*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.*

# PDE5 inhibitors (tadalafil, sildenafil, vardenafil)

**Evidence Summary**

PDE5 inhibitors are effective in treating erectile dysfunction and pulmonary hypertension; research is underway to test whether it can also treat cognitive decline or dementia.

**Neuroprotective Benefit:** The evidence is mixed on the acute cognitive effects of PDE5 inhibitors, and no studies have tested whether PDE5 inhibitors can prevent age-related cognitive decline or dementia.

**Aging and related health concerns:** PDE5 inhibitor treatment reduces mortality in patients with pulmonary arterial hypertension, but no research has addressed whether PDE5 inhibitors increase lifespan or prevent age-related diseases.

**Safety:** PDE5 inhibitors are well-tolerated in most people and side effects are generally mild, but should not be used if you take nitrate drugs for chest pain or heart problems as this can lead to a sudden and serious drop in blood pressure.

**What is it?** There are 3 oral drugs available in the USA that are reasonably selective inhibitors of PDE5 (phosphodiesterase 5): Tadalafil (Cialis® or Adcirca®), Sildenafil (Viagra®, Revatio®), Vardenafil (Levitra®). PDE5 inhibition relaxes muscles and increases blood flow to specific areas of the body, largely through increasing cyclic GMP. The specificity of these drugs for PDE5 versus other phosphodiesterases varies. Tadalafil has some activity on PDE11 while sildenafil and vardenafil acts on PDE6 and other PDEs (detailed in Table 2 here[1]). Sildenafil and tadalafil are approved for erectile dysfunction and pulmonary arterial hypertension. Tadalafil is also approved for benign prostatic hyperplasia (enlarged prostate). Another PDE5 inhibitor, Udenafil, is not available in the United States.

**Neuroprotective Benefit:** The evidence is mixed on the acute cognitive effects of PDE5 inhibitors, and no studies have tested whether PDE5 inhibitors can prevent age-related cognitive decline or dementia.

Types of evidence:

- 3 randomized controlled trials examining acute effects of PDE5 inhibitors on cognitive functions
- 1 uncontrolled clinical trial examining the effects of udenafil (Zydena™) on cognitive functions
- Numerous preclinical studies

Several labs report that PDE5 inhibitors might protect against dementia but the studies for neuroprotection are limited to rodent studies and plagued by discrepancies.

Specifically, various rodent studies have reported that PDE5 inhibitors can reverse cognitive impairments and pathology in aged wild-type mice and transgenic Alzheimer's mouse models through mechanisms including reduced tau hyperphosphorylation (via GSK3b activation), increased BDNF, anti-inflammatory action, increased pCREB signaling, and reduced apoptosis and cell death [2; 3; 4; 5]. Beta-amyloid pathology has been reversed in some [3; 6] but not all [2; 5] studies.

Whether these effects will occur in humans has yet to be tested. No human studies, observational or randomized, have examined if the use of PDE5 inhibitors can protect against dementia or brain aging. Given the widespread use of the drugs, the lack of observational data across many health indications is surprising but possibly related to a concern that the use of the drugs is underreported. Clinical trials are underway to test Viagra® in traumatic brain injury (NCT01762475,NCT02114775) but not neurodegenerative disease. The molecular target, PDE5, appears to be expressed in the human brain despite one study that reported otherwise (reviewed in [7]).

Two small human studies in men have reported improved cognitive function with PDE5 inhibition. In young, healthy men, an acute high dose of sildenafil (100mg) had effects on event-related potentials that suggested improved attention abilities in a 2001 double-blind randomized trial [8]. In 27 Korean men with erectile dysfunction between 40-70 years of age, 2 months of treatment with Udenafil (100 mg every 3 days) improved cognitive function in a trial that was neither randomized nor controlled [9]. Sildenafil was also reported to improve performance by 20% in a memory task dependent on the prefrontal cortex in adult monkeys[10].

In an EEG study in healthy adults, no effects of vardenafil on memory or executive function were found [11].

In a double-blind, 6-way crossover clinical trial in 15 occasional cannabis users, pretreatment with vardenafil did not prevent the cannabis-induced memory impairment [12].

