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

Evidence Summary

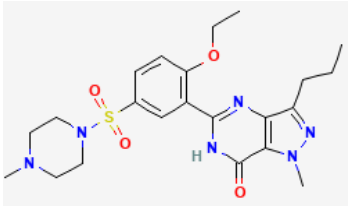
PDE5 inhibitors promote activity-dependent blood flow and may protect against metabolic stress or inflammatory tissue damage. They are better suited for prevention than treatment, with good safety.

Neuroprotective Benefit: PDE5 inhibitors may improve cerebral blood flow, and reduce neuroinflammation, but may not have a significant impact on cognition. Sildenafil may have utility for dementia prevention.

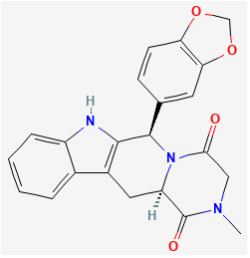
Aging and related health concerns: PDE5 inhibitors may help protect against cardiovascular disease, colorectal cancer, and bone loss. Benefits tend to be more apparent with mild disease and of limited value in moderate to severe disease.

Safety: PDE5 inhibitors are well-tolerated in most people and side effects are generally mild, including headaches, flushing, and gastrointestinal symptoms. Visual disturbances and muscle pain can also occur. Higher doses are associated with worse side effects. They should not be taken with nitrate vasodilators.

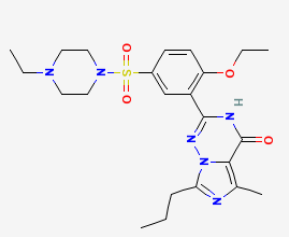
Sildenafil

Availability: Rx	**Dose**: Viagra® for ED: As needed 50 mg (range 25 to 100 mg). Oral tablets. Revatio® for PAH: 5 or 20 mg 3X/day 4-6 hours apart (oral tablets or oral suspension. 2.5 or 10 mg 3X/day (i.v.).	**Chemical formula:** $C_{22}H_{30}N_6O_4S$ **MW**: 474.6 g/mol  Source: PubChem
Half-life: 4 hours		
Clinical trials: Tested in thousands of patients for numerous indications. There have been Phase 3 RCTs for erectile dysfunction (ED), pulmonary hypertension (PAH), heart failure, scleroderma, Raynaud's, and cancer (as an adjunct).	**BBB**: Penetrant **Observational studies**: Sildenafil use is associated with reduced risk for Alzheimer's disease, cardiovascular disease, and colorectal cancer.	

Tadalafil

Availability: Rx	**Dose**: Cialis®: 2.5 mg daily dosing, up to 5 mg or as needed dosing at 10 mg (range 5 to 20 mg) for ED. 5 mg daily for BPH. Oral tablets. Adcirca® for PAH: 40 mg once daily. Oral tablets.	**Chemical formula:** $C_{22}H_{19}N_3O_4$ **MW**: 389.4 g/mol  Source: PubChem
Half-life: 18 hours		
Clinical trials: Tested in thousands of patients for numerous indications. There have been Phase 3 RCTs for erectile dysfunction (ED), benign prostate hyperplasia (BPH), pulmonary hypertension (PAH), scleroderma/Raynaud's, and cancer (as an adjunct).	**BBB**: Penetrant **Observational studies**: Tadalafil use is associated with reduced risk for cardiovascular disease and colorectal cancer.	

Vardenafil

Availability: Rx	**Dose**: Levitra® for ED: As needed 10 mg (5 mg for > age 65), range 5 to 20 mg. Oral tablet. Staxyn® for ED: Same dosing as Levitra. Orally disintegrating tablets.	**Chemical formula:** $C_{23}H_{32}N_6O_4S$ **MW**: 488.6 g/mol  Source: PubChem
Half-life: 4-6 hours		
Clinical trials: Tested in 1000s of patients. There have been Phase 3 RCTs in erectile dysfunction (ED), pulmonary hypertension, and Raynaud syndrome.	**BBB**: Penetrant	
	Observational studies: Vardenafil use reduces inflammatory mediators associated with cardiovascular disease.	

What is it?

Phosphodiesterase 5 (PDE5) inhibitors act on cyclic nucleotide signaling pathways [1]. PDE5 degrades cyclic GMP (cGMP) into 5'-GMP, which results in the attenuation of cGMP-mediated signaling. By targeting cGMP, PDE5 primarily influences nitric oxide (NO)-mediated signaling. Nitric oxide activates guanyl cyclase, which converts GTP to cGMP, which then goes on to activate cGMP-dependent protein kinase (PKG). This pathway leads to a variety of downstream effects, in a context-dependent manner, depending on the downstream effectors present in a given cell. One of the most prominent downstream effects is on vascular endothelial cells, which results in a vasodilatory response, thereby increasing blood flow. There is cross-talk amongst the cyclic nucleotide signaling pathways, such that changes in cGMP levels and signaling can also impact cAMP and the activation of its associated kinase, cAMP-dependent kinase (PKA). Modulation of cyclic nucleotide signaling impacts the induction of endogenous antioxidants, such as Nrf2, pro-inflammatory signaling cascades, namely those mediated by NF-kB, calcium homeostasis and calcium-regulated proteins, such as cAMP response element-binding protein (CREB), which is important for learning and memory, and mitochondrial biogenesis/metabolism via the induction of the transcriptional regulator PGC-1α [2]. Different PDEs (1-11) have different affinities for different cyclic nucleotides, thus the effect of a PDE inhibitor will depend on its selectivity profile toward the different PDEs as well as the overall expression profile of the different PDEs in a given cell type.

Since PDE5 inhibitors act by inhibiting the degradation of cGMP, and thus prolonging cGMP-dependent signaling, their efficacy can also be dependent on the induction capacity of nitric oxide. If an individual has a regional or systemic deficit in nitric oxide production and/or the ability of nitric oxide to produce cGMP, then cGMP levels will be chronically reduced. Although the PDE5 inhibitors can be beneficial toward helping restore cGMP signaling, the level of benefit is likely to decrease as the deficit in cGMP production becomes more severe. Thus, epidemiological studies suggest that there is greater benefit for PDE5 inhibitors in the prevention of age-related diseases associated with declines in these protective signaling pathways than for the treatment of chronic conditions where significant tissue damage has already taken place. Due to their primary effect on vascular dynamics, PDE5 inhibitors are primarily used for indications aimed at restoring activity-dependent blood flow. The activity-dependency stems from local elevations of nitric oxide/cGMP to stimulate the blood flow to that area.
This report will focus on the major PDE5 inhibitors, sildenafil, tadalafil, and vardenafil. Other PDE5 inhibitors include, avanafil (Stendra®) which is available in the U.S. and Europe, udenafil (Zydena®), which is available in South Korea, and mirodenafil (Mvix®), which is available in South Korea, and lodenafil (Helleva®), which is available in Brazil.

