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.

Vinpocetine

Evidence Summary

A few clinical trials suggest several potential benefits of vinpocetine including memory improvement and increased cerebral blood flow and metabolism. It is likely safe for short term use, but the safety of chronic use has not been tested.

Neuroprotective Benefit: Several short clinical trials and preclinical studies suggesting small potential neuroprotective effects against damage, as well as potentially improved memory and increased cerebral blood flow and metabolism.

Aging and related health concerns: There is some preclinical evidence that vinpocetine may help conditions associated with inflammation.

Safety: Seven clinical studies and meta-analyses have reported few adverse effects; however, evidence for long-term use is lacking.

What is it? Vinpocetine is a man-made derivative of the alkaloid vinacamine, which is extracted from the seeds of the periwinkle plant (*Vinca minor*). While the available scientific evidence varies, it is suggested to enhance cerebral blood flow and have neuroprotective effects for epilepsy, stroke, and dementia. It is widely used in Japan, Russia, and Europe for the treatment of cerebrovascular disorders. Vinpocetine is not approved in the United States as a pharmaceutical, but can be purchased as a dietary supplement (Monograph 2002, WebMD).

Neuroprotective Benefit: Several short clinical trials and preclinical studies suggesting small potential neuroprotective effects against damage, as well as potentially improved memory and increased cerebral flow and metabolism.

Types of evidence:

- 3 clinical trials reviewed in 4 meta-analyses and systematic reviews
- 8 preclinical studies
- 1 review including mostly preclinical evidence

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

There is limited evidence of vinpocetine's usefulness in improving memory (Heckman et al., 2015). Reaction time in a memory test was reported in healthy female volunteers after vinpocetine administration (Subhan et al., 1985) as well as a phase IV non-controlled, open-label clinical trial evaluating the effectiveness of Cognitex™, a nutritional supplement containing several components including vinpocetine (as well as Alpha-GPC, phosphotidyl serine, ashwagandha, among other things) (Richter et al., 2011). Researchers found that a treatment with 3 capsules of Cognitex™ per day (20mg total of vinpocetine) for 12 weeks resulted in statistically significant improvements of treatment in memory recognition, memory recall, and spatial short-term memory at the 2-week follow-up. This observed improvement was maintained after an additional 10 weeks of treatment; however there were no additional significant changes between 2 and 12 weeks (Richter et al., 2011).

Human research to suggest benefits to patients with dementia:

A Cochrane meta-analysis of 3 trials (Szatmari et al., 2003) concluded that, although vinpocetine might benefit patients with cognitive impairment, the evidence is inconclusive and does not support clinical use because of the small size and duration of the trials and the inconsistent reporting of adverse effects. Specifically, the three RCTs assessed the effect of vinpocetine treatment on 583 mild to moderate

dementia patients. Doses ranging from 30mg to 60mg per day for a duration of 12 to 16 weeks demonstrated statistically significant improvements on the Clinical Global Impression Scale (CGI Scale), which evaluates both severity of illness and clinical improvement between baseline to follow-up, and the Syndrom-Kurztest (SKT), a measure made up of nine subtests examining memory and attention deficit. Participants receiving 15mg doses of vinpocetine did not show a statistically significant difference between groups. Overall, when examining results without respect to differences in dosage or treatment duration, there was a statistically significant difference in favor of vinpocetine treatment versus placebo. Researchers concluded that while benefits were seen, these studies included small sample sizes and determined the results inconclusive and unable to support clinical use (Szatmari et al., 2003, Fenzl et al., 1986, Blaha et al., 1989, Hindmarch et al., 1991).

Additionally, a clinical trial of 15 Alzheimer's patients who were treated with increasing doses of vinpocetine (30, 45, and 60 mg per day) over the course of a year was negative. Results did not show an improvement in cognition as assessed by psychometric testing or through CGI measures at any dose tested (Thal et al., 1989). The available evidence does not appear strong enough to support clinical implementation (Heckman et al., 2015).

Another prospective clinical study in Nigeria evaluated the effect of Cognitol™ (vinpocetine) between 56 cognitively impaired patients (diagnosed with either dementia or epilepsy), and 56 controls matched on age, sex, and education. At baseline, study participants were assessed with a short cognitive test, and the cognitively impaired group did significantly worse than the controls. Following treatment with 5 mg Cognitol™ two times a day for 12 weeks that was administered for every participant, the cognitively impaired group demonstrated a statistically significant improvement in memory and concentration from baseline (Ogunrin 2014).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Vinpocetine has been shown to enhance long-term potentiation (LTP) (Molnar and Gaal, 1992), improve structural development of dendritic spines (Lendvai et al., 2003), and improve memory recall (DeNoble 1987).

