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Vortioxetine: A Review in Cognitive Dysfunction in Depression

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Abstract Vortioxetine (Brintellix®; Trintellix®), a generally efficacious and well tolerated antidepressant agent, is approved in the EU and USA for the treatment of major depressive disorder (MDD) in adults. The drug has a distinctive pharmacological profile (combining inhibition of the serotonin transporter with modulation of multiple serotonin receptors) and has been shown to enhance cognitive performance in various animal models and clinical trials. Across three large, placebo-controlled studies in adults with recurrent MDD, short-term treatment with vortioxetine almost always resulted in statistically significant and clinically meaningful improvements in performance on two objective measures (the Digit Symbol Substitution Test and Rey Auditory Verbal Learning Test) that together cover a broad range of cognitive domains, including executive function, attention, processing speed, learning and memory. Vortioxetine also significantly improved a subjective measure of cognitive function (the Perceived Deficits Questionnaire) and an objective measure of functional capacity (the University of San Diego performance-based skills assessment). In general, the beneficial effects of vortioxetine on these measures were largely independent of its effect on improving depressive symptoms. Based on the available data, therefore, vortioxetine is a useful treatment option in patients with MDD where impaired cognitive function is apparent.

Vortioxetine: clinical considerations in MDD
Novel, multimodal antidepressant
Administered once daily
Improves measures of cognitive performance in patients with MDD
Antidepressive efficacy and an overall safety profile similar to that of existing first-line antidepressants
Most common adverse events include nausea and vomiting
Associated with a low level of sexual dysfunction

1 Introduction

Major depressive disorder (MDD) is frequently accompanied by cognitive deficits that contribute to a diminished quality of life and reduced psychosocial functioning, particularly in terms of workplace productivity [1–5]. Reduced role functioning is the principal source of cost and illness-associated morbidity in MDD, which is the leading cause of disability worldwide [6].

Cognitive dysfunction in MDD encompasses several domains, most commonly small to moderate deficits in attention, memory, learning, processing speed and executive function [4]. Importantly, it is often an epiphenomenon,

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correlating with, but dissociable from, affective symptoms; impairments in cognitive functioning (as well as in psychosocial functioning) may persist even after patients have met conventional criteria for remission of depressive symptoms [4, 6, 7]. As it may assist in achieving and sustaining a full functional recovery, reaching 'cognitive remission' is increasingly being promulgated as an important additional goal in the treatment of MDD [4, 5, 7].

Vortioxetine (Brintellix®; Trintellix®) is a novel multimodal antidepressant with two types of action towards the serotonergic neurotransmitter system: it inhibits the serotonin transporter (SERT) and, additionally, modulates the effects of several serotonin (5-HT) receptors [8, 9]. In 2013, vortioxetine was approved for the treatment of MDD in adults in the EU [10] and the USA [11]. Subsequently, in 2015, the EU summary of product characteristics (SPC) [10] was updated to include the effects of the drug on certain aspects of cognitive and general functioning in patients with MDD. This narrative review, which is written from a European perspective, summarizes the pharmacological properties and tolerability of vortioxetine and focuses on its effects on cognitive and general functioning in adults with MDD. Detailed discussion of the antidepressive efficacy of vortioxetine (reviewed in detail elsewhere [8, 9, 12–15]) is beyond the scope of the current article.

2 Pharmacological Properties of Vortioxetine

The pharmacodynamic and pharmacokinetic properties of vortioxetine have been reviewed previously [9, 12, 14]; therefore, this section provides only a very brief overview.

Vortioxetine binds to human SERT with high affinity ($K_i = 1.6$ nM) and potently and selectively inhibits 5-HT reuptake (half maximal inhibitory concentration = 5.4 nM) [11, 12]. It is an agonist at the human 5-HT_{1A} receptor (binding with a K_i of 15 nM), a partial agonist at the human 5-HT_{1B} receptor (K_i of 33 nM), an antagonist at the human 5-HT_3 receptor (K_i of 3.7 nM), an antagonist at the human 5-HT_7 receptor (K_i of 19 nM), and an antagonist at the human 5-HT_{1D} receptor (K_i of 54 nM) [11, 12]. The concerted effect of vortioxetine on these multiple serotonergic targets appears to directly and indirectly modulate neurotransmission in several systems, including the serotonergic, noradrenergic, dopaminergic, histaminergic, cholinergic and glutaminergic systems (in which neurotransmission is increased) and the GABAergic system (in which neurotransmission is decreased) [9, 10, 12]. This activity across several systems is thought to account for the antidepressant, anxiolytic-like and procognitive effects of vortioxetine seen in preclinical studies, although the exact underlying mechanism(s) of action have yet to be fully elucidated [10, 12]. In addition to the direct and indirect modulation of several neurotransmitter systems through interactions with multiple 5-HT targets, other aspects of the pharmacological profile of vortioxetine that differ from that of selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitor (SNRIs) include activity in SSRI/SNRI-insensitive models of depression and the reversal of cognitive deficits in various animal models [9].

