Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Vortioxetine

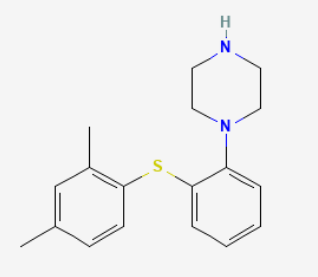
Evidence Summary

Vortioxetine may improve cognitive function in people with depression, but effects in other conditions are inconclusive. Nausea and diarrhea are common adverse events. It may also increase bleeding.

Neuroprotective Benefit: In people with depression, vortioxetine appears to improve multiple domains of cognitive function independent of its effects on mood and depression. Cognitive effects in neurodegenerative diseases are mixed and inconsistent.

Aging and related health concerns: Vortioxetine is an effective treatment for major depressive disorder. Potential efficacies in post-COVID19 condition and neuropathic pain are preliminary and need to be confirmed with further clinical trials.

Safety: Common adverse events include nausea, diarrhea, and headache. Vortioxetine may increase bleeding when combined with antiplatelet drugs, NSAIDs, or blood-thinners. It must not be taken with serotonergic drugs, as it can lead to serotonin syndrome.

Availability: Rx	**Dose**: The initial dose for major depressive disorder in adults is 10 mg orally once a day, with a maintenance dose of 5 to 20 mg orally once daily.	**Chemical formula:** $C_{18}H_{22}N_2S$ **MW**: 298.4  Source: PubChem
Half-life: 57-66 hours	**BBB**: penetrant	
Clinical trials: A 2022 meta-analysis included 20 randomized controlled trials with 8,547 participants total, of whom 4,598 received vortioxetine.	**Observational studies**: Meta-analyses of observational studies have included a total of thousands of patients with major depression.	

What is it?

Vortioxetine is an atypical antipsychotic and antidepressant used to treat major depressive disorder in adults. Vortioxetine has a multimodal mechanism of action towards the serotonin system, by modulating several serotonin receptors while inhibiting the reuptake of serotonin (DrugBank.ca). Specifically, vortioxetine is a full agonist of the 5-HT1A receptor (Ki=15 nM), a partial agonist of the 5-HT1B receptor (Ki = 33 nM), an antagonist of the 5-HT3 (Ki = 3.7 nM), 5-HT1D (Ki = 54 nM), and 5-HT7 receptors (Ki = 19 nM), and inhibits the serotonin transporter (SERT) with high affinity (Ki=1.6 nM), increasing serotonin levels in the postsynaptic space (reviewed in Adamo et al., 2021). Vortioxetine binds poorly to the norepinephrine and dopamine transporters. Vortioxetine is considered a serotonin modulator and simulator.

Neuroprotective Benefit: In people with depression, vortioxetine appears to improve multiple domains of cognitive function independent of its effects on mood and depression. Cognitive effects in neurodegenerative diseases are mixed and inconsistent.

Types of evidence:

- 7 meta-analyses or systematic reviews in people with major depressive disorder
- 5 clinical trials in people with major depressive disorder
- 1 double-blind randomized controlled trial in Alzheimer's patients with depression

- 1 Delphi Consensus publication on treating depression in Alzheimer's disease
- 1 Delphi Consensus publication on treating depression in Parkinson's disease
- 1 open-label study in people with mild cognitive impairment without depressive symptoms
- 2 open-label studies in people with prodromal/mild Alzheimer's disease with depression
- 1 open-label study in people with Parkinson's disease with major depressive disorder
- 2 observational studies in people with major depressive disorder and Alzheimer's disease
- 1 case series of patients with multiple sclerosis and major depressive disorder
- Numerous laboratory studies
- 7 reviews

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

In a 2022 meta-analysis of 6 randomized controlled trials including a total of 1,782 patients with major depressive disorder and cognitive impairment, treatment with vortioxetine (10 and 20 mg daily doses, orally) for 2-8 weeks significantly improved cognitive function, as measured by the Digit Symbol Substitution Test (DSST)(Huang et al., 2022). Both the 10- and 20-mg doses of vortioxetine had significantly greater change from baseline in DSST scores compared to placebo: for the 10 mg dose, the weighted mean difference was 1.75 (p=0.03), and for the 20 mg dose, the weighted mean difference was 2.23 (p=0.003). Further longer-term studies are needed to determine whether the improvement in cognitive function lowers the risk of dementia in patients with major depressive disorder. As expected, vortioxetine treatment also improved a depression rating scale (measured by the Montgomery-Asberg Depression Rating Scale [MADRS]) and function (measured by the Perceived Deficits Questionnaire [PDQ]) compared to placebo.

In a 2022 meta-analysis of 20 randomized controlled trials including a total of 8,547 people with major depressive disorder, vortioxetine treatment significantly improved cognitive function, measured by DSST, compared to placebo (standardized mean difference of 0.34; 95% CI, 0.16 to 0.52, p=0.0003)(Zhang et al., 2022).

In a 2023 meta-analysis of 11 real-world studies (excluding randomized controlled trials) including a total of 3139 participants, vortioxetine treatment was associated with a significant improvement in cognitive function, assessed by the Perceived Deficits Questionnaire-Depression (combined standardized mean difference of 1.71)(Li Z et al., 2023). However, there was heterogeneity among studies, which persisted across subgroups.

In a 2021 systematic review of 3 clinical trials in older adults (over 65 years old), vortioxetine treatment (5-15 mg/day, orally) appeared to improve cognition (Bishop et al., 2021). Two of the studies were double-blind randomized controlled trials and 1 study was a randomized open-label parallel-group study. One of the studies combined vortioxetine treatment with computerized cognitive training (Lenze et al., 2020). Additional well-designed larger, long-term clinical studies are needed to evaluate the potential cognitive benefits of vortioxetine in older adults.