Sildenafil is a PDE5 inhibitor, which was developed by Pfizer. It is marketed under the tradename Viagra® for the treatment of erectile dysfunction, and under the tradename Revatio® for the treatment of WHO Group 1 pulmonary arterial hypertension (PAH). It is also used off-label for Raynaud's phenomenon, female sexual arousal disorder, and altitude sickness. Sildenafil has an IC_{50} of 3.5 nM for PDE5 [3]. Sildenafil only has an approximately 10-fold higher selectivity for PDE5 relative to PDE6 (IC_{50} 34 nM). PDE6 is expressed exclusively in the retina, thus at higher doses, it can impact vision. Sildenafil has a 40-fold higher selectivity toward PDE5 relative to PDE1 and 200-fold relative to PDE11 [4]. It has a 400 to >1000-fold selectivity against the other PDEs. Overall, sildenafil has lowest relative selectivity profile and potency of the major PDE5 inhibitors.

Tadalafil is a PDE5 inhibitor developed by Eli Lilly and Co. It is marketed under the tradename Cialis® for erectile dysfunction and benign prostatic hyperplasia (BPH) (enlarged prostate), and under the tradename Adcirca® for pulmonary WHO Group 1 pulmonary arterial hypertension. It is used off-label for altitude sickness and ureteral stones. Tadalafil has an IC_{50} of 0.94 nM for PDE5, and is one of the more selective PDE5 inhibitors [4]. It is >1000 fold more selective for PDE5 relative to the other PDEs, with the exception of PDE11, where it is about 40-fold more selective (IC_{50} 37 nM), which leads to the side effect of myalgia at higher doses.

Vardenafil is a PDE5 inhibitor developed by Bayer Pharmaceuticals. It is marketed under the trade name Levitra® as oral tablets and as Staxyn® as oral disintegrating tablets for erectile dysfunction. It is the most potent PDE5 inhibitor, with an IC_{50} of 0.7 nM, but shows a lower C_{max} relative to sildenafil and tadalafil, suggesting it may have lower bioavailability, which may account for its lower general efficacy [5]. It is structurally similar to sildenafil, and also shows relatively high inhibition toward PDE6 (IC_{50} 11 nM), with only 15-fold higher selectivity for PDE5, and 130-fold higher selectivity relative to PDE1 [4]. Thus, it can also lead to visual disturbances at high doses.

Neuroprotective Benefit: PDE5 inhibitors may improve cerebral blood flow, and reduce neuroinflammation, but may not have a significant impact on cognition. Sildenafil may have utility for dementia prevention.

Types of evidence:

- 1 systematic review for studies assessing PD5 inhibitors for cerebral blood flow
- 5 clinical trials assessing the effect of PDE5 inhibitors on cognition
- 3 clinical trials assessing the effect of PDE5 inhibitors on cerebral blood flow
- 1 clinical trial for sildenafil in traumatic brain injury
- 1 observational study for sildenafil and AD risk
- Numerous laboratory studies

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

PREVENTION: POTENTIAL BENEFIT

Sildenafil was identified as a potential modifier of Alzheimer's disease (AD) risk in an endophenotype-based epidemiological study [6]. Based on the analysis of insurance claims from 7.23 million individuals in the United States, sildenafil use was found to be associated with a 69% lower AD risk (Hazard ratio [HR]: 0.31, 95% confidence interval [CI] 0.25 to 0.39, $P < 1.0 \times 10^{-8}$), relative to non-users. Notably, sildenafil users were also found to have lower AD risk relative to those using other drugs associated with AD risk reduction. Sildenafil users showed a 55% lower risk relative to users of the antihypertensive losartan, and a 63% lower risk relative to users of the antidiabetic metformin. Sildenafil use was also associated with lower AD risk in populations with higher relative AD risk due to cardiometabolic diseases, such as those with type 2 diabetes, hypertension, and coronary artery disease. The reduction

in risk was seen in patients with sildenafil prescriptions for erectile dysfunction or pulmonary hypertension. The results of this analysis could potentially be confounded by prescribing practices, as individuals in better general health and with higher socioeconomic status may be more likely to be prescribed sildenafil. Additionally, since the majority of the prescriptions were for erectile dysfunction, the participants in this analysis were primarily men.

Tadalafil was tested in a placebo-controlled, cross-over RCT in patients with small vessel disease without dementia (NCT02450253) (n=55) [7]. Cerebral blood flow was measured using an arterial spin labeling MRI protocol within three to five hours of a single 20 mg dose of tadalafil. The study was designed to detect a 15% change in cerebral blood flow. The increases in cerebral blood flow detected in the deep gray matter nuclei, normal appearing white matter, white matter hyperintensities (WMH), and total gray matter did not reach this threshold, with the greatest increase seen in the WMH at 9.8% [8]. This study suggests that tadalafil may modestly improve cerebral blood flow, but it has not been established whether this has a meaningful impact on cognition or dementia risk. Although preclinical animal studies indicate that tadalafil can get into the brain, it is generally considered to have poorer BBB penetration relative to other PDE5 inhibitors [9].

COGNITION: NO CLEAR BENEFIT

Sildenafil: 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 [10]. Sildenafil was also reported to improve performance by 20% in a memory task dependent on the prefrontal cortex in adult monkeys [11].

Udenafil: In 27 Korean men with erectile dysfunction between 40-70 years of age, two months of treatment with Udenafil (100 mg every 3 days) improved cognitive function in a trial that was neither randomized nor controlled [12].