In a randomized functional magnetic resonance imaging study in patients with recurrent MDD (abstract presentation [16]), patients remitted from MDD ($n = 48$), but not healthy controls ($n = 48$), who were treated with vortioxetine 20 mg/day for 2 weeks demonstrated significantly reduced neural activity within the right dorsolateral prefrontal cortex ($p < 0.05$ vs. placebo) and left hippocampus ($p < 0.01$) during completion of a working memory (N-back) test. Significantly ($p = 0.03$) reduced activity within these areas was also seen when the two subject groups were analysed together [17]. Acute and remitted MDD has previously been associated with increased activity within these regions; this raises the possibility that the cognitive effects seen in patients with MDD (Sect. 3) may be mediated, at least in part, by normalizing effects of vortioxetine on neural systems supporting working memory [16].

The pharmacokinetic profile of vortioxetine is linear and dose-proportional over the range 2.5–60 mg/day, and is unaffected by the presence of food [10]. The drug is slowly, but well absorbed, after oral administration, with a time to peak plasma concentration of 7–11 h and an absolute bioavailability of 75%. Steady-state plasma concentrations are achieved in ≈2 weeks. Vortioxetine is almost entirely (98–99%) bound to plasma proteins and has a mean volume of distribution of 2600 L [10].

Vortioxetine is extensively metabolized in the liver, primarily through oxidation (mainly mediated by CYP2D6) and subsequent glucuronidation [10, 12]. The resulting inactive metabolites are excreted in the urine (approximately two-thirds) and faeces (approximately one-third) [10, 12]. The drug has a mean oral clearance of 33 L/h and a mean terminal elimination half-life of 66 h [10].

Plasma concentrations of vortioxetine are approximately two times higher in CYP2D6 poor metabolizers than extensive metabolizers; however, there are no specific dosing recommendations in relation to CYP2D6 metabolizer status [10]. Exposure to vortioxetine is increased when coadministered with a strong CYP2D6 inhibitor (e.g. bupropion, fluoxetine, paroxetine or quinidine) and decreased when coadministered with a broad CYP inducer (e.g. rifampicin, carbamazepine, phenytoin). Accordingly, depending on the individual patient response, a lower dosage may be considered if vortioxetine is coadministered with a strong CYP2D6 inhibitor, and a dose adjustment

(i.e. increase) may be considered if the drug is coadministered with a broad CYP inducer [10]. Vortioxetine shows no significant in vitro inhibition or induction of CYP isoenzymes or P-glycoprotein [9, 10, 12].

The pharmacokinetics of vortioxetine are not affected to a clinically relevant extent by sex [12], race [12], renal impairment (mild, moderate, severe or endstage renal disease [12]) or hepatic impairment (mild, moderate or severe [18]). Exposure to vortioxetine was up to 27% higher in healthy volunteers aged ≥65 years compared with those aged ≤45 years [10]; dosing recommendations for elderly patients are summarized in Sect. 5.

3 Therapeutic Efficacy of Vortioxetine

The short-term effects of vortioxetine on cognitive functioning in patients with recurrent, moderate to severe MDD have been investigated in three randomized, double-blind, placebo-controlled, multinational studies of 8 weeks' duration [19–21]. Assessing the efficacy of vortioxetine on cognitive function was the primary aim of two of these studies (FOCUS [19] and CONNECT [20]); it was a secondary objective of the third—and earliest—study (ELDERLY) [21]. The short-term effect of vortioxetine on functional capacity was also examined in CONNECT [20].

Eligible patients ($n = 602$ [19], 602 [20] and 453 [21] randomized) were men and women aged 18–65 [19, 20] or ≥65 [21] years, and were required to have: a primary diagnosis of MDD (according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision) criteria; [19–21]; a current major depressive episode (MDE) of ≥4 weeks' [21] or ≥3 months' [19, 20] duration; and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score ≥26 at screening and baseline visits [19–21]. Additionally, all patients enrolled in CONNECT reported subjective cognitive dysfunction (e.g. difficulty concentrating, slow thinking, and difficulty in learning new things or remembering things) [20].

Patients randomized to vortioxetine received either fixed (5 [21], 10 [19] or 20 [19] mg/day) or flexible (10–20 mg/day [20]) dosages of the drug. Two [20, 21] of the three studies included duloxetine 60 mg/day as an active reference for assay sensitivity.