Older meta-analyses of randomized controlled trials have also found similar results regarding the effects of vortioxetine on cognitive function in people with major depressive disorder (McIntyre et al., 2017; McIntyre et al., 2016; Baune et al., 2017). In one meta-analysis comparing the effects of vortioxetine (5, 10, or 20 mg/day), duloxetine (60 mg/day), and placebo, vortioxetine, but not duloxetine, significantly improved cognitive function as measured by DSST (attention and psychomotor speed), independent of depressive symptoms (McIntyre et al., 2016). In a different meta-analysis that included 72 randomized controlled trials of various antidepressants, vortioxetine treatment showed a statistically significant improvement in cognitive function (DSST) compared to escitalopram, nortriptyline, SSRIs, and tricyclic antidepressants (McIntyre et al., 2017).

In a double-blind randomized controlled trial of 602 patients with major depressive disorder, vortioxetine (10 and 20 mg/day) had a multi-domain beneficial effect on cognitive performance, as evidenced by improvements in measures of executive function, attention/speed of processing, and memory (Harrison et al., 2016). Effect sizes for DSST (attention/psychomotor speed) were large (over 0.5)—0.51 for 10 mg/day and 0.52 for 20 mg/day.

In a randomized controlled superiority trial of 357 older people with major depressive disorder (VESPA study; mean age, 73.7 years old), there were no significant differences between vortioxetine and SSRIs with regards to response rates, depressive symptoms, and quality, of life, but SSRIs outperformed vortioxetine in terms of cognitive performance (Ostuzzi et al., 2024).

In a small pilot trial of 21 peri- and early menopausal women with major depressive disorder, an open-label flexible-dose of vortioxetine significantly improved cognitive function (DSST), menopause-specific quality of life, anxiety, and frequency and severity of hot flashes (Freeman et al., 2017). The full text of this publication was inaccessible.

A double-blind randomized controlled trial using brain imaging (fMRI) reported that vortioxetine (20 mg/day) for 14 days modulated neural responses across a circuit subserving working memory (dorsolateral prefrontal cortex and hippocampus) in a direction opposite to the changes described in depression (Smith et al., 2017). These effects were seen across both depressed and healthy subjects (48 people in each group), suggesting that vortioxetine may directly affect neural circuitry supporting cognitive function independent from its effects on mood or depression.

In a randomized controlled trial of 121 depressed patients, vortioxetine treatment (5-20 mg/day) for 4 weeks improved cognitive functions evaluated by the F-A-S test ($p<0.001$), Digit Symbol Coding Test ($p<0.001$), Digit Span Test-Backward Span ($p=0.001$), and Digit Span Test-Forward Span ($p<0.001$)(Sagud et al., 2021). Vortioxetine treatment increased plasma BDNF levels from 0.326 at baseline to 0.445 after treatment ($p=0.018$). In patients treated with vortioxetine, higher baseline plasma BDNF levels were significantly associated with greater improvements in F-A-S test (measuring verbal fluency) and Digit Span Test-Forward span score (measuring working memory); these correlations were not seen in patients treated with escitalopram.

In an open-label single-arm clinical study of 111 Asian community-dwelling adults with mild cognitive impairment without depressive symptoms, vortioxetine treatment (5-10 mg/day, orally) for 6 months improved cognitive function, as measured by the Montreal Cognitive Assessment (MoCA: 24.2 points at baseline to 29.7 points at 6 months)(Tan and Tan, 2021). Vortioxetine treatment also improved MoCA and Digit Symbol Substitution Test (DSST) scores at 1, 3, and 6 months. Global Clinical Dementia Rating (CDR) scores were also improved from baseline to 6 months with vortioxetine treatment (mean change, -0.37 points, $p<0.001$); significant improvement was observed only in the memory domain, which was "very mild impairment" at baseline (mean of 0.51 points) to a cognitively normal range (mean of 0.13 points) at 6 months. This study was an investigator-initiated study with grant support from Lundbeck Southeast Asia.

In an open-label single-arm clinical study of 45 cancer patients with major depressive disorder, vortioxetine treatment (flexible doses, 5-20 mg/day) for 6 months significantly improved depression symptoms (MADRS scores from 29.89 ± 5.997 at baseline to 11.59 ± 4.629 at 6 months) while also improving cognitive function (Perceived Deficits Questionnaire-5 items; PDQ-5)(Ng et al., 2023). The PDQ-5 assessed perceived cognitive difficulties in concentration, executive functioning, and memory. Because of the open-label design, placebo effects cannot be ruled out. This study was an investigator-initiated trial with grant support from Lundbeck Southeast Asia.

Human research to suggest benefits to patients with dementia:

A Delphi Consensus on Etiology, Risk Factors, and Clinical Management gathered opinions from a panel of 37 expert physicians in neurodegenerative diseases regarding risk factors, symptoms, diagnosis, and treatment of depression in dementia, with a particular focus on Alzheimer's disease (Aguera-Ortiz et al., 2021). Depression in the elderly was considered by the panel to be an early sign and/or a dementia risk factor. Regardless of the stage of dementia, depression accelerates its course, whereas antidepressant treatment would counter this progression. Experts unanimously considered that the gold standard antidepressants for Alzheimer's patients are those that improve cognitive function and/or have a dual or multimodal mode of action, including vortioxetine, duloxetine, venlafaxine/desvenlafaxine, tianeptine, and mirtazapine. The support for the use of vortioxetine was based on a meta-analysis of 3 randomized controlled trials that concluded that vortioxetine improved cognitive function independent of depressive symptoms compared with duloxetine (McIntyre et al., 2016). Further support was provided by an observational study in 108 Alzheimer's patients that showed cognitive advantages with vortioxetine treatment (15 mg/day) compared to other common antidepressants (Cumbo et al., 2019). Although antidepressants may be less effective in dementia patients compared to cognitively healthy patients, the same dosage and treatment duration should be used (Aguera-Ortiz et al., 2021). Experts also noted that cholinesterase inhibitors may have a synergistic effect with antidepressants.

However, in a more recent double-blind randomized controlled trial of 100 patients with Alzheimer's disease and depression, vortioxetine treatment (5 mg/day) for 12 weeks did not significantly improve depressive symptoms (Cornell Scale for Depression in Dementia score), cognitive functions, or activities of daily living compared to placebo (Jeong et al., 2022). No significant vortioxetine effects were observed for the Mini Mental State Examination, word fluency, naming, construction, word list memory, word list recognition, word list recall, digit symbol substitution test, contrasting, go-no-go, Shiraz verbal learning test (SVLT), SVLT delay, SVLT recognition, and Basic and Instrumental Activities of Daily Living (BADL), ($p>0.05$ for all).

