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.

Pridopidine

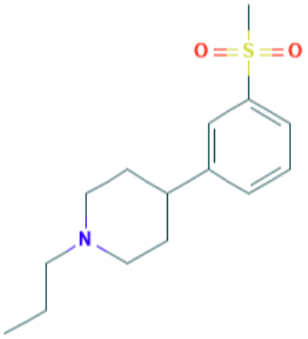
Evidence Summary

Some evidence suggests pridopidine is beneficial in animal models of neurodegenerative disease, though its effects in human patients with Huntington's disease is mixed.

Neuroprotective Benefit: Pridopidine is beneficial in multiple disease models, though its effectiveness in Alzheimer's patients is unclear.

Aging and related health concerns: There is a hypothetical risk for overexpression of the sigma 1 receptor in some other diseases and little evidence that pridopidine would be effective for age-related disorders.

Safety: Current studies in Huntington's patients have suggested pridopidine is generally well-tolerated for up to 3 years, though there are some side effects.

Availability: Not available, in development by Prilenia Therapeutics	**Dose**: 45mg bid	**Chemical formula:** $C_{15}H_{23}NO_2S$ **MW:** 281.4g/mol  **Source:** Pubchem
Half life: 0.25-0.5 hours in mice; 2.5 hours in primates	**BBB**: Penetrant (in mice and primates)	
Clinical trials: 4 completed in Huntington's; 1 ongoing in Parkinson's	**Observational studies**: 0	

What is it?

Pridopidine was originally developed as a 'dopamine stabilizer' for its low-affinity regulation of the dopamine receptor D_2. However, it was later discovered to also act as a high-affinity agonist of the sigma 1 receptor. The sigma 1 receptor is a transmembrane protein in mitochondria endoplasmic reticulum which acts as a chaperone for many proteins, including several ion channels. Since the sigma 1 receptor has many binding partners, alteration in its activity can have many pleotropic effects including alterations in membrane excitability, promoting BDNF expression, and modulation of lipid dynamics. In Alzheimer's disease, the sigma 1 receptor is reduced, and activating the receptor may increase its activity. Mutations in the sigma 1 receptor gene are implicated in ALS/FTD and Alzheimer's disease (Ryskamp et al, 2019).

Johnston et al (2019) showed that pridopidine also binds to many other receptors which may mediate some of its effects.

Pridopidine is currently under development by Prilenia Therapeutics for use in Parkinson's disease.

Neuroprotective Benefit for: Pridopidine is beneficial in multiple disease models, though its effectiveness in Alzheimer's patients is unclear.

Types of evidence:

- Biomarker studies in Alzheimer's disease
- 4 RCTs in Huntington's patients
- Preclinical studies in Alzheimer's, ALS, Parkinson's, and Huntington's disease

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

None

Human research to suggest benefits to patients with dementia

A PET study suggested that sigma 1 receptors were reduced in the frontal, temporal, and occipital lobes, the cerebellum, and the thalamus in patients with Alzheimer's disease (note: the Alzheimer's patients were ~12 years older than the control individuals) (Mishina et al, 2008). Another post-mortem study suggested a reduction of 26% of sigma 1 binding in a postmortem study of Alzheimer's patients (Jansen et al, 1993). Several studies have investigated the relationship between the SIGMA1R polymorphisms and Alzheimer's risk with mixed results in different populations (Feher et al, 2012; Huang et al, 2011; Maruszak et al, 2007; Uchida et al, 2005).

*Human research to suggest benefits to patients with **Huntington's***

Pridopidine was found to improve behavior in multiple preclinical studies of Huntington's disease (Reilmann et al, 2019). It was first tested (50mg/day) in a phase 2 study in 58 patients with Huntington's disease. There were no significant benefits in the primary outcomes (a weighted cognitive score). However, there were trends in secondary outcomes, such as a trend toward improvement in affective measures and a significant benefit in severe voluntary motor symptoms (though no changes in other secondary outcomes such as executive function, depression, or anxiety). Notably, there were numerical benefits in all outcome measures in both the placebo and drug group (Lundin et al, 2010).

In a follow-up phase 3 study (MermaiHD) in 437 patients with Huntington's disease over 26 weeks, there were no significant benefits in a change in the modified motor score in the 45mg/day group, though in the 90mg/day group there was a benefit in the modified motor score (-0.99; 95%CI -2.08 to 0.10, p=0.042) that did not reach significance due to a pre-specified multiple comparisons two-sided significance level of α=0.025. In the per-protocol group (those with at least 70% drug compliance), the

benefit was significant (-1.29; 95%CI -2.47 to -0.12, p=0.014). There were no significant changes in secondary measures of cognition, anxiety, or depression. There were also significant benefits on a tertiary endpoint, the unified Huntington's disease rating's scale total motor score (UHDRS-TMS – from which the modified motor score is derived). These results suggest that pridopidine may have some beneficial effects on motor symptoms in Huntington's (de Yebenes et al, 2011). Similar results were seen in a concurrent study (HART) testing the effect of three doses of pridopidine (20, 45, and 90mg/day) over 12 weeks in 271 Huntington's patients, with trends toward motor benefits in the 90mg/day group, nominally significant benefits in the UHDRS-TMS, and no significant effect on secondary outcome measures (The Huntington Study Group HART Investigators, 2012).