3.1 Cognition Outcomes

Short-term treatment with vortioxetine 5–20 mg/day significantly improved cognitive function in adults with recurrent MDD (including those with self-reported cognitive dysfunction), based on the results of various objective neuropsychological tests covering multiple domains, notably the Digit Symbol Substitution Test (DSST), which measures executive functioning, processing speed and attention, and the Rey Auditory Verbal Learning Test (RAVLT), which measures learning (RAVLT acquisition; $RAVLT_{acq}$) and memory (RAVLT delayed recall; $RAVLT_{delay}$) [19–21] (Table 1).

In particular, fixed [19] or flexible [20] dosages of vortioxetine 10–20 mg/day were more effective than placebo for the primary (cognition) endpoint in CONNECT (change from baseline to week 8 in DSST score) and FOCUS (change from baseline to week 8 in a weighted composite z-score of DSST, $RAVLT_{acq}$ and $RAVLT_{delay}$) (see Table 1). DSST and RAVLT scores were secondary endpoints in FOCUS [19] and ELDERLY [21]; these were significantly ($p < 0.05$) improved with vortioxetine compared with placebo, with the exception of the $RAVLT_{delay}$ score in vortioxetine 20 mg/day recipients in FOCUS (Table 1). Moreover, where reported, the statistically significant improvements in these cognitive measures were clinically meaningful, based on Cohen's d effect sizes that exceeded the standard 0.2 threshold for clinical relevance (Table 1).

In FOCUS, the favourable effect of vortioxetine on the DSST was seen in most subgroups of patients defined by age, sex, body mass index, educational level, working status, number of previous MDEs and duration of current MDE (abstract presentation [22]). A post hoc analysis suggested that the effect of vortioxetine on this measure of cognition was more pronounced in working patients with MDD than in the total MDD population [23]. The placebo-adjusted changes from baseline to week 8 in DSST scores with the 10 and 20 mg/day dosages were 4.0 and 4.0 in all patients ($n = 193$ and 204), 5.6 and 5.0 in the subgroup of working patients ($n = 108$ and 117), and 9.2 and 9.0 in the subgroup of working patients identified as 'professional' (e.g. manager/administrator positions; $n = 31$ and 38) [all $p \leq 0.006$ versus placebo; higher values indicate better performance] [23]. Standardized effect sizes with the 10 and 20 mg/day dosages were 0.48 and 0.48 in all patients, 0.61 and 0.56 in working patients, and 0.71 and 0.79 in 'professionals' [23].

Importantly, the beneficial effects of vortioxetine on these measures of cognitive functioning were mostly independent of its effect on improving depressive symptoms, as assessed by the MADRS or HAM_{24} [19–21, 23, 24]. For example, the results of multiple regression analyses (path analysis) indicated that the direct effect of vortioxetine on DSST score ranged between 56 and 83% [19–21]. According to a meta-analysis of all three studies, vortioxetine significantly ($p < 0.0001$) improved the DSST score with a standardized effect size of 0.35 before, and 0.24 after, adjusting for the change in MADRS total score [24]. In FOCUS, the more pronounced effect of vortioxetine on the DSST in the subgroup of working

Table 1 Effect of vortioxetine on assessments of cognitive function in adults with recurrent, moderate-to-severe major depressive disorder. Summary of key neuropsychological test results from three placebo-controlled studies

Treatment[a] (mg/day) [no. of pts[b]]	FOCUS [19]		CONNECT [20]		ELDERLY [21]	
	VOR 10 [$n = 193$]	VOR 20 [$n = 204$]	VOR 10–20 [$n = 175$]	DUL 60 [$n = 187$]	VOR 5 [$n = 155$]	DUL 60 [$n = 148$]
Endpoint[c]						
Objective tests[d]						
$DSST/RAVLT_{acq}/RAVLT_{delay}$ (weighted composite z-score[e])	0.36***[f]	0.33***[f]				
DSST [SES[g]]	4.20*** [0.51]	4.26*** [0.52]	1.75*[f] [0.254]	1.21[f] [0.176]	2.79* [0.25]	0.77 [0.07]
$RAVLT_{acq}$ [SES[g]]	1.02* [0.23]	0.59 [0.13]			1.14* [0.27]	1.41** [0.33]
$RAVLT_{delay}$ [SES[g]]	0.71** [0.31]	0.65** [0.28]			0.47* [0.24]	0.64** [0.32]
TMT-A (s) [SES[g]]	−3.8** [0.29]	−3.8** [0.29]	−1.05	−1.41		
TMT-B (s) [SES[g]]	−7.6** [0.29]	−9.0*** [0.35]	−9.67***	−5.54		
$Stroop_{congruent}$ (s) [SES[g]]	−4.0** [0.33]	−4.5*** [0.37]	1.07	−0.18		
$Stroop_{incongruent}$ (s) [SES[g]]	−6.8*** [0.35]	−6.5*** [0.34]	−0.05	−1.72		
Subjective measures[h]						
$PDQ_{total\ score}$	−4.4***	−5.7***				
$PDQ_{attention/concentration\ subscore}$	−1.5***	−1.9***	−2.6***[i]	−3.0***[i]		
$PDQ_{planning/organization\ subscore}$	−1.0*	−1.6***	−2.6***[i]	−3.0***[i]		
$PDQ_{prospective\ memory\ subscore}$	−0.8**	−0.8**				
$PDQ_{retrospective\ memory\ subscore}$	−1.0**	−1.3***				
$CPFQ_{total\ score}$			−1.2	−1.7*		