Several other observational or open-label studies have evaluated the effects of vortioxetine in Alzheimer's patients with major depressive disorder:

- In an open-label clinical study of 115 patients with depression and prodromal or mild Alzheimer's disease, vortioxetine treatment (5 mg/day initially, increased up to 20 mg/day, orally) for 6 months significantly improved the Geriatric Depression Scale (GDS), Neuropsychiatric Inventory (NPI) total and subscore items, and cognitive function measured by

the Mini Mental State Examination compared to baseline (Padovani et al., 2024). A greater improvement in cognitive function was observed in prodromal patients compared to the mild-to-moderate Alzheimer's patients. Cognitive improvements were associated with baseline cognitive status, but independent of the antidepressant and behavioral changes (i.e., GDS, NPI). Because of the open-label study design, placebo effects and practice effects cannot be ruled out.

- In a prospective multicenter cohort study of 174 patients with major depressive disorder and Alzheimer's disease, vortioxetine treatment (5-15 mg/day, orally) for 6 months significantly improved depressive symptoms (MADRS), perceived deficits (PDQ-K), and cognitive function (DSST) compared to baseline (Cumbo et al., 2023). Mean changes in DSST total scores from baseline to 6 months was +3.8 points (p=0.0524). However, the authors noted that DSST was not completed at both baseline and subsequent visits in the majority of patients. With regards to depressive symptoms, treatment response (over 50% reduction in MADRS total score from baseline) was seen in 50% of patients (27 out of 54) at 6 months. Remission from depressive symptoms (MADRS total score ≤10) was achieved by 51.9% of patients (28 out of 54) at 6 months.

- In an open-label study of 82 patients with major depressive disorder and early-stage dementia (43% of whom had Alzheimer's disease), treatment with vortioxetine (initiated at 5 mg/day, titrated up to 20 mg/day) for 12 weeks significantly improved depressive symptom severity (measured by MADRS) and cognitive function (measured by DSST and Rey's Auditory Verbal Learning Test [RAVLT]) compared to baseline (Christensen et al., 2023). Improvement in DSST was seen from week 1 and improvement for RAVLT was seen from week 4. Patients also experienced improvements in daily and global functioning as well as health-related quality of life compared to baseline. The standard effect size for change in DSST total score from baseline was 0.2 at week 1 and 0.65 at week 12 (p<0.0001). Least squares mean change from baseline in RAVLT total score was statistically significant at week 4 (p=0.01) and week 12 (p=0.02). Improvements compared to baseline were also observed for short recall and delayed recall scores. Recognition improved only at week 4 before returning to levels comparable to baseline at week 12. Based on patients' subjective ratings, the percentage of patients who rated their memory as 'very poor or poor' decreased from 82% (67 out of 82) at baseline to 54% (39 ouot of 72) at week 12. Vortioxetine treatment also significantly improved daily functioning (IADL polytomous score; p=0.009), with female patients showing significant improvement within 1 week of vortioxetine initiation (p=0.04). Additionally, significant improvement in health-related

quality of life was seen from baseline to week 12. The authors speculate that the effects of vortioxetine is likely due to its multimodal mechanism of action, including modulation of the serotonergic, noradrenergic, dopaminergic, histaminergic, cholinergic, GABA, and glutamatergic systems. The main limitation of this study is the open-label design without a control group, thus, placebo effects and practice effects cannot be ruled out. This study was funded by H. Lundbeck A/S.

In a review of pharmacotherapy for depression in Alzheimer's patients, the authors discuss the possibility that the etiology of symptoms of depression in people with dementia may be fundamentally different from the etiology of depression in people without dementia, possibly due to damage and neuronal loss in the course of dementia (Lozupone et al., 2018).

Depression is also common in Parkinson's disease, affecting up to 50% of patients. A Delphi Consensus gathered opinions from a panel of 37 expert physicians in neurodegenerative diseases regarding the pathological mechanisms of depression in Parkinson's disease, clinical features, diagnostic criteria, and therapeutic options (Aguera-Ortiz et al., 2021). The experts agreed that regardless of the clinical severity, depression requires treatment. Pharmacological options considered efficacious and well-tolerated for Parkinson's comorbid depression include selective serotonin reuptake inhibitors (especially sertraline), dual-action serotonin and norepinephrine reuptake inhibitors (venlafaxine, desvenlafaxine, and duloxetine), multimodal agents (vortioxetine, bupropion, mirtazapine, and tianeptine), and anti-Parkinsonian dopamine agonists (pramipexole, ropinirole, and rotigotine). Electroconvulsive therapy was indicated for severe and drug-refractory cases. In cases of mild depression, cognitive behavioral therapy was recommended.

In an open-label prospective study of 27 patients with Parkinson's disease and major depressive disorder, vortioxetine treatment (10 mg/day, with possibility of increasing up to 20 mg/day) for 12 weeks significantly reduced depressive symptoms (Garcia et al., 2022). The depression score (total HAM-D17) was reduced by 52.7%, from 21.5 ± 4.75 at baseline to 10.44 ± 7.54 at 12 weeks ($p<0.001$), and response and remission rates were 50% and 43.4%, respectively. Cognition (PD-Cognitive Rating Scale; $p=0.007$), apathy (Apathy scale; $p<0.0001$), fatigue (Fatigue Severity Scale; $p=0.014$), and quality of life (PDQ-39; $p=0.001$) were improved at 3 weeks. Limitations of this study is the open-label study design without a comparative arm with a placebo. Therefore, placebo effects and practice effects cannot be ruled out. The sample size was also small. Due to the COVID-19 pandemic, the study was closed before reaching the originally planned sample size of 40.

