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 shows promise for neuroprotection with a multimodal action and potential to increase 4 neurotransmitters. Good safety profile in patients with depression, though drug interactions are known.

Neuroprotective Benefit: Although clinical evidence is limited to people with depression, vortioxetine appears to improve multiple domains of cognitive function independent of its effects on mood and depression.

Aging and related health concerns: No studies have examined the potential effectiveness of vortioxetine on age-related health concerns.

Safety: Short-term safety has been extensively studied in people with anxiety disorders, though it may increase bleeding when combined with antiplatelet drugs, NSAIDs, or blood-thinners.

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 an agonist of the 5-HT1A receptor, a partial agonist of the 5-HT1B receptor, an antagonist of the 5-HT3, 5-HT1D, and 5-HT7 receptors, and an inhibitor of the serotonin transporter. Vortioxetine binds poorly to the norepinephrine and dopamine transporters. Vortioxetine is considered a serotonin modulator and simulator.

Neuroprotective Benefit: Although clinical evidence is limited to people with depression, vortioxetine appears to improve multiple domains of cognitive function independent of its effects on mood and depression.

Types of evidence:

- 3 meta-analyses or systematic reviews in people with major depressive disorder
- 3 clinical trials in people with major depressive disorder
- Numerous laboratory studies
- 4 reviews

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

Numerous meta-analyses of randomized controlled trials have examined the effects of vortioxetine on cognitive function; however, all studies have been carried out in people with major depressive disorder (McIntyre et al., 2017; McIntyre et al., 2016; Baune et al., 2017). A review on vortioxetine stated that it is the first antidepressant agent to demonstrate meaningful clinical efficacy in the improvement of cognition in adults with depression (Al-Sukhni et al., 2015). 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 the Digit Symbol Substitution Test (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 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.

Human research to suggest benefits to patients with dementia:
No studies have examined the effects of vortioxetine in patients with dementia.

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.

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).

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: No studies have examined the potential effectiveness of vortioxetine on age-related health concerns.

Types of evidence:

- None

No studies have investigated whether vortioxetine prevents or ameliorates age-related diseases. No entries were found on DrugAge or Geroprotectors.

Safety: Short-term safety has been extensively studied in people with anxiety disorders, though it may increase bleeding when combined with antiplatelet drugs, NSAIDs, or blood-thinners.

Types of evidence:

- 12 meta-analyses or systematic reviews
- 1 double-blind randomized controlled trial in major depressive disorder
- 1 review

Numerous meta-analyses of double-blind randomized controlled trials have assessed the safety and adverse events of vortioxetine, though these studies only lasted up to 8 weeks (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).

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.

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.

Older adults may be more sensitive to side effects of this drug, 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 label includes a blackbox warning for suicidal thoughts and behavior in children, adolescents, and young adults (DrugBank.ca).

Drug interactions: There are many drug interactions with vortioxetine—225 major drug interactions and 303 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.

Sources and dosing: Vortioxetine (trade names, Trintellix, Brintellix) is a prescription drug available in tablet forms of 5, 10, and 20 mg.

Treato.com rates vortioxetine (Trintellix, Brintellix) 2.9 stars out of 5, with 3.0/5.0 points for "helpfulness for depression" and 2.9/5.0 points for "concern level". There are more "negative" (832) reviews compared to "positive" (599). Main concerns raised for vortioxetine were nausea (780), withdrawal symptoms (416), weight gain (336), tiredness (328), headaches (278), sexual dysfunction (246), and insomnia (240).

Research underway: There are 16 ongoing clinical trials testing the effects of vortioxetine based on ClinicalTrials.gov, with 12 in people with major depressive disorder, 1 in people with schizophrenia, 1 in binge eating disorder, 1 in social anxiety disorder, and 1 in posttraumatic stress disorder. In addition, there is one randomized double-blind clinical trial examining the potential benefits of vortioxetine in combination with a computerized cognitive training program in older people (age 65 and older) with age-related cognitive decline (NCT03272711). The experimental group is receiving vortioxetine (10 mg/day) plus cognitive training 5 times weekly for 30 minutes a day. The placebo group is receiving placebo plus the same cognitive training. This study is recruiting participants and is scheduled to be completed in January, 2019.

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 (17)
- Examine.com (0)
- Treato.com
- DrugAge (0)

- Geroprotectors (o)
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca

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