Vinpocetine's properties as a phosphodiesterase (PDE) type 1 inhibitor have garnered attention toward its neuroprotective potential. PDE1 inhibitors are able to improve levels of secondary messengers in the cAMP/cGMP pathway, which in turn activate a cascade of kinases and transcription factors that promote the expression of plasticity-related genes. Neuronal plasticity is critical to neuron proliferation, survival, and differentiation, and overall healthy brain development and maintenance (Medina 2010, Heckman et

al., 2015). Interruption of neuronal plasticity can lead to cognitive impairment, hinder brain development, and is related to neurodegenerative conditions such as Alzheimer's disease (Medina 2011).

Another study demonstrated that PDE type I inhibitors helped replenish neuronal plasticity, as measured by ocular dominance, in ferrets with early exposure to alcohol (Medina et al., 2006,). Similar results were observed in a study of rats that were exposed to alcohol during the third trimester equivalent to human gestation. Based on assessments using the Morris Water Maze, vinpocetine treatment resulted in significant improvement in performance of alcohol-exposed rats, suggesting improved learning performance (Filgueiras et al., 2010).

There has been additional moderate preclinical evidence which suggests neuroprotective effects following vinpocetine treatment for cerebrovascular diseases (Patyar et al., 2011). Cognition was enhanced after vinpocetine treatment following induced memory impairment by scopolamine and hypoxia in rats (DeNoble, 1987). Another study suggested vinpocetine's potential to mitigate NMDA lesion-induced attention deficits and learning disabilities in rats. Both lesion-induced attention deficit and learning disabilities were significantly reduced after vinpocetine treatment (Nyakas et al., 2009). Vinpocetine treatment for 21 days resulted in significant improvement following streptozotocin-induced learning and memory impairments in rats, including reduced oxidative-nitrosative stress, restored levels of reduced glutathione, reduced acetylcholinesterase activity, as well as improved spatial memory and neuronal preservation (Deshmukh et al., 2009).

Stroke:

Additional clinical trial studies have yielded various potential neuroprotective effects of vinpocetine in ischemic stroke patients. Two PET studies examined the effect of IV administration of vinpocetine on chronic ischemic stroke patients. One study reported that single-dose IV treatment (20mg) improved glucose metabolism in the brain (Bonoczk et al., 2000). In the other PET study, a 2-week IV vinpocetine treatment increased cerebral blood flow and glucose metabolism in the brain as. Vinpocetine treatment also resulted in an enhanced mitochondrial function, reduced oxidative stress and reduced toxicity in cells treated with β-amyloid (Szakall et al., 1998). An additional randomized clinical trial assessed vinpocetine treatment in acute ischemic stroke patients, where treatment group patients showed marginally significant improvement on the NIH Stroke Scale (Feigin et al., 2001).

A Cochrane meta-analysis evaluated its effectiveness in reducing fatality or dependency in survivors of acute ischemic stroke and found limited reliable studies and inconclusive evidence overall. Only two

studies were included in the analysis. These two studies totaled 70 acute ischemic patients who received either 40 mg of vinpocetine in 200 ml dextran intravenous infusion for three weeks (Werner, 1986), or a combination of intravenously administered vinpocetine in addition to 10mg of vinpocetine orally three times a day for five to seven days (Feigin et al., 2001). The outcome measure of stroke severity was determined by the NIH Stroke Scale and the Glasglow Coma Scale. Results did not show any statistically significant changes in systolic or diastolic blood pressure, and while vinpocetine treatment improved neurological recovery of impairment and functional outcome of disability, none of these changes were statistically significant (Feigin et al., 2001).

An additional randomized controlled trial including 43 ischemic stroke patients demonstrated that intravenous administration of vinpocetine in a saline solution resulted in an increase of cerebral blood flow as well as parenchymal oxygen extraction (Bonozck et al., 2002).

For both studies, there was no statistically significant difference between treatment and control groups for death or disability/dependency. The authors concluded that there was not enough evidence to support the efficacy of vinpocetine as a treatment for patients with acute ischemic stroke (Bereczki and Fekete, 2008).

Aging and related health concerns: There is some preclinical evidence that vinpocetine may help conditions associated with inflammation.
Types of evidence:

- 1 meta-analysis
- 1 systematic review
- 1 randomized controlled clinical trial
- 2 preclinical studies

As discussed in the neuroprotective benefits section, vinpocetine has shown anti-inflammatory properties, and has therefore been explored as a potential treatment for various age-related diseases. A review examining the effect of vinpocetine on atherosclerosis and ischemic stroke concluded that vinpocetine has the ability to greatly impact the development of both diseases, mainly due to its ability to inhibit the IKK/NF-kB pathway, a critical transcription factor process involved in the regulation of innate and adaptive immune responses. This type of regulation allows vinpocetine to reduce inflammation by limiting the proliferation of vascular smooth cells (VSMCs), and subsequently enhance cerebral blood flow and regulate the formation of atherosclerotic lesions (Zhang and Yang, 2014).