In a case series study of 17 patients with multiple sclerosis and major depressive disorder, vortioxetine treatment (5, 10, or 20 mg/day, orally) for 6 months significantly improved health status (EQ-5D; p=0.002), mood (Beck's Depression Inventory; p=0.006), anxiety (State-Trait Anxiety Inventory; p=0.021, and STAI-Trait; p=0.011), and in the general health test (Short Form Health Survey, SF-36) for the vitality (p=0.028) and mental health (p=0.025) domains compared to baseline (Gil-Sanchez et al., 2024). However, no statistically significant differences were observed in cognitive tests related to attention, information processing speed, and fatigue.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Vortioxetine has multimodal actions, which may enhance downstream release of 4 pro-cognitive neurotransmitters (Stahl 2015; Millan et al., 2016). Vortioxetine has a complex mechanism of action that includes not only inhibition of serotonin (5-HT) transporters (SERT), but also direct actions at multiple 5-HT receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT3, and 5-HT7 receptors). Vortioxetine directly stimulates 5-HT1A receptors on inhibitory GABA interneurons innervating the presynaptic nerve terminals of norepinephrine (NE), dopamine (DA), and acetylcholine (ACh) neurons. Theoretically, this action would disinhibit (enhance) the release of DA, NE, and ACh from their nerve terminals in the prefrontal cortex. Vortioxetine is also a partial agonist at 5-HT1B receptors and possibly a functional antagonist. Thus, occupancy of cortical 5-HT1B receptors localized on NE, ACh, DA, and histamine (HA) neurons by vortioxetine would disinhibit these neurons and enhance the release of these four neurotransmitters. Antagonism of 5-HT7 receptors by vortioxetine also increases ACh and NE levels in the medial prefrontal cortex (Adamo et al., 2021).

In addition to the various neurotransmitter systems, vortioxetine also increases the level of the neurotrophic factor, BDNF, in animal models (Sun et al.,2020; Unal et al., 2023). Also in preclinical studies, vortioxetine has demonstrated immunomodulatory properties, antioxidant activity, and anti-inflammatory effects (reviewed in Adamo et al., 2021).

A study in rodents revealed that vortioxetine modulates biomarkers involved in transcriptional regulation, neurodevelopment, neuroplasticity, and endocytosis (Waller et al., 2017). Protein-protein interactomes identified by a network analysis include genes that regulate neuronal activity (Arc), transcription (c-fos), endocytosis/neurotransmitter release (Epsin1), and neurodevelopment (Semaphorin 4g). In another study in hippocampal neuronal culture, vortioxetine induced dendritic spine enlargement, increasing the proportion of potentially functional synaptic contacts (Waller et al., 2016). In a mouse model of Alzheimer's disease (5xFAD mice), vortioxetine treatment (10 mg/kg, i.p., every

other day) for 6 weeks improved the impairment in recognition memory and spatial reference memory (Jiang et al., 2020). Vortioxetine treatment did not delay the formation of amyloid plaques, but increased the expression levels of synaptic proteins (PSD95, SYP, and SYT1) compared to the vehicle-treated group.

A study in mouse has shown that vortioxetine is not affected by P-glycoprotein-mediated efflux at the blood-brain-barrier (Bundgaard et al., 2016). Thus it is not actively pumped out of the brain.

APOE4 interactions: Unknown.

Aging and related health concerns: Vortioxetine is an effective treatment for major depressive disorder. Potential efficacies in post-COVID19 condition and neuropathic pain are preliminary and need to be confirmed with further clinical trials.

Types of evidence:

- Numerous meta-analyses and randomized controlled trials in major depressive disorder
- 2 randomized controlled trials in post-COVID19 condition
- Numerous observational studies in major depressive disorder
- 1 open-label study in post-COVID19 condition
- 1 open-label study in cancer patients with major depressive disorder
- 1 review of vortioxetine for the treatment of chronic neuropathic pain

Major depressive disorder: EFFICACIOUS

A 2017 Cochrane meta-analysis that included 15 randomized controlled trials including a total of 7,746 participants with depression reported that vortioxetine treatment is effective in 3 efficacy outcomes compared to placebo: response (Mantel-Haenszel, RR=1.35, 95% CI, 1.22 to 1.49), remission (RR=1.32, 95% CI, 1.15 to 1.53) and depressive symptoms (MADRS; score range, 0 to 34; higher score indicate worse outcome; mean difference=-2.94, 95% CI, -4.07 to -1.80)(Koesters et al., 2017). Vortioxetine treatment did not significantly alter response or remission compared to selective serotonin and noradrenalin reuptake inhibitors (SNRIs). When comparing individual antidepressants, vortioxetine may be less effective than duloxetine in terms of response rates (RR=0.86, 95% CI, 0.79 to 0.94) and depressive symptom scores (MADRS; mean difference=1.99, 95% CI, 1.15 to 2.83).

In a 2022 meta-analysis of 20 randomized controlled trials including a total of 8,547 adults with major depressive disorder (4,598 participants allocated to vortioxetine), vortioxetine treatment outperformed placebo in efficacy outcomes, including response (RR=1.35; 95% CI, 1.23 to 1.48; p<0.001) and remission (RR=1.33; 95% CI, 1.17 to 1.52; p<0.001)(Zhang et al., 2022). Compared with the SNRIs, vortioxetine was not significantly different in response rate (RR=0.91; p=0.06) or remission (RR=0.89; p=0.11). Vortioxetine treatment also did not significantly differ in response or remission when compared with SSRIs. The response rates were significantly lower for vortioxetine than duloxetine (pooled RR=0.86; 95% CI, 0.79 to 0.94; p=0.001). There was no significant difference in response rates between vortioxetine and venlafaxine (RR=1.03; 95% CI, 0.85 to 1.25; p=0.73). Remission rates were not significantly different between vortioxetine and venlafaxine, or between vortioxetine and duloxetine.

In a 2018 meta-analysis that analyzed 21 antidepressant drug studies in 522 trials, comprising a total of 116,477 participants with major depressive disorder, all antidepressants were more effective than placebo, with odds ratios ranging between 2.13 for amitriptyline and 1.37 for reboxetine (Cipriani et al., 2018). In head-to-head studies, agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than other antidepressants (range of ORs, 1.19 to 1.96); fluoxetine, fluvoxamine, reboxetine, and trazodone were the least efficacious.