Tadalafil: Changes in peripheral inflammation, cognitive function, and the auditory evoked potential were measured in patients with benign prostatic hyperplasia, low urinary tract symptoms, and erectile dysfunction (BPH/LUTS-ED) treated with low dose (5 mg) tadalafil for six months [13]. The study included nine patients and 12 controls. At baseline, scores on neuropsychological battery tests and the Stroop attentional test were lower in patients than healthy controls, but were restored to control levels following tadalafil treatment. Similarly, evoked potentials on an auditory discrimination task (mismatch negativity) were also normalized with tadalafil. These effects were correlated with a reduction in peripheral inflammatory markers (IL-6, IL-17, autoreactive T cells). This suggests that tadalafil may

protect against inflammation-related cognitive impairment, however, without a placebo control group, the robustness of this effect is unclear.
Vardenafil: In an EEG study in healthy adults, no effects of vardenafil on memory or executive function were found [14]. In a double-blind, six-way crossover clinical trial in 15 occasional cannabis users, pretreatment with vardenafil did not prevent the cannabis-induced memory impairment [15].

Human research to suggest benefits to patients with dementia:

Small pilot clinical trials provide evidence that PDE5 inhibitors can impact cerebral blood flow dynamics in patients with cognitive impairment, however, there is currently no clear evidence that these changes can meaningfully impact cognition or slow disease progression.

Sildenafil: POTENTIAL BENEFIT TO BLOOD FLOW BUT UNCLEAR IF CLINICALLY MEANINGFUL
Pilot clinical trials in Alzheimer's disease (AD) patients tested the ability of sildenafil to impact cerebrovascular dynamics. One study assessed the change in fractional amplitude of low frequency fluctuations (fALFF), which is a measure of spontaneous neural activity via resting state fMRI BOLD signal, one hour after a 50 mg dose of sildenafil [16]. These low frequency fluctuations stem from neurovascular mechanisms. AD patients have been shown to have altered resting-state brain function, with increased fluctuations in some areas and decreases in others. The study included ten participants, with an average MoCA score of 18.2. Treatment with sildenafil reduced fALFF in the right hippocampus, an area which typically shows increased fluctuations in this population, suggesting a normalization of activity. The effect on fALFF was not significantly correlated with a measure of cerebral vascular reactivity, which is indicative of the capability of blood vessels to dilate in response to increased blood demand. This suggests that the effect may have been mediated by a combination of changes in oxygen consumption and blood flow. Consistent with this finding, a separate pilot trial of AD patients (MMSE ≥20) showed significant increases in cerebral blood flow (+7.9%±3.7%) and cerebral metabolic rate of oxygen (+5.1%±2.3%) within one hour of 50 mg sildenafil treatment (n=12) [17]. Cerebral blood flow was measured using a phase-contrast MRI technique. There was also a trend toward decreased cerebrovascular reactivity (n=8). These findings suggest that the changes in blood flow with sildenafil treatment stem from neurovascular coupling, in that blood flow increases in particular brain regions occurred in response to increased metabolic demand. The decrease in cerebrovascular reactivity suggests that the increased blood flow following acute sildenafil administration may come at the cost of reduced cerebrovascular reserve capacity, however, chronic use may induce adaptations that restore reserve.

Tadalafil: POTENTIAL BENEFIT TO BLOOD FLOW BUT UNCLEAR IF CLINICALLY MEANINGFUL
In an open-label study in Korea, men (ages 50-75) with erectile dysfunction and mild cognitive impairment (MoCA ≤ 22) were treated with low dose (5 mg) tadalafil for eight weeks [18]. Twenty-five of the 30 participants completed the study. The change in regional cerebral blood flow was measured using a SPECT scan. Tadalafil treatment led to increased regional cerebral blood flow in the postcentral gyrus, precuneus, and brainstem, relative to baseline, but a decrease in the hippocampus. Mean scores on the MoCA increased by 2.88 ± 1.61 points, relative to baseline, suggestive of an improvement in cognitive function. However, due to the small size and lack of a placebo group, it is unclear whether this is a true treatment effect, and if so, whether it is related to the reported changes in cerebral blood flow.

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

The neuroprotective effects of PDE5 inhibitors are primarily mediated through the NO-cGMP-PKG pathway [2]. The activation of this pathway is impaired in the context of AD. Nitric oxide synthase (NOS) activity is reduced, while protein levels are increased in regions of the AD brain, such as the temporal cortex [19; 20]. Levels of cGMP have been found to be reduced in the CSF of AD patients, and the reduction is associated with levels of CSF Aβ42 [21]. Activation of cGMP-associated signaling results in the activation of the Nrf2 endogenous antioxidant system, and inhibition of pro-inflammatory NF-kB signaling [2]. cGMP can also lead to the induction of cell survival pathways. Upregulation of this signaling can protect against learning and memory deficits through the induction of CREB and BDNF. Activation of the NO-cGMP-PKG pathway can also lead to induction of PGC-1α, the master transcriptional regulator of mitochondrial biogenesis, via activation of sirtuin-1. This can improve cellular bioenergetics. Therefore, by prolonging cGMP signaling, PDE5 inhibitors can reverse the deficits in energy production, stress resistance, cell survival induction, neurogenesis, and neuronal plasticity that stem from the reduction in cGMP levels in the AD brain. Some studies have also found that PDE5 inhibitors can reduce pathogenic tau hyperphosphorylation through the inhibition of GSK-3β, and promoting phosphorylation at residues that reduce the propensity for aggregation [6; 22].
These neuroprotective effects have been demonstrated in a variety of preclinical rodent and cell models [2]. Most studies have used sildenafil, but similar neuroprotective mechanisms have also been elicited in studies using tadalafil and vardenafil. Due to the context-dependent nature of cyclic nucleotide signaling, the outcomes and efficacy of PDE5 inhibitors may depend on the overall concentration of the different types of cyclic nucleotides, the activity level of the different PDEs as well as the dose of PDE5 inhibitors. The latter may be particularly important for sildenafil, which has the lowest level of selectivity for PDE5. Lower doses show greater benefit than higher doses due to cross-talk with PDE3 and PDE2. At

low doses, sildenafil indirectly inhibits PDE3, leading to an elevation of cAMP, whereas at high doses it indirectly activates PDE2, leading to a decrease in cAMP and the suppression of the neuroprotective pathways. Thus, when used at a high dose, sildenafil may need to be combined with a non-selective PDE inhibitor [2].
While the modulation of these pathways has been consistently seen in preclinical models, it is not yet clear the degree to which they are activated in humans in response to PDE5 inhibitor use. The capacity to induce nitric oxide and cGMP is likely to play a role in efficacy, as PDE5 inhibitors prolong signaling by extending the half-life of cGMP, thus their potential efficacy is likely diminished if there is a deficit in the generation of cGMP.