Based on the results of these two trials, a final dose-finding phase 2 study (Pride-HD) was conducted to test the effects of pridopidine (45, 67.5, 90, or 112.5 mg twice per day) in 408 patients with Huntington's disease over 26 weeks. They reported there were no significant effects on the UHDRS-TMS at any dose (Reilmann et al, 2019).

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
In vitro, pridopidine increased spine density and long-term potentiation in neurons from Alzheimer's mice and neurons treated with beta-amyloid. These beneficial effects were prevented with coadministration of an siRNA against the sigma 1 receptor. Spine density was also restored with 1-month treatment of oral pridopidine (30mg/kg) in five-month old Alzheimer's mice (Ryskamp et al, 2019).

Other neurodegenerative disease models
ALS – In an *in vitro* ALS model of neuromuscular junctions, pridopidine increased the number of neuromuscular junctions and reduced motor neuron death in neurons from an ALS mouse model. Pridopidine also improved axonal transport in spinal cord explants from ALS mice. Genetic knockout of the sigma 1 receptor showed that this effect was mediated through sigma 1 – though it did have a beneficial effect in these cultures at higher concentration suggesting at high doses it may have off-target effects. *In vivo*, 11-week treatment of pridopidine in ALS mice reduced SOD1 accumulation by ~50% in the spinal cord, improved muscle fiber density and increased the number of neuromuscular junctions – though it had no effect on mortality (Ionescu et al, 2019).

Parkinson's disease – Five-weeks administration of pridopidine improved behavioral deficits in a mouse model of Parkinson's disease with stronger effects at lower doses (0.3mg/kg vs. 1mg/kg). In mice genetically lacking the sigma 1 receptor there were no improvements. At lower doses (but not higher),

there was also a significant increase of dopaminergic neurons and decrease of microglia. Low-dose pridopidine also increased the expression of GDNF, BDNF, and pERK1/2 in the striatum (Francardo et al, 2019).

In an L-dopa-induced dyskinesia in Parkinson's macaque model, pridopidine reduced dyskinesia and decreased the duration of on-time dyskinesia(Johnston et al, 2019).

APOE4 interactions:
None Reported

Aging and related health concerns: There is a hypothetical risk for overexpression of the sigma 1 receptor in some other diseases and little evidence that pridopidine would be effective for age-related disorders.

Types of evidence:

- 1 review on the use of sigma 1 receptor antagonists in other disorders

Although pridopidine is not expected to have any specific effects on lifespan. The sigma 1 receptor has been implicated in a few non-CNS diseases.

Sigma 1 receptors can modulate opioid receptors, with agonists inhibiting opioid signaling and antagonists potentiating opioid signaling. For this reason, sigma 1 receptor *antagonists* (as opposed to pridopidine's agonist activity) have been studied for their use in peripheral neuropathy. They are not reported to alter sensory thresholds under physiological conditions but may reduce pain due to sensitization of sensory receptors.

Increased sigma 1 receptor expression has also been reported in several types of cancer, and sigma 1 receptor *antagonists* have been investigated for oncology for their antiproliferative effects.

Sigma 1 receptor *antagonists* have also been investigated for their use in different psychiatric disorders (Arena et al, 2018).

Despite the use of sigma 1 receptor *antagonists* for these disorders, there is no current evidence that the use of pridopidine will increase the risk. However, it is a hypothetical concern.

Safety: Current studies in Huntington's patients have suggested pridopidine is generally well-tolerated for up to 3 years, though there are some side effects.

Types of evidence:

- 3 RCTs

In the Huntington's studies, serious adverse events were similar to placebo in the MermaiHD study and higher than placebo in the Pride-HD study (0% vs. 10%-11% in all drug groups), though it was generally well tolerated with most adverse events mild or moderate in severity. The most common serious adverse events in the Pride-HD study were gastrointestinal (up to 5%) and injury, poisoning, or procedural (14% in 45mg group, up to 4% in other groups). In the high-dose Pride-HD study, adverse events leading to study discontinuation show a dose-dependent effect (7% in placebo up to 18% in 112.5mg bid). Generally adverse events were balanced between placebo and doses under 90mg/day in both studies. The most common treatment-related adverse events deemed to be study related were insomnia, diarrhea, nausea, and dizziness, though these were similar to placebo at doses under 90mg/day. In open-label extension studies, pridopidine was generally safe and tolerable in patients with Huntington's disease up to 3 years (de Yebenes et al, 2011; The Huntington Study Group HART Investigators, 2012; Reilmann et al, 2019; McGarry et al, 2017).

Drug interactions:
Although there are no reported drug interactions, pridopidine may be metabolized by CYP2D6 so likely could have several drug interactions (Rabinovich-Guilatt et al, 2017). In an open label extension study, there were not reported to be additional adverse events based on concomitant antipsychotics (Squitieri et al, 2013).

Sources and dosing:
Pridopidine is under development and is not currently available. The most effective dose in clinical trials without too many safety concerns was 90mg/day (at 45mg twice per day).

Research underway:
One phase 2 study is underway for levodopa-induced dyskinesia in Parkinson's patients (NCT03992711).

Search terms:

- Pridopidine
- Sigma 1 receptor + Alzheimer's, cancer, cardiovascular, neuropathy

Websites:

- Clinicaltrials.gov
- Pubmed
- Pubchem
- Drugbank.ca

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.