In a meta-analysis of 11 real-world studies (excluding randomized controlled trials) in people with major depressive disorder, vortioxetine treatment significantly relieved depression symptoms as assessed by both patients and physicians (Li et al., 2023). The estimated response and remission rates were 66.4% (95% CI, 51.2-81.5%) and 58.0% (95% CI, 48.9% to 67.1%), respectively. Geographic location and medication regimen (whether combined with other antidepressants) were factors that influenced effectiveness, and potentially contributed to heterogeneity. The authors also noted that more rigorous, large-scale, multicenter longitudinal studies of vortioxetine are needed, along with direct comparisons with other antidepressants in real-world settings.

In a retrospective study of 1,242 patients with major depressive disorder, vortioxetine treatment (5 mg at start, ranged from 5-20 mg/day, orally) for 12 weeks significantly improved patient-reported outcome measures, including the Patient Health Questionnaire-9 (14.15 ± 5.8 at baseline to 9.62 ± 6.03 at 12 weeks; $p < 0.001$), anxiety ($p < 0.001$), sexual dysfunction ($p < 0.01$), sleep disturbance ($p < 0.01$), cognitive function ($p < 0.001$), work/social functioning ($p = 0.021$), and appetite ($p < 0.001$)(McDaniel et al., 2023). Prior to the study, most participants had 3 or more psychiatric diagnoses (63.9%) and were taking 3 or more medications (65.9%). After 12 weeks of treatment, the response and remission rates were 31.0% and 23.1%, respectively, and 67% of patients continued vortioxetine treatment. Due to the

design of the study, the observed improvement in outcomes with vortioxetine cannot be solely attributed to vortioxetine, as there was no comparator group that began other medications. Also, the patient sample is primarily White (91.1%) and results may not be generalizable to other races and ethnicities. This study was funded by Takeda Pharmaceuticals USA Inc., but data extraction, review, and analysis were performed without influence from Takeda.

In a prospective cohort study, 737 outpatients with major depressive disorder (RELIEVE study) were included from the US, Canada, France, and Italy (Mattingly et al., 2022). Vortioxetine treatment (5-20 mg/day, orally) for 6 months resulted in improvement in patient functioning (Sheehan Disability Scale; by 8.7 points, from 19.6 points at baseline to 11.0 points at week 24), depression severity (PHQ-9), and health-related quality of life. The percentage of patients with severe disease (CGI-S score 5-7) decreased from 41.0% at baseline to 10.7% at week 12 and 6.1% at week 24. The greatest benefit was observed in patients when vortioxetine was used as a first-line treatment. The RELIEVE study was funded by H. Lundbeck A/S, whose personnel contributed to the data analysis, review of the data, and review of the manuscript. Medical writing was funded by H. Lundbeck A/S.

Neuropathic pain: POTENTIAL BENEFIT
Chronic neuropathic pain is caused by a lesion or disease of the somatosensory nervous system and is a disabling condition that impairs the quality of life of affected patients (Scholz et al., 2019). Management of chronic neuropathic pain is complex and often multidisciplinary because it is composed of both a perceptive and an emotional component, and therefore, often associated with anxiety, depression, and sleep disturbance. SNRIs are considered useful in the modulation of pain and in the treatment of mood disorder associated with chronic neuropathic pain. In a review examining the pharmacology and clinical applications of vortioxetine, the authors highlight that vortioxetine is a multimodal serotonergic antidepressant with a unique mechanism of action (Adamo et al., 2021). The efficacy of vortioxetine in the treatment of chronic neuropathic pain is exerted through the increase in serotonergic transmission, inhibition of the 5-HT3 receptors resulting in a decrease in hyperalgesia, and modulation of the 5-HT7 receptors resulting in increased analgesia.

In open-label clinical studies in patients with chronic orofacial pain (burning mouth syndrome), vortioxetine treatment significantly reduced pain (VAS, T-PRI), anxiety, depression, and clinical impression scores (Adamo et al., 2020; Adamo et al., 2021). While other antidepressants (paroxetine, sertraline, escitalopram, or duloxetine) also showed pain relief, only vortioxetine showed marked effects on clinical remission and functional recovery (Adamo et al., 2021). Given the open-label design of the

studies, placebo effects cannot be ruled out. It is not known how efficacious vortioxetine may be in other types of neuropathic pain.

In a mouse model of chronic neuropathic pain (induced by chronic constriction injury), vortioxetine treatment (10 mg/kg/day, i.p.) for 27 days resulted in robust analgesia, similar to the effect produced by venlafaxine, an SNRI (but not fluoxetine, an SSRI)(Zuena et al., 2018). Vortioxetine treatment also increased mechanical pain thresholds in these mice without altering motor activity.

Post-COVID19 condition: POTENTIAL BENEFIT; EFFECTS LIKELY DEPEND ON MANY FACTORS
The common symptoms of post-COVID19 condition include cognitive deficits, fatigue, and mood symptoms. In a double-blind randomized controlled trial of 149 patients with post-COVID19 condition, vortioxetine treatment (5-20 mg/day, orally) for 8 weeks did not significantly change cognitive function, as measured by the Digit Symbol Substitution Test (DSST)(McIntyre et al., 2024). However, in patients who had baseline CRP levels (inflammation marker) above the mean, vortioxetine treatment significantly improved DSST scores compared to placebo (p=0.045). This study was sponsored by H. Lundbeck A/S, Copenhagen, Denmark, but the funder did not have any role in the study design, data collection, data analysis, interpretation of the results, or writing of the manuscript for publication.

In another double-blind randomized controlled trial of 147 people with post-COVID19 condition, vortioxetine treatment (5-20 mg/day) for 8 weeks improved depressive symptoms (measured by QIDS-SR-16) and cognitive deficits (measured by DSST) compared to the placebo group (Kwan et al., 2024; Kwan et al., 2024). In people with baseline markers of increased inflammation, metabolic disruption, and elevated BMI, there were pronounced effects on depressive symptoms (p<0.001) and cognitive function (p=0.047) with vortioxetine after 8 weeks.