Cerebrovascular mechanisms: INCREASES ACTIVITY-DEPENDENT BLOOD FLOW
Changes in cerebrovascular dynamics are the primary effects of PDE5 inhibitors, thus the restoration of blood flow to hypoperfused areas is expected to be the major mechanism by which PDE5 inhibitors protect against tissue damage. A systematic review of 16 studies including 353 participants assessed the effect of PDE5 inhibitors on cerebral blood flow [23]. Consistent with their role in activity-dependent blood flow regulation, PDE5 inhibitors were found to improve cerebrovascular regulation and responsiveness, but had minimal effects on resting cerebral blood flow. These findings suggest that PDE5 inhibitors may not necessarily improve blood flow to brain regions of damage unless it is coupled with an increase in neuronal activity or stimulation to that area. This may account for the modest effects on outcome measures typically seen in clinical trials. If, as suggested by some trials, that PDE5 inhibitors can also increase bioenergetics, then the increased metabolic demand may help promote blood flow to these brain regions [17].

Traumatic brain injury: POTENTIAL MINOR BENEFIT
Sildenafil was tested in a Phase 2a, placebo-controlled, crossover RCT in traumatic brain injury (TBI) to test its ability to mitigate cerebrovascular injury (NCT01762475) [24]. Relative to healthy controls, cerebrovascular reactivity was significantly increased in patients with TBI following a single 50 mg dose of sildenafil (n=43). Baseline cerebrovascular reactivity was reduced in the TBI population, and acute sildenafil treatment provided for a near-normalization. In an 18-week chronic dosing study (n=23), there was a trend toward correlation between improvement on the neurophysiological test, trail-making-test-A (TMT-A), and the change in cerebrovascular reactivity (Spearman's r = 0.55, P = 0.028). Six subjects (27%) noted clinical improvement during the sildenafil phase, while only two (9%) noted improvement during the placebo phase. Based on a Fisher test analysis, sildenafil use showed a trend toward benefit in this population (Relative risk [RR] 4.00 (95% CI 0.95 to 16.8, P = 0.069).

APOE4 interactions: Not established

Aging and related health concerns: PDE5 inhibitors may help protect against cardiovascular disease, colorectal cancer, and bone loss. Benefits tend to be more apparent with mild disease, and of limited value in moderate to severe disease.

Types of evidence:

- 4 meta-analyses for PDE5 inhibitors in pulmonary hypertension
- 2 meta-analyses of observational studies for PDE5 inhibitors and cancer risk
- 1 meta-analysis of sildenafil RCTs in diabetics
- 1 systematic review for sildenafil in exercise/hypoxia
- 1 systematic review of preclinical studies for PDE5 inhibitors in stroke
- 3 clinical trials for PDE5 inhibitors as adjunct cancer therapies
- 2 clinical trials for PDE5 inhibitors in acute kidney injury
- 1 clinical trial for sildenafil in liver disease (NAFLD)
- 1 clinical trial for tadalafil in stroke
- 2 observational studies for PDE5 inhibitors and cardiovascular disease risk
- 1 prospective study of vardenafil on cardiovascular risk in diabetics
- 1 retrospective observational study for PDE5 inhibitors and cancer risk
- Numerous laboratory studies

Pulmonary hypertension: BENEFIT FOR PULMONARY ARTERIAL HYPERTENSION
A Cochrane meta-analysis of 36 studies including 2999 participants testing PDE5 inhibitors in pulmonary hypertension found that the efficacy of PDE5 inhibitors depended on the type of pulmonary hypertension [25]. The six-minute walk distance test (6MWD) is a measure of cardiopulmonary exercise capacity, and is commonly used as a primary outcome measure for pulmonary hypertension trials. ***Pulmonary arterial hypertension***: In patients with WHO Group 1 pulmonary arterial hypertension (PAH), treatment with PDE5 inhibitors led to an improvement in WHO functional class (Odds Ratio [OR] 8.59, 95% CI 3.95 to 18.72; 4 trials, 282 participants), the ability to walk 48 meters further in the 6MWD (95% CI 40 to 56 meters; 8 trials, 880 participants), and were 22% less likely to die over a mean duration of 14 weeks (95% CI 0.07 to 0.68; 8 trials, 1119 participants) relative to placebo-treated participants [25]. Thirty-two participants needed to be treated with PDE5 inhibitors to prevent one additional death. These results stem from high-certainty evidence. ***Sildenafil*** was associated with the best treatment

effect, but this may be a sampling bias, because the majority of the studies used sildenafil. In a Bayesian network meta-analysis involving 50 trials and 10,966 participants with PAH, the combination of sildenafil with the endothelial receptor antagonist, bosentan, had the highest probability of being the best treatment option, based on surface under the cumulative ranking curve (SUCRA) [26]. This drug combination was also most effective for the 6MWD (weighted mean difference [WMD] 98.53, 95% CI 69.13 to 127.94). The combination of tadalafil with bosentan was associated with the lowest proportion of clinical worsening, and the combination of tadalafil with ambrisentan was most effective for improving WHO functional class.

Pulmonary hypertension due to heart disease: In patients with pulmonary hypertension secondary to left-heart disease (PH-LHD), the evidence was mixed, which may be reflective of different treatment effects for different underlying causes of heart disease [25]. Overall, treatment with PDE5 inhibitors was associated with reduced odds of WHO functional class improvement (OR 0.53, 95% CI 0.32 to 0.87; 3 trials, 285 participants), a 34-meter improvement in 6MWD (95% CI 23 to 46; 3 trials, 284 participants), and no significant difference in mortality. The poor functional outcomes were largely driven by a trial including patients with valvular disease, suggesting that PDE5 inhibitors may be harmful in this population. Individuals with valvular disease may not be able to tolerate the increased blood flow. Patients with heart failure with reduced left ventricular ejection fraction appear to benefit, as a meta-analysis of 14 studies including 928 patients found that PDE5 inhibitor use reduced the risk of hospitalizations and death (OR: 0.28, 95% CI 0.10 to 0.74; 7 RCTs) [27].

Pulmonary hypertension due to lung disease: It is unclear whether PDE5 inhibitors offer benefit in this population. An analysis of five trials (350 participants) found a minor improvement in 6MWD, but not in functional outcomes or mortality [25]. Although the evidence is limited, PDE5 inhibitor treatment may worsen ventilation problems in patients with pulmonary hypertension due to lung disease by promoting blood flow to poorly ventilated regions of the lung, leading to a perfusion-ventilation mismatch [28]. A separate meta-analysis of nine RCTs (579 participants) found minor improvements in 6MWD and pulmonary artery systolic pressure (PASP), but not in dyspnea or quality of life [29]. There was also very high heterogeneity across trials.