CPFQ Cognitive and Physical Functioning questionnaire, *DSST* Digit Symbol Substitution Test (number of correct symbols) score, *DUL* duloxetine, *PDQ* Perceived Deficits Questionnaire, *pts* patients, $RAVLT_{acq}$ Rey Auditory Verbal Learning Test acquisition score, $RAVLT_{delay}$ Rey Auditory Verbal Learning Test delay recall score, *SES* standardized effect size, *TMT-A/-B* Trail Making Test part A/B, *VOR* vortioxetine

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

[a] All treatments were administered orally, once-daily

[b] Full analysis set

[c] All values are mean [19, 21] or least-squares mean [20] placebo-adjusted changes from baseline to week 8

[d] DSST measures executive functioning, processing speed and attention; $RAVLT_{acq}$ measures learning; $RAVLT_{delay}$ measures memory; TMT-A measures processing speed; TMT-B measures executive function; Stroop Tests measure executive function. For all tests except TMT-A/-B and $Stroop_{congruent}/Stroop_{incongruent}$, higher scores indicate better performance; for TMT-A/-B and $Stroop_{congruent}/Stroop_{incongruent}$, lower times indicate better performance. Only baseline values for DSST [41.6–46.3 correct symbols across all study groups (score range 0–133)] [19–21], $RAVLT_{acq}$ [22.0–22.6 words (score range 0–45)] [19, 21] and $RAVLT_{delay}$ [5.7–6.6 words (score range 0–15)] [19, 21] are available from two or more studies

[e] DSST, $RAVLT_{acq}$ and $RAVLT_{delay}$ were assigned weights of 0.5, 0.25 and 0.25, respectively

[f] Primary outcome measure

[g] Cohen's d vs. placebo. A SES of 0.2 is the threshold for clinical relevance; scores of 0.2, 0.5 and 0.8 indicate small, medium and large effect sizes, respectively

[h] For PDQ (total score range 0–80; subscore range 0–20), higher scores indicate greater perceived cognitive impairment. For CFPQ (score range 0–36), higher scores indicate greater patient-reported dysfunction

[i] Attention/concentration and planning/organization (summed subscore)

patients with MDD did not appear to be mediated by the larger antidepressant response that was observed in this population [23]. After adjusting for the change in MADRS total score, the placebo-adjusted changes from baseline to week 8 in DSST scores with vortioxetine 10 and 20 mg/day were 2.6 and 2.2, respectively, in all patients, and 3.8 and 2.8, respectively, in the subgroup of working patients (all $p \leq 0.021$ versus placebo) [23].

Significant ($p < 0.001$) improvements with vortioxetine versus placebo were seen on all other neuropsychological tests that were secondary cognition endpoints in FOCUS, namely the Trail Making Test part A (TMT-A; a measure of processing speed) (Table 1), the Trail Making Test part B (TMT-B; a measure of executive functioning) (Table 1), the Stroop Tests (measures of executive functioning) (see Table 1), the Simple reaction time task (SRT; a measure of

processing speed) and the Choice reaction time task (CRT; a measure of attention) [19]. In the post hoc analysis [23], both vortioxetine dosages significantly ($p \leq 0.036$ vs. placebo) improved the TMT-A, TMT-B and Stroop Tests in working patients and 'professionals', with only one exception, namely the 10 mg dosage did not significantly improve the $\text{Stroop}_{\text{congruent}}$ test in 'professionals'.

In CONNECT, the TMT-B was the only secondary cognition endpoint to show a significant ($p < 0.001$) improvement with vortioxetine relative to placebo (Table 1); no significant improvements were seen on the Groton Maze Learning Test (a measure of visual learning and memory), the Detection Task (a measure of processing speed), the Identification Task (a measure of attention) and the One-Back Task (a measure of attention and memory) [20].

Regarding subjective (patient-reported) cognitive measures, vortioxetine was associated with significant ($p < 0.05$) improvements on the Perceived Deficits Questionnaire (PDQ), which was administered in FOCUS and CONNECT, but not the Cognitive and Physical Functioning Questionnaire (CPFQ), which was only administered in CONNECT (Table 1). The post hoc analysis of FOCUS [23] suggested that the effect of vortioxetine on the PDQ was more pronounced in 'professionals' with MDD. The placebo-adjusted changes from baseline to week 8 in PDQ total scores with the 10 and 20 mg/day dosages were −4.4 and −5.7 in all patients, −4.9 and −5.7 in the subgroup of working patients, and −8.3 and −11.5 in the subgroup of 'professionals' (all $p \leq 0.048$ versus placebo; larger negative values indicate greater improvements in perceived cognitive dysfunction) [23].

