment with vortioxetine is not recommended in these patients in the US [4]; caution should be exercised with these patients in the EU [5]. The safety and efficacy of vortioxetine in paediatric patients have not been established; treatment is not recommended in this group [4, 5].

The US prescribing information contains a boxed warning regarding an increased risk of suicidal thoughts and behaviour in children, adolescents and young adults receiving antidepressants in acute-treatment studies (Sect. 5) [4]. As a result of this class warning, close monitoring is required with vortioxetine treatment (as with all antidepressants) [4, 5].

Local prescribing information should be consulted for detailed information, including contraindications, precautions, drug interactions and use in special patient populations.

7 Place of Vortioxetine in the Management of Major Depressive Disorder

Vortioxetine is one of very few novel antidepressants filed or approved in the last few years. As a drug that interacts with multiple receptors, vortioxetine exhibits several different effects on the nervous system; one or more of these may be the cause of the observed antidepressant, anxiolytic and cognitive effects in clinical and preclinical trials (see Sect. 2).

Vortioxetine was efficacious at at least one investigated dosage in many of the placebo-controlled, phase III studies. Importantly, vortioxetine 5 or 10 mg/day was significantly more efficacious than placebo at preventing relapses in a 24-week trial in patients with MDD who had achieved remission with acute vortioxetine treatment (Sect. 4.4). Vortioxetine recipients had a longer time to relapse, and vortioxetine was associated with a lower relapse rate than placebo (approximately half).

Vortioxetine was shown to be generally more efficacious than placebo at higher dosages of 15 or 20 mg/day (the indicated initial dosage is 10 mg/day) and was either more efficacious or did not significantly differ from placebo at lower dosages of 5 or 10 mg/day at improving MDD symptoms in several phase III, acute-treatment trials (Sect. 4.1.2). Secondary and other endpoint results were mixed, with some trials showing significant differences from placebo, and others not. A meta-analysis of nine acute-treatment trials showed that vortioxetine 5, 10 and 20 mg/day were significantly more efficacious than placebo in improving MADRS total score and in important secondary measures. Moreover, results were generally positive with regard to improvements in HR-QOL, both in individual trials and in a meta-analysis. Vortioxetine was also more efficacious than placebo in patients with high baseline anxiety levels (Sect. 4.1.2.1) and elderly patients (Sect. 4.1.4). Vortioxetine was associated with continued lowering of MDD symptoms and high response rates in longer-term, extension studies of 52 weeks (Sect. 4.5).

Acute treatment with vortioxetine was more efficacious than agomelatine in patients with MDD that had not adequately responded to SSRI/SNRI monotherapy, with regard to MADRS total score and several secondary endpoints, including HR-QOL measures (Sect. 4.2). As neither drug is the standard SSRI or SNRI treatment, this trial is of interest to patients who do not respond adequately to these treatments. A further trial showed that vortioxetine is non-inferior to venlafaxine in improving depression scale scores in Asian patients with MDD, with regard to change in MADRS total score, and had similar results in secondary endpoints. While these trials are of interest, further head-to-head trials would be of great use in the placement of vortioxetine in the treatment of MDD.

A full scientific report of the efficacy of vortioxetine has been published by the European Medicines Agency (EMA) [71]. Overall, the summary states that vortioxetine demonstrated efficacy in at least one dosage group across nine (seven positive and two supportive) of the twelve studies investigated, and showed an at least 2-point (clinically relevant) difference to placebo in the change from baseline in MADRS or $HAMD_{24}$ total scores [71].

One of the acute-treatment, placebo-controlled trials [45] was classified as a 'failed' trial, as it did not show a

significant difference in the primary endpoint between placebo and the active reference duloxetine. Moreover, several trials did not show any difference between vortioxetine and placebo recipients in efficacy endpoints (Sect. 4.1.2). While the reasons for the differences between clinical vortioxetine trials are not fully understood, various theories have been floated. Antidepressant clinical trials are notorious for having a high placebo response rate [72], contributing to almost half of the trials having a negative result [50]. In some trials, it is possible that a lower adverse event rate in vortioxetine than in active-reference recipients may have led to a perception of not being on an active drug, affecting informant reports concerning depressive symptoms [50]. It has also been suggested that antidepressant efficacy is less likely to be detected in trials with multiple arms and fixed dosages, or in trials with a low proportion of placebo recipients [50]. Other theories include a conservative impact of the imputation methods

trial was in Asian patients only; further trials in other patient populations are required.

In conclusion, vortioxetine is generally efficacious in the short term in patients with MDD, including elderly patients, and is more efficacious than agomelatine in patients with MDD that has not adequately responded to selective serotonin reuptake inhibitor or serotonin/norepinephrine reuptake inhibitor monotherapy. Vortioxetine is, moreover, non-inferior to venlafaxine in improving depression scale scores in Asian patients with MDD. It was also efficacious in a placebo-controlled relapse-prevention trial and in open-label extension trials. Vortioxetine is associated with improved cognitive function in patients with MDD; this does not occur solely via improvement in depressive symptom severity. It is well tolerated, but is associated with significantly increased sexual dysfunction at the highest dosage; however, vortioxetine was shown to improve previous-treatment-emergent sexual dysfunction in patients with well-treated MDD to a greater degree than escitalopram. Vortioxetine extends the available treatment options for patients with MDD, and further investigation into its comparative efficacy versus other antidepressants will allow for more accurate placement among these treatment options.

Data selection sources: Relevant medical literature (including published and unpublished data) on vortioxetine was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 1 August 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: Vortioxetine, LU-AA21004
Study selection: Studies in patients with depression who received vortioxetine. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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