Exercise: POTENTIAL BENEFIT FOR LUNG PARAMETERS UNDER HYPOXIC CONDITIONS

Preclinical and clinical studies suggest that ***sildenafil*** may act as an ergogenic aid to enhance exercise capacity, particularly under hypoxic conditions by decreasing pulmonary vascular resistance and increasing VO_2 max. A systematic review of 14 studies including 210 subjects found that there was a large effect size for sildenafil over placebo in decreasing pulmonary artery pressure (PAP) during exercise (effect size −1.195, 95% CI −0.262 to −2.128) [30]. There was a moderate effect on increasing

pulse oxygen saturation (SPO2) (0.47, 95% CI 0.22 to 0.73). There were small effects for improving cardiac output during exercise (0.303, 95% CI 0.011 to 0.595) and increasing performance at altitude (0.474, 95% CI 0.012 to 0.936). The effects were more apparent at hypobaric altitude, and there were no significant differences between 50 mg and 100 mg sildenafil on these measures.
A preclinical study in rodents suggests that sildenafil may also act as an ergogenic aid by reducing central fatigue via inhibition of the serotonin (5-HT) system [31].

Cardiovascular disease: POTENTIAL BENEFIT FOR PREVENTION IN THOSE AT HIGHER RISK
Erectile dysfunction has been shown to be a predictor of future risk for adverse cardiovascular events in men [32]. While this population is at higher theoretical risk, a Danish cohort study of 71,710 men aged 40–80 years old found that the risk for cardiovascular disease was decreased during the first three years of erectile dysfunction medication use, which was primarily ***sildenafil*** during the time period of this study, (RR: 0.94, 95% CI 0.90 to 0.97), relative to the general population [33]. The risk of myocardial infarction was also reduced (RR: 0.72, 95% CI 0.63 to 0.82). This suggests that PDE5 inhibitors may mitigate the risk for adverse cardiovascular events in a population with elevated risk. A study assessing the association between PDE5 inhibitor use and outcomes in stable coronary artery disease included16,548 Swedish men treated with PDE5i and 1,994 treated with the prostaglandin E1 analog, alprostadil, which is also used for the treatment of erectile dysfunction [34]. Compared with those treated with alprostadil, those taking PDE5 inhibitors had lower rates of mortality (hazard ratio [HR]: 0.88, 95% CI 0.79 to 0.98), a lower risk of myocardial infarction (adjusted HR: 0.81, 95% CI 0.70 to 0.93), and a lower risk of cardiovascular-related death (adjusted HR: 0.83, 95% CI 0.70 to 0.98). Those with the most filled PDE5 inhibitor prescriptions had the lowest mortality rates relative to those with the least number of prescriptions, with a 27% adjusted lower risk of death. The use of PDE5 inhibitors has been shown to improve endothelial function parameters, reduce endothelial inflammatory mediators, and increase levels of endothelial progenitor cells in high-risk individuals [5]. This suggests that the preservation of the vascular endothelium may be a primary mechanism by which PDE5 inhibitors exert their protective effects in the context of cardiovascular disease.

Ischemic stroke: POTENTIAL MINOR BENEFIT
Tadalafil was tested in a pilot placebo-controlled RCT (NCT02801032) in patients (n=20) with small vessel occlusion stroke [35]. Tadalafil (20 mg) was administered twice, with at least one week between doses. There was a minor potentially beneficial effect on some vascular parameters. There was an increase (mean difference 1.57 ± 3.02%) in blood oxygen saturation in the cortical microvasculature 180 minutes post treatment, as measured by near-infrared spectroscopy. There was also a reduction in

diastolic blood pressure (mean difference 7.89 ± 7.34 mmHg). However, there were no significant effects on blood flow velocity in the middle cerebral artery, as measured by transcranial Doppler, or on peripheral endothelial function, measured by EndoPAT.
A systematic review of 32 preclinical studies testing PDE5 inhibitors in ischemic stroke models found that the protective effects were dependent on the NO-cGMP-PKG-pathway as well as PKA signaling [36]. In these studies, PDE5 inhibitors improved cerebral blood flow to ischemic regions, leading to enhanced functional recovery, and were most effective when given within 24 hours of the ischemic event. The studies were mixed as to whether PDE5 inhibitors could impact the ischemic lesion itself. Some studies noted an increase in neurotrophic factors. These studies suggest that the efficacy of PDE5 inhibitors may depend on the timing of administration, as well as the injury microenvironment.

Diabetes: UNCLEAR BENEFIT
There is evidence to indicate increased insulin action via improving muscle glucose uptake through nitric oxide signaling [37]. A meta-analysis of four studies including 198 participants with type 2 diabetes, found that ***sildenafil*** treatment did not show a benefit on glycemic control, as measured by glycated hemoglobin (HbA1c) levels (weighted mean difference [WMD] 0.17%, 95% CI −0.64 to 0.97) [38]. However, the dose varied across the studies (50 to 100 mg, from once daily to twice weekly). An RCT (NCT02219646) including 54 participants with type 2 diabetes found that treatment with ***vardenafil*** (10 mg 2X/day) for 24 weeks did not significantly impact predicted ten-year cardiovascular risk using three different algorithms [39]. However, vardenafil treatment did significantly decrease levels of the inflammatory cytokine IL-6, and elevated levels of IL-6 itself is a risk factor for cardiovascular disease. Since in the context of erectile dysfunction the therapeutic response rate in diabetic men tends to be lower than the general population (50-60% vs 74-97%), there may have been inadequate dosing in some of these studies [38]. Alternatively, the reduced ability of diabetics to produce nitric oxide may limit their ability to benefit, as PDE5 inhibitors primarily prolong nitric oxide's stability rather than promote its generation. These studies suggest that PDE5 inhibitors may be less effective in inducing metabolic benefits in patients with diabetes relative to non-diabetics.