Unlike vortioxetine, duloxetine did not significantly improve performance on the DSST (Table 1). Although the effect of vortioxetine on the DSST did not differ significantly from that of duloxetine in CONNECT (which was not powered to detect differences between the two treatments) [20], it did differ significantly from that of duloxetine in a meta-analysis of CONNECT and ELDERLY (standard effect size of 0.16; $p < 0.05$) [24]. Like vortioxetine, duloxetine significantly improved performance on the RAVLT (Table 1); overall, the cognitive effects of this SNRI, in particular in ELDERLY, were consistent with those seen in an earlier trial in elderly patients with recurrent MDD [25].

3.2 Functional Capacity

In contrast to patients receiving duloxetine 60 mg/day in CONNECT, those receiving vortioxetine 10–20 mg/day demonstrated significant ($p < 0.001$) improvement versus placebo on the University of San Diego performance-based skills assessment (UPSA), an objective measure of functional capacity [20]. The least-squares mean placebo-adjusted change from baseline to week 8 in the UPSA composite score was 2.94 versus 0.38 in the vortioxetine and duloxetine groups, respectively ($p = 0.001$ for the between-group comparison) [20]. In the vortioxetine group, the magnitude of the change in UPSA composite score from baseline exceeded the proposed minimal clinically important difference on this measure (abstract presentation [26]). Moreover, path analysis indicated that almost all ($\approx$97%) of the effect of vortioxetine on the UPSA composite score was direct (abstract presentation [27]). The favourable effect of vortioxetine on the UPSA was seen in all patient subgroups based on age, sex, baseline disease severity, educational level, number of previous MDEs and duration of current MDE (post hoc analyses; abstract presentations [28, 29]).

4 Tolerability of Vortioxetine

Vortioxetine was generally well tolerated, both in short- and longer-term studies [9, 12, 30]. Nausea, the most common treatment-emergent adverse event (TEAE) associated with the drug, was dose-related; it occurred in 20.9–31.2% of vortioxetine 5–20 mg/day recipients ($n = 3018$) versus 8.1% of placebo recipients ($n = 1817$), 33.6% of venlafaxine extended-release (ER) 225 mg/day recipients ($n = 113$) and 34.1% of duloxetine 60 mg/day recipients ($n = 753$), based on data pooled from 11 short-term (6–8 weeks), placebo-controlled studies in patients with MDD [30], including two [19, 21] of the three trials discussed in Sect. 3. In ELDERLY [21], nausea was the only TEAE reported with an incidence ≥5% that occurred more than two times more frequently in the vortioxetine 5 mg/day group than in the placebo group (21.8 vs. 8.3%; $p < 0.01$). Nausea associated with vortioxetine was dose-related, usually of mild to moderate severity, most commonly occurred in the first week of treatment, and was most often transient (median duration 9–16 days) [9, 12, 30]. Apart from nausea, vomiting was the only other TEAE reported by more than twice as many vortioxetine-treated patients compared with placebo-treated patients; it was also dose-related, occurring in 2.9–6.5% of vortioxetine 5–20 mg/day recipients versus 1.1% of placebo recipients, 3.5% of venlafaxine ER recipients and 4.1% of duloxetine recipients [30].

Similar proportions of vortioxetine 5–20 mg/day and placebo recipients reported serious TEAEs (0.6 vs. 0.5%), suicide-related events (0.4 vs. 0.3%), TEAEs possibly associated with hostility/aggression (1.6 vs. 2.5%), insomnia (2.0–5.1 vs. 4.0%) and sexual dysfunction (1.6–1.8 vs. 1.0%). For men and women, respectively, the incidences of sexual function TEAEs were 2.8–3.6 and

0.6–1.1% with vortioxetine versus 1.6 and 0.7% with placebo, 21.6 and 4.8% with venlafaxine ER, and 11.7 and 1.2% with duloxetine [30].

Discontinuations due to TEAEs occurred in 4.5–7.8% of vortioxetine 5–20 mg/day recipients versus 3.6% of placebo recipients, 14.2% of venlafaxine ER recipients and 8.8% of duloxetine recipients [30]. For vortioxetine, the most common TEAE leading to cessation of therapy was nausea (in 1.2–3.8% of patients) [30].

Vortioxetine 5–20 mg/day showed no effect relative to placebo in terms of changes from baseline in bodyweight, clinical laboratory values and cardiovascular and ECG parameters [30].