In a retrospective open-label clinical study of 80 patients with post-COVID19 major depressive episodes, vortioxetine treatment (5-20 mg/day, orally) reduced depressive symptoms (HDRS; p<0.001), improved physical features, and improved cognitive functioning (DSST; p=0.02; PDQ-D5, p<0.001) (Nicola et al., 2023). Because this study did not have a control group, placebo effects and practice effects cannot be ruled out.

Sleep: MAY IMPROVE SLEEP QUALITY AND DECREASE REM SLEEP
In a double-blind randomized placebo-controlled crossover study in 24 healthy young men, vortioxetine treatment (20 mg or 40 mg) for 3 consecutive days significantly increased REM sleep onset latency and decreased time spent in REM sleep (Wilson et al., 2015).

In open-label studies, vortioxetine treatment (10-20 mg/day) has improved sleep quality (measured by the Pittsburgh Sleep Quality Index and others) after 8 weeks of treatment (Liguori et al., 2019; Cao et al., 2019). Because of the open-label design, placebo effects cannot be ruled out.

Safety: Common adverse events include nausea, diarrhea, and headache. Vortioxetine may increase bleeding when combined with antiplatelet drugs, NSAIDs, or blood-thinners. It must not be taken with serotonergic drugs, as it can lead to serotonin syndrome.

Types of evidence:

- 17 meta-analyses or systematic reviews
- Numerous double-blind randomized controlled trials in major depressive disorder
- 1 double-blind randomized controlled trial in people with depression and Alzheimer's disease
- 1 double-blind randomized controlled trial in people with post-COVID19 condition
- 9 open-label studies
- 1 case series in patients with multiple sclerosis and major depressive disorder
- Numerous reviews

Adverse reactions:

Based on Drugs.com, common side effects with vortioxetine include nausea, constipation, and vomiting. The adverse reactions in order of incidence include nausea (>10%), headache, diarrhea, and dry mouth (reviewed in Adamo et al., 2021).

Vortioxetine may also cause serious side effects including racing thoughts, decreased need for sleep, unusual risk-taking behavior, vision changes, eye pain, eye swelling, bruising, unusual bleeding, coughing up blood, or low sodium levels (more likely in older adults)(Drugs.com). Vortioxetine can also cause "serotonin syndrome", a potentially life-threatening problem that can happen when you take it with other serotonergic drugs (for more details, see the "*Drug interactions*" section below). In adolescents and young adults, thoughts of suicide may occur when first taking an antidepressant. The vortioxetine label includes a blackbox warning for suicidal thoughts and behavior in children, adolescents, and young adults (DrugBank.ca). For any changes in mood or symptoms, consult your doctor.

Pharmacokinetics:

Bioavailability of vortioxetine is high and is independent of food intake (reviewed in Adamo et al., 2021). It takes 3-16 hours to attain maximum plasma concentration, with a terminal half-life of 60-70 hours. A steady-state concentration in the plasma is maintained for up to 2 weeks after drug administration. Vortioxetine is metabolized extensively in the liver.

Clinical trial findings:

Patients with major depressive disorder:
Numerous meta-analyses of double-blind randomized controlled trials have assessed the safety and adverse events of vortioxetine in people with major depressive disorder (Baldwin et al., 2016; Fu et al., 2016; Li et al., 2016; Meeker et al., 2015; Pae et al., 2015a, Pae et al., 2015b; Berhan et al., 2014; Koesters et al., 2017; Cipriani et al., 2018; Zhang et al., 2022).

A 2016 meta-analysis of 10 randomized controlled trials including a total of 2,357 patients with major depressive disorder reported that the most common adverse effects with vortioxetine (5-20 mg/day) were nausea, headache, dizziness, dry mouth, diarrhea, nasopharyngitis, constipation, and vomiting (Baldwin et al., 2016). The incidence of serious treatment-emergent adverse events (TEAEs) was 1.3% for placebo and under 1.3% for vortioxetine (across doses). Nausea was the only adverse event with an overall incidence over 2 times higher in the vortioxetine arms (22.5-31%) than the placebo arm (9.4%), which followed a dose-related trend. Rates of serious TEAEs and discontinuations due to serious TEAEs were similar to placebo in all vortioxetine dose groups. Another 2016 meta-analysis of 4 randomized controlled trials including 1,843 adults with generalized anxiety disorder also reported similar findings, with nausea and headache as the most common adverse effects (Fu et al., 2016). Nausea was found to be more frequent in the vortioxetine (5 and 10 mg/day) group (OR=2.99, 95% CI=1.31-6.84; OR=2.80, 95% CI=1.85-4.25, respectively), but no significant differences were observed for headache. A different 2016 meta-analysis of 6 randomized controlled trials including 1,801 patients with major depressive disorder examined the effects of a specific dose of vortioxetine (10 mg/day)(Li et al., 2016). In this study, in addition to nausea (RR =3.44; 95% CI: 2.63-4.48), incidences were higher for vomiting (RR =2.78; 95% CI: 1.32-5.85), constipation (RR =2.03; 95% CI: 1.15-3.58), and hyperhidrosis (excessive sweating; RR =4.44; 95% CI: 1.29-15.26) with 10 mg vortioxetine compared to placebo. For the 7 other adverse events (headache, diarrhea, dizziness, dry mouth, fatigue, insomnia, and nasopharyngitis), there were no significant differences between the vortioxetine and placebo groups.

In a 2017 Cochrane meta-analysis that included 15 randomized controlled trials including a total of 7,746 participants with depression, more participants discontinued vortioxetine treatment than placebo because of adverse effects (RR=1.41; 95% CI, 1.09 to 1.81), but fewer discontinued due to inefficacy (RR=0.56; 95% CI, 0.34 to 0.90; p=0.02)(Koesters et al., 2017). Based on "very low quality evidence", there were no significant differences between vortioxetine and SNRIs for total dropout rates (RR=0.89; 95% CI, 0.73 to 1.08), dropouts due to adverse events (RR=0.74; 95% CI, 0.51 to 1.08) and dropouts due to inefficacy (RR=1.52; 95% CI, 0.70 to 3.30). In terms of the number of patients reporting at least 1 adverse effect, vortioxetine was better than SNRIs (RR=0.90; 95% CI, 0.86 to 0.94) and duloxetine (RR=0.89; 95% CI, 0.84 to 0.95). However, the sensitivity analysis casts doubts on this finding, due to the presence of only 2 studies with comparable dosing.