Cancer

PREVENTION: POTENTIAL BENEFIT FOR COLORECTAL CANCER
Melanoma: A meta-analysis of five studies including 866, 049 men found evidence for higher risk for melanoma with PDE5 inhibitor use (relative risk [RR]: 1.11, 95% CI 1.02 to 1.22) [40]. However, the association did not satisfy Hill's criteria for causality as there was no dose-response relationship. The

association was only found with low exposure to PDE5 inhibitors and for early stage (0) disease, suggesting that it was confounded by UV light exposure. Furthermore, there was an association for lower risk of advanced stage melanoma (II to IV) with PDE5 inhibitor use (RR: 0.67, 95% CI 0.46 to 0.97). ***Colorectal cancer***: A meta-analysis of four retrospective studies including 965,044 participants, with a mean follow-up of 12.7 years, found that use of PDE5 inhibitors was associated with lower risk for colorectal cancer (RR: 0.85, 95% CI, 0.76 to 0.95) [41]. The effect was not restricted to a particular PDE5 inhibitor, as ***sildenafil, tadalafil, and vardenafil*** all showed a protective association, though the association is less strong with vardenafil. The risk reduction was driven by chronic use of PDE5 inhibitors, as in subgroup analysis it was only significant in those who had taken PDE5 inhibitors for at least five years (RR: 0.63, 95% CI 0.59 to 0.68). A separate retrospective cohort analysis including 221,538 patients in the Veterans Affairs healthcare system similarly found a greater protective effect with longer PDE5 inhibitor use [42]. PDE5 inhibitor exposure was associated with an 18% lower colorectal cancer risk, with an additional 2.4% reduction for each additional 100 mg dose of sildenafil and a 1.7% reduction for each 10 mg dose of tadalafil. Vardenafil was not associated with lower cancer risk, in this study. The protective effect was driven by patients with at least ten filled prescriptions (11–15 prescriptions HR: 0.878, 95% CI 0.774 to 0.995; 16–20 HR: 0.841, 95% CI 0.73 to 0.968; 21+ HR: 0.536, 95% CI 0.486 to 0.59). The protective effect is thought to be related to their ability to improve intestinal epithelial barrier function [41].

TREATMENT: POTENTIAL BENEFIT AS ADJUNCT WITH IMMUNOTHERAPIES
While PDE5 inhibitors would be expected to have context-dependent effects in cancer, as they can impact immune function and promote cell survival pathways, the majority of preclinical studies, primarily in tumor cell lines, point to an anti-cancer effect [43]. PDE5 inhibitors have also been found to enhance the permeation and retention of chemotherapeutics within tumor tissue by inhibiting the activity of drug efflux transporters in these models [3]. The most promising area for PDE5 inhibitors appears to be in the augmentation of anti-cancer immunotherapies, as there have been a few pilot clinical trials confirming the translatability of this effect. Whether PDE5 inhibitors can have a meaningful impact on patient outcomes remains to be determined.

Prostate cancer: PDE5 inhibitors have been used to help alleviate urinogenital symptoms associated with prostate cancer and its treatment. In an open-label trial (n=96), treatment with tadalafil resulted in similar efficacy on lower urinary tract symptoms in prostate cancer patients, relative to the standard-of-care, tamsulosin [44]. A meta-analysis of nine studies (n=32,629) found that PDE5 inhibitor use was not

associated with a higher risk for prostate cancer (OR: 0.71, 95% CI 0.40 to 1.29), and that its use was not associated with recurrence in patients with a history prostate cancer (RR: 1.09, 95% CI 0.89 to 1.34) [45].

Melanoma: In an open-label trial, patients with pretreated metastatic melanoma (n=12), were given tadalafil as a palliative treatment for four weeks [46]. ***Tadalafil*** was able to penetrate the tumor tissue at dose proportional concentrations. Patients with stable disease show higher levels of CD8+ tumor-infiltrating lymphocytes within metastatic tissue. Treatment with tadalafil led to increased expression of T cell activation markers in CD4+ and CD8+ tumor-infiltrating lymphocytes in the peripheral blood, suggesting that it may enhance the immune system's antitumor response. Tadalafil treatment did not lead to an upregulation of immune checkpoint molecules, such as PD-L1, suggesting that it may be useful in conjunction with checkpoint inhibitors to boost antitumor immunity.

Head and neck squamous cell carcinoma: Tadalafil has been tested as an adjuvant to boost immune responses to immune system-targeted cancer therapies. ***Tadalafil*** (10 mg) was tested in combination with the anti-PD-1 antibody nivolumab (240 mg i.v.) in patients (n=45) with resectable head and neck squamous cell carcinoma (NCT03238365) [47]. Although the four-week tadalafil treatment did not significantly increase the pathologic treatment response, there is evidence that tadalafil altered the immune microenvironment of the tumor. There was an enrichment of natural killer (NK) cells in the tumor and an enhancement to the peripheral effector T cell response. Analysis of cryopreserved PBMCs showed that tadalafil reduced levels of immunosuppressive myeloid derived suppressor cells (MDSCs) and regulatory T cells (Tregs) [48]. Tadalafil (10-20 mg/day based on weight) was also tested in a Phase 1 trial (NCT02544880) as an adjuvant to the antitumor vaccine composed of Mucin1 (MUC1) and polyICLC in patients (n=14) with recurrent head and neck squamous cell carcinoma [48]. This combination reduced the number of exhausted PD-L1+ macrophages in the tumor environment, and increased activated tumor infiltrating T cells. However, there was an upregulation of PD-L1 on CD163 negative macrophages in response to treatment, suggesting that a checkpoint inhibitor may also be needed to achieve a durable antitumor immune response.

Osteoporosis: POTENTIAL BENEFIT (Preclinical)
Preclinical models suggest that PDE5 inhibitors may promote bone formation and inhibit bone loss. PDE5A is expressed in the bone [49]. PDE5 inhibitors increase the expression of vascular endothelial growth factor (VEGF) and VEGF receptor 2 (VEGFR2) in osteoblasts, in a nitric oxide-dependent manner [49]. The prolongation of nitric oxide signaling inhibits bone absorbing osteoclasts, and promotes the activity of bone forming osteoblasts. Treatment with tadalafil or vardenafil for six weeks increases the

bone formation rate in mice [49]. In a separate study, sildenafil and vardenafil for six weeks were shown to increase bone regeneration, restore bone mass, and increase bone strength in mice with osteopenia [50]. Notably, the drug concentrations used (6 mg/kg for sildenafil and 2.5 mg/kg for vardenafil) are approximately half of their respective human equivalent recommended doses, suggesting that the bone stimulating effects of PDE5 inhibitors can be achieved at a low dose, which would be more amenable for chronic use. PDE5 inhibitors were also found to protect against bone loss through the mitigation of oxidative stress in rats with ovariectomy-induced osteoporosis [51].