No new types of TEAEs were seen in five long-term (52-week), open-label extensions of short-term placebo-controlled studies [30]. The mean change in bodyweight from baseline in the core studies to the last assessment in the extension studies was 0.8 and 0.7 kg in vortioxetine 5–10 and 15–20 mg/day recipients, respectively ($n = 1297$ and 1105) [30].

Abrupt discontinuation of vortioxetine after short- (6–12 weeks) or longer-term (24–64 weeks) treatment was associated with a low/placebo level of discontinuation symptoms [10, 30]; this may be a reflection of its relatively long terminal elimination half-life (Sect. 2) [9, 30].

5 Dosage and Administration of Vortioxetine

In the EU, the recommended starting dosage of vortioxetine is 10 mg/day (5 mg/day in adults aged ≥65 years), taken once daily with or without food [10]. Depending on the individual patient response, the dosage may be increased to a maximum of 20 mg/day or reduced to a minimum of 5 mg/day. However, caution is advised if dosages higher than 10 mg/day are used in patients aged ≥65 years (as only limited data are available) [10]. Caution is also advised when treating patients with severe renal impairment (as only limited data are available) or severe hepatic impairment (as this population has not been studied) [10]. Treatment for ≥6 months after resolution of depressive symptoms is recommended for consolidation of the antidepressive response [10]. Vortioxetine treatment can be terminated abruptly, i.e. without gradually reducing the dose [10].

The concomitant use of vortioxetine and nonselective monoamine oxidase inhibitors (MAOIs) is contraindicated, as there is an increased risk of serotonin syndrome. The combination of vortioxetine with a reversible, selective monoamine oxidase type A inhibitor is also contraindicated [10].

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

6 Current Status of Vortioxetine in the Management of Cognitive Dysfunction in Depression

Some conventional antidepressants, including SSRIs and SNRIs, may to a degree improve cognitive deficits associated with MDD, although the majority of supporting studies have been limited by small sample sizes, absence of placebo controls, a lack of pre-specification of cognition as a primary outcome, and an inability to differentiate between direct and indirect effects [4, 31, 32].

Against this background, vortioxetine is a generally efficacious and well tolerated antidepressant already approved in the EU and USA for the treatment of MDD in adults [12] (Sect. 1). The drug has a distinctive pharmacological profile comprising multiple activities (SERT inhibitor, 5-HT_{1A} agonist, 5-HT_{1B} partial agonist, and 5-HT_3, 5-HT_7 and 5-HT_{1D} antagonist) (Sect. 2); it has also been shown to augment cognitive performance in various preclinical (Sect. 2) and clinical (Sect. 3) studies. The 5-HT system is thought to have a role in regulating prefrontal cortical circuitries involved in cognitive processing; several possible pathways whereby drugs acting through multiple serotonergic targets (e.g. vortioxetine) may robustly improve cognitive dysfunction have been postulated [1, 33].

Across three large, placebo-controlled studies in adults with recurrent MDD, short-term treatment with vortioxetine improved performance on the DSST and RAVLT, two objective measures that together cover a broad range of cognitive domains, including executive function, attention, processing speed, learning and memory (Sect. 3.1). Moreover, although generally modest in magnitude, the observed improvements in these measures of cognitive function were, in most cases, clinically meaningful (Table 1) and largely independent of the observed improvements in depressive symptoms (Sect. 3.1). Based on the results of FOCUS and CONNECT, vortioxetine is the first antidepressant to demonstrate replicated evidence of efficacy in mitigating cognitive dysfunction in studies in which a cognitive endpoint was the pre-specified primary outcome [6, 13]. Vortioxetine recipients also showed a significant improvements on the PDQ, but not the CFPQ (both subjective measures of cognitive function) (Sect. 3.1), and a significant and clinically meaningful improvement on the UPSA (an objective measure of functional capacity) (Sect. 3.2). Interestingly, a post hoc analysis of data from FOCUS suggested that the beneficial effects of vortioxetine on objective (DSST) and subjective (PDQ) measures of cognitive function were more pronounced in working patients with MDD (particularly those in manager/administrator positions) than in the total trial

population, which included both working and non-working patients (Sect. 3.1). However, this study was not designed to directly compare cognitive outcomes with vortioxetine in working versus non-working patients with MDD; therefore, further research to more definitively address this issue would be welcome [23].

The effects of vortioxetine on the DSST, PDQ, CPFQ and UPSA are acknowledged in the EU SPC [10] (Sect. 1); the drug is currently unique among antidepressants in this regard. The DSST data have yet to achieve similar status in the US PI; however, along with issuing a complete response letter, the FDA has expressed the view that cognitive dysfunction is a legitimate target for drug development [34].