In a 2018 meta-analysis that analyzed 21 antidepressant drug studies in 522 trials, comprising a total of 116,477 participants with major depressive disorder, agomelatine, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants (range of ORs=0.43 to 0.77) (Cipriani et al., 2018).

In a 2022 meta-analysis of 20 randomized controlled trials including a total of 8,547 adults with major depressive disorder (4,598 participants allocated to vortioxetine), patients taking vortioxetine experienced more adverse effects than placebo (RR=1.12; 95% CI, 1.07 to 1.17, p<0.001) and had a higher dropout rate due to adverse events than placebo (RR=1.40; 95% CI, 1.09 to 1.79; p=0.009)(Zhang et al., 2022). However, when compared to patients treated with SNRIs, patients treated with vortioxetine experienced fewer adverse effects (RR=0.90; 95% CI, 0.86 to 0.94; p<0.001). Patients receiving vortioxetine treatment had fewer adverse effects than those treated with duloxetine (RR=0.89; 95% CI, 0.84 to 0.95; p<0.001), but no significant differences were seen between vortioxetine and venlafaxine (RR=0.91; 95% CI, 0.82 to 1.00; p=0.06). There were no significant differences in dropout rate due to adverse events between vortioxetine and SNRIs.

In a meta-analysis of 11 real-world studies (excluding randomized controlled trials) in people with major depressive disorder, vortioxetine treatment was well-tolerated with a pooled dropout rate of 3.5% (Li et al., 2023). Common adverse events associated with vortioxetine were nausea, headache, dizziness, and pruritus. Nausea was the most frequently reported adverse event, with a rate of 8.9%. Severe adverse drug reactions were reported in only 2 studies, affecting 6 participants (0.48%).

A double-blind randomized controlled trial of 600 people with major depressive disorder reported that all 11 serious adverse events (7 in drug, 4 in placebo; e.g., drug hypersensitivity, herpes zoster, injury,

cancers, convulsion, cerebrovascular accident, ectopic pregnancy, spontaneous abortion) were considered unrelated to the study drug (Jain et al., 2013). There were no clinically significant changes in laboratory values or vital signs. No clinically meaningful differences between treatment groups were observed at any time-point for systolic or diastolic blood pressure, pulse, body temperature or weight.

In a prospective cohort study of 737 outpatients with major depressive disorder (RELIEVE study), vortioxetine treatment (5-20 mg/day, orally) for 6 months resulted in 21.2% of patients reporting at least 1 adverse event (Mattingly et al., 2022). The most commonly reported adverse events were nausea (81 patients; 8.2%), headache (15 patients; 1.5%), pruritus (15 patients; 1.5%), and anxiety (14 patients; 1.4%). With regards to less frequently reported adverse events, insomnia was reported by 5 patients (0.5%), weight increase by 4 patients (0.4%), decreased libido by 3 patients (0.3%), loss of libido by 1 patient (0.1%), and sexual dysfunction by 1 patient (0.1%). Of the 29 serious adverse events reported in 23 patients, 3 were considered to be at least possibly related to treatment (pancreatitis, serotonin syndrome, and suicidal ideation, n=1 for each). Two patients died during the study (one due to pneumonia and one due to chronic obstructive pulmonary disease); neither were considered to be related to study treatment.

Adults over 65 years old:
Older adults may be more sensitive to side effects of vortioxetine, such as bleeding (WebMD.com). Also, older adults are more likely to develop salt imbalance (hyponatremia), especially if they are also taking diuretics with vortioxetine. The EU health authories recommend initiating treatment in the elderly with a 5 mg/day dose and exercise caution when prescribing at a dose of 10 mg/day, due to the 27% higher exposure of vortioxetine in people over 65 years old compared to those aged 45 years old (Adamo et al., 2021).

In a 2021 systematic review of 3 clinical trials in older adults (over 65 years old), vortioxetine treatment (5-15 mg/day, orally) resulted in adverse events including nausea and headache (Bishop et al., 2021). In two of the studies, the occurrence of nausea was greater for vortioxetine compared to placebo (21.8% vs 8.3% for one study, 29.4% vs 4.1% for the other study), but one of the studies showed no significant difference between vortioxetine and placebo. Other adverse effects included headache, which was not statistically diferent between vortioxetine and placebo in two of the trials.

In an open-label single-arm clinical study of 111 Asian community-dwelling adults with mild cognitive impairment without depressive symptoms, vortioxetine treatment (5-10 mg/day, orally) for 6 months resulted in nausea in 2 people, headache in 1 person, and gastritis in 1 person (Tan and Tan, 2021).

In a randomized controlled superiority trial of 357 older people with major depressive disorder (VESPA study; mean age, 73.7 years old), 78 patients (44%) randomized to vortioxetine discontinued treatment due to adverse events at 6 months, compared to 59 (33%) of those randomized to SSRIs (OR=1.56; 95% CI, 1.01 to 2.39)(Ostuzzi et al., 2024). The most common adverse events causing treatment discontinuation were vomiting (6 vortioxetine, 6 SSRIs), anxiety/irritability (6 vortioxetine, 3 SSRIs), confusion (2 vortioxetine, 3 SSRIs), and diarrhea (3 vortioxetine, 0 SSRIs). In this trial of older people, vortioxetine treatment did not show a better tolerability profile compared to SSRIs.

Dementia patients:
In a double-blind randomized controlled trial of 100 patients with Alzheimer's disease and depression, vortioxetine treatment (5 mg/day) for 12 weeks led to the same percentage of patients (32%) discontinuing the trial due to an adverse event compared to those receiving placebo (Jeong et al., 2022). The most commonly reported adverse events were nausea (14.29%) and diarrhea (6.12%) in the vortioxetine group and dizziness (9.80%) and nausea (3.92%) in the placebo group. No deaths or serious adverse events occurred during the study.