Acute kidney injury: POTENTIAL MINOR BENEFIT BUT MAY NOT BE CLINICALLY MEANINFUL
PDE5 inhibitors were found to have renoprotective properties in a systematic review of 83 studies in the context of acute kidney injury [52]. The vast majority of these studies were in preclinical models, as only four were human studies, two of which were clinical trials. PDE5A1 and PDE5A2 are widely expressed in tubular epithelial cells in the kidney. The protective effects are likely related to an improvement in medullary blood flow and the maintenance of renal vascular endothelium integrity. Other potential mechanisms include the modulation of cellular bioenergetics through mitochondrial biogenesis via PGC-1α, the induction of pro-survival pathways, and the mitigation of NF-kB-mediated inflammatory processes. The protective effects were less apparent in clinical trials. In a non-randomized trial in patients with renal tumors undergoing open nephron-sparing surgery after renal artery clamping (n=49), ***tadalafil*** pre-treatment reduced some measures of post-surgery kidney dysfunction [53]. The elevation in serum creatinine was attenuated in tadalafil treated patients, and levels of the urinary kidney injury molecule-1 (Kim-1) were reduced, though levels of a different injury marker, urinary NGAL, were not significantly affected by treatment. There was no significant difference in glomerular filtration rate (GFR), a measure of kidney function, between groups in an RCT in which 40 patients undergoing robot-assisted partial nephrectomy after hilar clamping were treated with 100 mg ***sildenafil*** or placebo immediately prior to clamping [54]. The difference between the studies is more likely attributable to the outcome measure than the PDE5 inhibitor used. The positive effect on a biomarker measure, but lack of effect on a functional measure suggests that PDE5 inhibitors exert beneficial effects in the kidney, but that these effects alone are insufficient to demonstrate clinically meaningful effects in the context of a severe injury. While the population and timing of administration may play a role, these studies suggest that PDE5 inhibitors may be better suited to preserving kidney function by protecting against minor insults, and less effective when function has already been lost.

Liver disease: POTENTIAL MINOR BENEFIT BUT MAY NOT BE CLINICALLY MEANINFUL
In patients with non-alcoholic fatty liver disease (NAFLD) (n=91) ***sildenafil*** was tested in a Phase 2 RCT (NCT 02546609) in combination with leucine and metformin, in a formulation called NS-200, at low (1.1 g leucine/0.5 g metformin/0.5 mg sildenafil) or high-dose (1.1 g leucine/0.5 g metformin/1.0 mg sildenafil) twice daily for 16 weeks [55]. This combination was selected to synergistically activate the Sirt1-AMPK-eNOS pathway. There were no significant differences across groups on hepatic fat content or liver enzymes. In the context of subgroup analysis, participants with the highest baseline liver enzymes (ALT > 50 U/L) showed a significant reduction in hepatic fat relative to baseline in the high-dose group, but not in the other groups. Metabolomic analysis also showed a change in the lipidomic profile in this group with treatment. Preclinical comparative effectiveness studies suggest that sildenafil may not be the optimal drug for this indication. In the high-fat diet-induced NAFLD rat model, PDE5 inhibitors, such as sildenafil, were less effective alone, or in combination with metformin, relative to less selective PDE inhibitors, such as pentoxifylline [56; 57].
Preclinical studies suggest that the hepatoprotective effects of PDE5 inhibitors stem from the mitigation of oxidative stress and inflammatory damage. Vardenafil protected against lithocholic acid-induced cholestatic liver damage in male mice through the preservation of the endogenous antioxidant response (Nrf2) and mitigation of NF-kB-mediated inflammation [58]. Sildenafil showed a similar effect on Nrf2 and NF-kB a cholestatic liver disease model in male rats [59]. Pre-treatment with tadalafil protected against thioacetamide-induced liver fibrosis in rats through its anti-inflammatory effects [60]. Vardenafil protected also against concanavalin A-induced hepatitis in male mice through the attenuation of NF-kB-related inflammation [61]. These studies suggest that PDE5 inhibitors may be most beneficial as a preventative to mitigate metabolic-related insults in the liver, and that combination therapy may be needed for PDE5 inhibitors to have an effect once damage has already occurred.

Safety: PDE5 inhibitors are well-tolerated in most people and side effects are generally mild, including headaches, flushing, and gastrointestinal symptoms. Visual disturbances and muscle pain can also occur. Higher doses are associated with worse side effects. They should not be taken with nitrate vasodilators.

Types of evidence:

- 6 meta-analyses of studies assessing PDE5 inhibitor safety
- 1 clinical trial assessing visual side effects of vardenafil
- Several case reports
- Numerous laboratory studies

Multiple meta-analyses show that adverse events are generally mild, including headache, flushing, back pain, diarrhea, and gastric symptoms [62; 63; 64]. Incidence of symptomatic hypotension and other serious adverse events was not statistically different between people taking PDE5 inhibitors versus placebos [63].

A meta-analysis examining 23 studies, including 154,796 participants taking PDE5 inhibitors for erectile dysfunction found that low dose sildenafil (25 mg) and tadalafil (5 mg) had the best therapeutic profile [65]. High dose sildenafil (100 mg) was associated with the most treatment-related adverse events. Similarly, a network meta-analysis of 179 RCTs including 50,620 participants taking PDE5 inhibitors for erectile dysfunction, found that low dose sildenafil (25 mg) had the highest probability of being the best intervention, while intermediate dose sildenafil (50 mg) was best for cardiovascular disorders [66]. High dose mirodenafil (150 mg) was associated with the highest level of adverse events, followed by high dose sildenafil (100 mg). The most common adverse events were flushing and headaches. The side effect profile varied slightly with the different PDE5 inhibitors, such that high dose sildenafil (100 mg) showed the highest incidence of visual disturbances, while vardenafil and udenafil were more likely to result in nasal congestion. Tadalafil had lower incidences of flushing and headaches, particularly at low doses (2.5-5 mg). In a Cochrane meta-analysis of 36 trials testing PDE5 inhibitors in pulmonary hypertension (n=2999 participants), tadalafil was associated with a greater incidence of headaches (OR 2.46 vs OR 1.43), gastrointestinal events (OR 1.93 vs OR 1.50), and muscle and joint pain (OR 4.02 vs OR 1.48), relative to sildenafil [25].