An additional preclinical study using a mouse model of hyperlipidemia-induced atherosclerosis in ApoE knockout mouse demonstrated that vinpocetine treatment of 5mg every other day was able to reduce atherosclerosis formation. Reduction of LOX-1 expression was observed through vinpocetine treatment, suggesting that vinpocetine-mediated inhibition of LOX-1 expression is a probable mechanism through which vinpocetine mitigates lipid accumulation and atherosclerosis formation. These results demonstrate the potential for vinpocetine as a therapy for atherosclerosis (Cai et al., 2013).

Vinpocetine has also been examined in a preclinical study as a therapy for breast cancer. Results *in vivo* and *in vitro* demonstrate that vinpocetine treatment effectively inhibited proliferation of various types of human breast cancer cells by obstructing the cell cycle at the G_0/G_1 phase. It was also observed that vinpocetine stimulated cell apoptosis through a mitochondria-dependent pathway and was able to limit the migration of MDA-MB-231, a highly-metastatic cell. It is suggested that vinpocetine acts on Akt/STAT3 signal transduction pathway as well as the IKK/NF-kB pathway in order to inhibit breast cancer development (Huang et al., 2012).

Inflammation:

Vinpocetine has also demonstrated anti-inflammatory properties through a mechanism other than PDE inhibition, but through an inhibition of the IkB kinase complex (IKK). This pathway involves the reduction of TNFα-induced expression of proinflammatory molecules. Following vinpocetine treatment, researchers have observed significantly reduce polymorphonuclear neutrophil infiltration in lung tissues of mice. The combination of both anti-inflammatory and cognitive improvement effects generates a strong interest for continued research on vinpocetine's potential role in treating neurodegenerative conditions such as Alzheimer's and Parkinson's disease (Jeon et al., 2010, Medina 2010). However, no long-term clinical evidence is currently available and is necessary in order to solidify these suggested implications.

Safety: Seven clinical studies and meta-analyses have reported few to none adverse effects; however evidence for long-term use is lacking.

Types of evidence:

- Several short clinical trials

While vinpocetine has been shown in various clinical studies to be safe, evidence for clinical long-term use is limited. Based on the reviews and clinical trials previously discussed, doses ranging from 5 mg to 60 mg daily appear generally safe when taken for up to 16 weeks with few reported adverse effects (Bonoczk et al., 2000, Feigin et al., 2001, Szatmari et al., 2003, Bereczki and Fekete, 2008, Patyar et al., 2011, Richter et al., 2011, Ogurin 2014). Additionally a study evaluating the safety and effectiveness of vinpocetine treatment of 10 mg three times a day for 30 days and then 5mg three times a day for 60 days, in patients with chronic vascular senile cerebral dysfunction, reported no serious related side effects (Balestreri et al., 1987).

There is a lack of evidence on the safety of vinpocetine in pregnant women and use should be avoided. Additionally, due to the fact that vinpocetine decreases platelet aggregation, it should be avoided by patients on blood thinning medications (Patyar et al., 2011). There has been interaction shown with warfarin (Coumadin™), which is used to slow blood clotting. Vinpocetine may increase the amount of time warfarin remains in the body and subsequently increase the chances of bruising and bleeding (WebMD). Vinpocetine is also not recommended for use by anyone with hemophilia, heart problems, or low blood pressure (Drugs.com).

Dosing and Sources:

There is not enough available evidence to suggest that one form of vinpocetine supplementation is superior to another. Dosing depends on specified use, the source of the supplement, and various other factors.

Vinpocetine supplements are distributed by various manufacturers and are available in capsules and tablets in doses ranging from 10 to 30 mg in quantities ranging from 60 to 120 capsules for $15-30. No specific dose has been shown to improve cognitive health because no studies have been completed on this assessment. For the studies reviewed it is difficult to make a comparison between human and animal doses used for treatment.

Research underway:

To our knowledge, no studies are underway to evaluate vinpocetine treatment on cognitive aging or age-related disease. Further clinical trials with longer treatment duration and larger study samples are needed in order to more thoroughly evaluate the potential of vinpocetine as a prevention or treatment for cognitive decline. Many treatments involve vinpocetine as a component of a combination therapy, and these also need to be included for further evaluation or development in order to fully assess the

clinical value of vinpocetine. These combination treatments might also benefit from different trial designs in order to fully assess its potential.

Search terms:

- Pubmed and Google Scholar: "Vinpocetine", "Vinpocetine" + "dementia", "Vinpocetine" + "Alzheimer's disease", "Vinpocetine" + "aging", "Vinpocetine" + "cognitive aging", "Vinpocetine" + "memory", "Vinpocetine" + "neuroprotective", "Vinpocetine" + "mortality", "Vinpocetine" + "longevity", "Vinpocetine" + "lifespan", "Vinpocetinve" + "preventative", "Vinpocetine" + "safety", "Vinpocetine" + "adverse effects", "Vinpocetine" + "age-related disease"

- Clinicaltrials.gov: "Vinpocetine", "Vinpocetine" + "dementia", "Cialis" + "dementia", "PDE inhibitor" + "dementia"