In a prospective multicenter cohort study of 174 patients with major depressive disorder and Alzheimer's disease, vortioxetine treatment (5-15 mg/day, orally) for 6 months resulted in 27 patients (13.0%) reporting adverse events, of which 89.2% were mild (Cumbo et al., 2023). The only adverse event reported by more than 1 patient was decreased appetite (4 patients; 1.9%) and nausea, dizziness, and lower limb fracture (each reported by 2 patients; 1.0%). There were 4 moderate adverse events and no severe adverse events. There were no significant changes in mean body weight from baseline with 24 weeks of vortioxetine treatment.

In an open-label clinical study of 115 patients with depression and prodromal or mild Alzheimer's disease, vortioxetine treatment (5 mg/day initially, increased up to 20 mg/day, orally) for 6 months resulted in adverse events including nausea (4.5%), diarrhea (3.4%), and dizziness (2.2%)(Padovani et al., 2024). No deaths or serious adverse events occurred during the study.

In an open-label prospective randomized study of 108 patients with mild Alzheimer's disease and depressives symptoms, vortioxetine treatment (15 mg/day) for 12 months resulted in adverse events that included nausea and headache, while in the control group (receiving other antidepressants), nausea was reported (Cumbo et al., 2019).

In an open-label study of 82 patients with major depressive disorder and early-stage dementia (43% of whom had Alzheimer's disease), treatment with vortioxetine (initiated at 5 mg/day, titrated up to 20 mg/day) for 12 weeks was well-tolerated and no unexpected treatment-emergent adverse events were reported (Christensen et al., 2023). During the study, 56 adverse events were reported by 38 patients (46%). The most commonly reported treatment-emergent adverse events were nausea and abdominal pain, each occurring in 9 patients (11%). Adverse events were mostly of mild or moderate intensity. There was one serious adverse event, a case of COVID-19 pneumonia, which was considered by the investigator to be unrelated to vortioxetine. Six patients (7 %) withdrew from the study due to a treatment emergent adverse event (n=8): headache (n=2), nausea (n=2), anxiety (n=1), pruritus (n=1), psychomotor hyperactivity (n=1), and COVID-19 pneumonia (n=1). No deaths were reported during the study.

In an open-label prospective study of 27 patients with Parkinson's disease and major depressive disorder, vortioxetine treatment (10 mg/day, with possibility of increasing up to 20 mg/day) for 12 weeks led to a total of 11 adverse events in 10 patients (33%)(Garcia et al., 2022). One adverse event was severe: a patient experienced vomiting and discontinued treatment, but fully recovered 6 days after drug withdrawal. Common adverse events included nausea (n=5; 18.5%) and dizziness (6.6%)

People with Post-COVID19 condition:
In a double-blind randomized controlled trial of 149 patients with post-COVID19 condition, vortioxetine treatment (5-20 mg/day, orally) for 8 weeks resulted in 26.8% of patients experiencing a treatment-emergent adverse event (40 out of 149), compared to 22.1% in the placebo group (33 out of 149)(McIntyre et al., 2024). The percentage of patients who discontinued treatment were 3% (n=4) and 0% (n=0) for the vortioxetine and placebo group, respectively.

Drug interactions:

There are many drug interactions with vortioxetine—93 major drug interactions and 252 moderate interactions (Drugs.com; WebMD.com). Vortioxetine can increase the risk of bleeding when taken with other drugs that cause bleeding or bruising, including antiplatelet drugs such as clopidogrel, NSAIDs such as ibuprofen and aspirin, and blood-thinners such as warfarin and dabigatran. However, vortioxetine is not known to act at the 5-HT2A receptor, the subtype associated with platelet aggregation (so the risk for this interaction is likely lower than other serotonergic drugs that bind to this target)(Nagatomo et al., 2004; Al-Sukhni et al., 2015).

Vortioxetine must not be taken with MAO inhibitors (e.g., rasagiline, selegiline, isocarboxazid, methylene blue, etc.) as they can result in a serious (possibly fatal) drug interaction. The risk of serotonin syndrome (toxicity) increases if you are taking other drugs/agents that also increase serotonin levels, such as MDMA ("ecstasy"), St. John's wort, and antidepressants (SSRIs such as fluoxetine and paroxetine; SNRIs such as duloxetine and venlafaxine). Vortioxetine should not be taken with alcohol as there may be a negative interaction.

Vortioxetine is a substrate for the cytochrome P450 enzyme CYP2D6, so adjustment of dose may be required when taking CYP2D6 inhibitors (bupropion, fluoxetine or paroxetine) or CYP inducers (carbamazepine, phenytoin or rifampicin)(reviewed in Adamo et al., 2021).

Sources and dosing: Vortioxetine (trade names, Trintellix, Brintellix) is a prescription drug available in tablet forms of 5, 10, and 20 mg. The initial dose for major depressive disorder in adults is 10 mg orally once a day, with a maintenance dose of 5 to 20 mg orally once daily.

On Drugs.com, vortioxetine had an average rating of 6.3 out of 10 from a total of 558 reviews as of April 2024. Of the 558 reviews, 48% reported a positive experience while 32% reported a negative experience.

Research underway: There are 10 ongoing clinical trials testing the effects of vortioxetine based on ClinicalTrials.gov, with 7 in people with major depressive disorder, 2 in people with schizophrenia, and 1 in burning mouth syndrome.

Search terms:

Pubmed, Google: Vortioxetine (or Brintellix or Trintellix or Lu AA21004)

- + cognitive, + memory, + Alzheimer's, + dementia, + ApoE, + clinical trial, + meta-analysis, + cardiovascular, + atherosclerosis, + diabetes, + cancer, + lifespan

Websites visited for vortioxetine:

- Clinicaltrials.gov
- PatientsLikeMe
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com
- WebMD.com

- PubChem
- DrugBank.ca

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