The side effect profile of the different PDE5 inhibitors is largely reflective of their relative PDE selectivity profile [5]. Since it has the least relative specificity for PDE5, sildenafil leads to higher activity towards other PDEs at high doses, leading to off-target side effects. In particular, sildenafil also inhibits PDE6, which is found exclusively in the retina, thus leading to temporary visual disturbances. Vardenafil can also inhibit PDE6 at high doses, but due to higher relative selectivity for PDE5, the visual effects may be less severe. A clinical trial including 24 healthy male subjects found that electroretinogram b-wave amplitudes were reduced at one hour following administration of two 20 mg tablets of vardenafil, and remained lower for six hours [67]. This was accompanied by increased errors on the Farnsworth-Munsell 100-hue test, which measures illumination discrimination ability during the same time frame. The FDA labels for sildenafil and vardenafil contain warnings for the risk of vision loss due to non-arteritic anterior ischemic optic neuropathy (NAION), which can lead to permanent loss of vision in some cases (Viagra label, Levitra label). There is an approximately two-fold increase in the risk of NAION within five half-lives of PDE5 inhibitor use. The FDA labels for sildenafil, tadalafil, and vardenafil all contain warnings

for the risk of sudden hearing loss, though it has not been established whether this effect is drug-related. At high doses, tadalafil inhibits PDE11, which is expressed in muscle, leading to the side effect of muscle and back pain. Overall, the risk of side effects increases with dose, such that low doses offer the best benefit-to-risk profile.

The FDA adverse event reporting system reported that sildenafil had a negative impact on emotional and aggressive behaviors [68]. Preclinical studies show that chronic sildenafil use can increase aggressive behaviors in male mice. Thus, PDE5 inhibitors, such a sildenafil, may worsen aggressiveness in some people, though they may benefit some individuals at the other end of the spectrum, via their antidepressant properties.

In preclinical studies, PDE5 inhibitors show the capacity to both increase and decrease risk for seizures, depending on the model used [69; 70; 71]. It is not clear how this translates to humans, therefore due to its potential to lower induction threshold for some types of seizures, caution is warranted in individuals with a history of seizures.

Rare cases of hemorrhages have been reported [72; 73]. These tend to occur in individuals with underlying vascular pathology and/or in the context of higher than recommended doses.

A case report of transient global amnesia was related to an MRI lesion consistent with cytotoxic edema following the use of 100 mg sildenafil [74]. It is hypothesized that sildenafil may increase the risk for hippocampal ischemia or edema by altering blood flow in a manner that induces venous congestion or cortical spreading depression. The individual had a history of migraine, and it is thought that those with migraine may be most susceptible to this rare effect.

Drug interactions:
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. PDE5 inhibitors may also interact with antihypertensives, stemming from its vasodilatory properties. There is also a potential risk for increased bleeding. Due to its mechanism of metabolism, PDE5 inhibitors have moderate interactions with CYP34A inhibitors. There is an interaction with the protease inhibitor, ritonavir, used for HIV, which can dramatically increase serum levels of the PDE5 inhibitor. Dose adjustments are needed in patients with hepatic or renal impairment, as well as in geriatric patients. There are also negative interactions with grapefruit juice and alcohol, and possible

interactions with several other drugs. (FDA label: Sildenafil, Tadalafil, Vardenafil) (Drugs.com: Sildenafil, Tadalafil, Vardenafil).

Sources and dosing:
Meta-analyses have found that doses in the lower end of the recommended range are associated with a better therapeutic profile [65; 66]. Sildenafil is marketed by Pfizer as Viagra® or Revatio® and is also available as a generic. Sildenafil is most commonly dosed at 50 mg orally, as needed, in the context of erectile dysfunction, though it can be prescribed at 25, 50, or 100 mg, with a maximum dose of 100 mg. In the context of pulmonary hypertension, sildenafil is dosed at 5 to 20 mg 3X/day in the form of oral tablets or an oral suspension. Alternatively, sildenafil can be administered intravenously at 2.5 or 10 mg 3X/day for this indication. Tadalafil is marketed by Eli Lily and Co. as Cialis® or Adcirca®, and is also available as a generic. Tadalafil is commonly dosed at 10 mg, as needed though doses range from 5 to 20 mg in the form of oral tablets. For daily maintenance use the dose is typically 2.5 mg oncer per day, but can go up to 5 mg per day. In the context of pulmonary hypertension, tadalafil is dosed at 40 mg once per day. Vardenafil is marketed by Bayer Pharmaceuticals as Levitra® in the form of oral tablets, and as Staxyn® in the form of oral disintegrating tablets. Vardenafil is commonly dosed at 10 mg orally, as needed, with a dosing range from 5 to 20 mg for erectile dysfunction. Dosing for geriatric patients is 5 mg. (FDA label: Sildenafil, Tadalafil, Vardenafil) (Drugs.com: Sildenafil, Tadalafil, Vardenafil).

Research underway:
Sildenafil: According to Clinicaltrials.gov, there are currently 56 active trials for sildenafil. Indications include pulmonary hypertension, liver fibrosis, exercise, female sexual arousal disorder, TBI, newborn brain hypoxia, choroidal ischemia, urinary incontinence, heart failure, cerebrovascular disease, depression, fetal distress, covid-19, cancer, peripheral artery disease, lung disease, and the safety/pharmacokinetics of new formulations.

Tadalafil: According to Clinicaltrials.gov, there are currently 38 active trials for tadalafil. Indications include urinary incontinence, cancer, prostate hyperplasia, diabetes/obesity, depression, pulmonary hypertension, and safety/pharmacokinetics of novel formulations.

Vardenafil: According to Clinicaltrials.gov, there is currently one active trial for vardenafil for pulmonary arterial hypertension.

Search terms:

Pubmed, Google: Sildenafil, Tadalafil, Vardenafil +

- Alzheimer's disease, neurodegeneration, cognition, cerebrovascular, aging, lifespan, cardiovascular, cancer, meta-analysis, systematic review, clinical trial, safety

Websites visited for Sildenafil, Tadalafil, and Vardnafil:

- Clinicaltrials.gov (Sildenafil, Tadalafil, Vardenafil)
- Drugs.com (Sildenafil, Tadalafil, Vardenafil)
- WebMD.com (Sildenafil, Tadalafil, Vardenafil)
- PubChem (Sildenafil, Tadalafil, Vardenafil)
- DrugBank.ca (Sildenafil, Tadalafil, Vardenafil)
- Cafepharma (Sildenafil, Tadalafil)

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