**Aging and related health concerns:** PDE5 inhibitor treatment reduces mortality in patients with pulmonary arterial hypertension, but no research has addressed whether PDE5 inhibitors increase lifespan or prevent age-related diseases.

Types of evidence:

- 1 meta-analyses in pulmonary arterial hypertension
- 1 open-label study

Little research exists on whether PDE5 inhibitors increase lifespan or slow aging in general, apart from the potential effects on the aging brain reported like increased BDNF. One 2006 open-label study in 20 patients reported that sustained resumption of sexual activity with 12 months of Cialis treatment (10-20mg on demand) decreased estrogen levels but not testosterone levels in middle-aged men but the reliability of this result and its relevance to lifespan and aging is unclear.

In a meta-analysis of 6 RCTs in patients with pulmonary arterial hypertension, the PDE5 inhibitor group had reduced mortality, increased 6-min walk distance, and improved hemodynamic parameters compared to the placebo group [13].

**Safety:** PDE5 inhibitors are well-tolerated in most people and side effects are generally mild, but should not be used if you take nitrate drugs for chest pain or heart problems as this can lead to a sudden and serious drop in blood pressure.

Types of evidence:

- 2 meta-analyses in pulmonary arterial hypertension (6RCTs)
- 1 meta-analysis in erectile dysfunction (5 RCTs)
- 1 meta-analysis in women with sexual dysfunction (14 RCTs)
- 1 meta-analysis in studies with cardiovascular outcomes (24 RCTs)
- 2 reviews

Although men with erectile dysfunction are at higher risk of coronary artery disease and all-cause mortality, the use of PDE5 inhibitors does not appear to increase the risk of mortality more than placebo in people healthy enough for some exercise [14]. A systematic review of randomized trials compared treatments for pulmonary arterial hypertension and reported that PDE5 inhibitors reduced hospitalization, increased walking distance, and increased headache incidence. Insufficient data was available for mortality rates but the meta-analysis trended towards decreased mortality rates [15]. Long-term observational studies would be more accurate but some researchers argue that the risk of cardiovascular adverse events including mortality are higher than placebo and difficult to gauge because of widespread underreporting of PDE5 inhibitor use by men [16].

Common side effects of PDE5 inhibitors include headache [15], flushing, symptoms of the common cold, upset stomach, muscle pain, and back pain (Drugs.com). Rare side effects may include sudden vision loss, in response to decreased blood flow to the optic nerve of the eye, particularly in people with comorbidities of heart disease, diabetes, and other conditions. Sudden hearing loss has also been reported although very rarely (15 reports with sildenafil). People are recommended to avoid PDE5 inhibitors if they are taking nitrate drugs (eg. nitroglycerin, isosorbide dinitrate or mononitrate, amyl nitrate or nitrate "poppers") because of a risk of a rapid and serious drop in blood pressure. Drugs.com also reports negative interactions with grapefruit juice and alcohol, and possible interactions with several other drugs.

Multiple meta-analyses show that adverse events are generally mild, including headache, flushing, back pain, diarrhea, and gastric symptoms [13; 17; 18]. Incidence of symptomatic hypotension and other serious adverse events was not statistically different between people taking PDE5 inhibitors versus placebos [18].

**Sources and dosing:** Viagra® and Cialis® have both been reported in rodent studies to have neuroprotective properties. Cialis® does appear to cross into the brain [5], despite some initial reports to the contrary[6]. Doses for chronic daily Cialis® use are 2.5 mg/day, up to 5 mg/day.

**Research underway:** With seed-funding from the ADDF in 2009-2010, Otavio Arancio has been developing novel PDE5 inhibitors that are quinoline derivatives with greater blood-brain-barrier penetrance compared to commercially-available PDE5 inhibitors. A 2013 review of these compounds can be found at pubmed/23313637 [1].

ADDF is sponsoring a clinical trial led by Dr. Atticus Hainsworth at St. George's, University of London, which examines the effectiveness of Cialis® in treating people with vascular cognitive impairment (a potential precursor to vascular dementia). Details of this trial can be found at clinicaltrials.gov.

A clinical trial is also underway to test Viagra® in traumatic brain injury (NCT02114775), which is scheduled to be completed in December 2017.

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