Among the various antidepressant agents thus far assessed, evidence for a positive, direct effect across multiple cognitive domains is relatively strong for vortioxetine, but relatively weak for other agents (e.g. SSRIs, SNRIs and buproprion). For duloxetine (an SNRI), there is relatively strong evidence for an effect on learning and memory only [6]. Since head-to-head trials help confirm the relative benefits (and harms) of interventions, the results of a completed phase 3 comparison of vortioxetine versus escitalopram on cognitive dysfunction in patients with an inadequate response to current antidepressant treatment (NCT02272517) are awaited with interest. In addition, as it is currently unclear whether treatments capable of improving cognitive function can also improve overall health outcomes (e.g. workplace performance) [6], the results of exploratory studies (NCT02279966; NCT02332954) evaluating vortioxetine in this area of interest are keenly anticipated. Given that the principal determinant of costs in MDD is impaired role function, notably in the workplace [13], pharmacoeconomic assessments of vortioxetine in working patients with MDD are also desirable.

Vortioxetine has an antidepressive efficacy and overall safety profile similar to that of existing first-line agents (SSRIs and SNRIs) [14]. Notably, however, it has shown low rates of sexual dysfunction [15], similar to placebo (Sect. 4). Additionally, it appears to have a favourable weight-gain profile [35] (Sect. 4). Currently, the drug is viewed as being a good first- and/or second-line treatment option [8, 14], although (the results of) comparative studies are needed to correctly place it relative to other antidepressants. Possible scenarios whereby clinicians could consider switching from the treatment in course to vortioxetine include when the patient is experiencing: (1) cognitive symptoms, despite an improvement in mood symptoms; (2) a treatment-related decline in sexual functioning; or (3) an inadequate therapeutic response [8].

In conclusion, based on positive cognitive outcomes from placebo-controlled clinical trials (FOCUS, CONNECT and ELDERLY), vortioxetine is a useful treatment option in patients with MDD where impaired cognitive function is apparent.

Data selection sources: Relevant medical literature (including published and unpublished data) on vortioxetine was identified by searching databases including MEDLINE (from 1946), PubMed (from 1946) and EMBASE (from 1996) [searches last updated 29 August 2016], 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, Brintellix, Trintellix, MDD, depress*, antidepressant, cognitive *function, memory, attention.
Study selection: Studies in patients with major depressive disorder 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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Compliance with Ethical Standards

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References

1. Pehrson AL, Sanchez C. Serotonergic modulation of glutamate neurotransmission as a strategy for treating depression and cognitive dysfunction. CNS Spectr. 2014;19(2):121–33.
2. Richelson E. Multi-modality: a new approach for the treatment of major depressive disorder. Int J Neuropsychopharmacol. 2013;16(6):1433–42.
3. Keefe RS, McClintock SM, Roth RM, et al. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. J Clin Psychiatry. 2014;75(8):864–76.
4. Bortolato B, Miskowiak KW, Kohler CA, et al. Cognitive remission: a novel objective for the treatment of major depression? BMC Med. 2016;14(1):9.
5. Lam RW, Kennedy SH, McIntyre RS, et al. Cognitive dysfunction in major depressive disorder: effects on psychosocial functioning and implications for treatment. Can J Psychiatry. 2014;59(12):649–54.
6. McIntyre RS, Xiao HX, Syeda K, et al. The prevalence, measurement, and treatment of the cognitive dimension/domain in major depressive disorder. CNS Drugs. 2015;29(7):577–89.
7. McIntyre RS, Lee Y, Mansur RB. Treating to target in major depressive disorder: response to remission to functional recovery. CNS Spectr. 2015;20(Suppl 1):20–30.
8. Alvarez E, Perez V, Artigas F. Pharmacology and clinical potential of vortioxetine in the treatment of major depressive disorder. Neuropsychiatr Dis Treat. 2014;10:1297–307.

9. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther. 2015;145:43–57.
10. H. Lundbeck A/S. Brintellix 5 mg film-coated tablets: EU summary of product characteristics 2015. http://www.ema.europa.eu. Accessed 26 Aug 2016.
11. Takeda Pharmaceuticals America Inc. Trintellix (vortioxetine) tablets, for oral use: US prescribing information. 2016. https://us.trintellix.com/. Accessed 12 May 2016.
12. Garnock-Jones KP. Vortioxetine: a review of its use in major depressive disorder. CNS Drugs. 2014;28(9):855–74.
13. Al-Sukhni M, Maruschak NA, McIntyre RS. Vortioxetine: a review of efficacy, safety and tolerability with a focus on cognitive symptoms in major depressive disorder. Expert Opin Drug Saf. 2015;14(8):1291–304.
14. Connolly KR, Thase ME. Vortioxetine: a new treatment for major depressive disorder. Expert Opin Pharmacother. 2016;17(3):421–31.
15. Tritschler L, Felice D, Colle R, et al. Vortioxetine for the treatment of major depressive disorder. Expert Rev Clin Pharmacol. 2014;7(6):731–45.
16. Browning M, Smith J, Conen S, et al. Vortioxetine reduces BOLD signal during performance of the N-back task in subjects remitted from depression and healthy control participants [abstract no. P.1.i.026]. Eur Neuropsychopharmacol. 2015;25(Suppl 2):S314–5.
17. Browning M, Smith J, Conen S, et al. Vortioxetine reduces bold signal during performance of the N-Back task in subjects remitted from depression and healthy control participants [abstract no. W12]. Neuropsychopharmacology. 2014;39:S480.
18. Chen G, Nomikos G, Affinito J, et al. Single-dose pharmacokinetics of vortioxetine in subjects with mild, moderate, or severe hepatic impairment [poster LB-005]. In: 117th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics; 2016.
19. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. Int J Neuropsychopharmacol. 2014;17(10):1557–67.
20. Mahableshwarkar AR, Zajecka J, Jacobson W, et al. A randomized, placebo-controlled, active-reference, double-blind, flexible-dose study of the efficacy of vortioxetine on cognitive function in major depressive disorder. Neuropsychopharmacology. 2015;40(8):2025–37.
21. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. Int Clin Psychopharmacol. 2012;27(4):215–23.
22. Lophaven S, Olsen CK, McIntyre RS. Effect of vortioxetine on cognitive dysfunction in subgroups of adult MDD patients: a randomized, double-blind, placebo-controlled study [abstract no. 54]. In: 168th Annual Meeting of the American Psychiatric Association; 2015.
23. McIntyre RS, Florea I, Tonnoir T, et al. Efficacy of vortioxetine on cognitive functioning in working subjects with major depressive disorder. J Clin Psychiatry. 2016. doi:10.4088/JCP.16m10744.
24. McIntyre RS, Harrison J, Loft H, et al. The effects of vortioxetine on cognitive function in patients with major depressive disorder: a meta-analysis of three randomized controlled trials. Int J Neuropsychopharmacol. 2016. doi:10.1093/ijnp/pyw055.
25. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. Am J Psychiatry. 2007;164(6):900–9.
26. Harvey P, Jacobson W, Zhong W, et al. Validation and determination of minimal clinically important differences and treatment response for the UCSD performance-based skills assessment (UPSA) in major depressive disorder [abstract W26]. In: Annual Meeting of the American Society of Clinical Psychopharmacology; 2016.
27. Jacobson W, Harvey P, Merikle E, et al. Impact of vortioxetine on functional capacity in MDD patients with subjective cognitive dysfunction: performance on the University of California San Diego performance-based skills assessment (UPSA) [abstract no. M71]. Neuropsychopharmacology. 2015;40:S150–1.
28. Jacobson W, Harvey PD, Zhong W, et al. Impact of vortioxetine on functional capacity in MDD patients with cognitive dysfunction: a USCD performance-based skills assessment [abstract TH24]. In: Annual Meeting of the American Society of Clinical Psychopharmacology; 2016.
29. Keefe R, Keefe RSE, Jacobsen W, et al. A post hoc subgroup analysis of the impact of vortioxetine on functional capacity, as measured by UPSA, in MDD patients with subjective cognitive dysfunction [abstract W21]. In: Annual Meeting of the American Society of Clinical Psychopharmacology; 2016.
30. Baldwin DS, Chrones L, Florea I, et al. The safety and tolerability of vortioxetine: analysis of data from randomized placebo-controlled trials and open-label extension studies. J Psychopharmacol (Oxf). 2016;30(3):242–52.
31. Rosenblat JD, Kakar R, McIntyre RS. The cognitive effects of antidepressants in major depressive disorder: a systematic review and meta-analysis of randomized clinical trials. Int J Neuropsychopharmacol. 2015;19(2):1–13.
32. Takeda Development Center Americas Inc., H. Lundbeck A/S. Sponsor briefing document. Brintellix (vortioxetine). Supplement for cognitive dysfunction in major depressive disorder. http://www.fda.gov. Accessed 2 Jun 2016.
33. Leiser SC, Li Y, Pehrson AL, et al. Serotonergic regulation of prefrontal cortical circuitries involved in cognitive processing: a review of individual 5-HT receptor mechanisms and concerted effects of 5-HT receptors exemplified by the multimodal antidepressant vortioxetine. ACS Chem Neurosci. 2015;6(7):970–86.
34. Takeda Pharmaceuticals America Inc. Takeda and Lundbeck receive complete response letter for Brintellix® (vortioxetine) sNDA [media release]. https://www.takeda.com. Accessed 30 May 2016.
35. Citrome L. Vortioxetine for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract. 2014;68(1):60–82.