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.

Fasudil

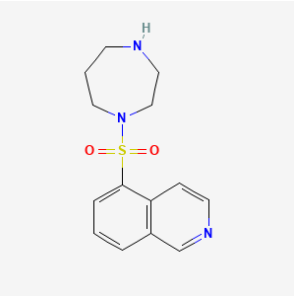
Evidence Summary

Fasudil is efficacious for use in certain cardiovascular conditions, and preclinical evidence suggests benefits of fasudil for neurodegenerative conditions. However, clinical evidence is needed.

Neuroprotective Benefit: A few small case reports or clinical trials have hinted at potential benefit of fasudil. However, larger, more rigorous studies are needed to determine biological efficacy. Ongoing studies may provide more insight and clarity.

Aging and related health concerns: Fasudil has clinical utility for certain specific cardiovascular conditions such as subarachnoid hemorrhage. Fasudil is being studied for other indications, cardiovascular and otherwise.

Safety: Short-term use of fasudil appears to be well-tolerated, with few adverse events reported. Little is known about long-term use of fasudil. Larger, longer studies with rigorous adverse event reporting are needed to fully understand the safety profile.

Availability: Under clinical development in US; prescription use in Japan and China.	**Dose**: Doses used in clinical trial for the oral formulation range from 20-80 mg three times per day and for the intravenous formulation 30 mg three times per day.	**Chemical formula:** $C_{14}H_{17}N_3O_2S$ **MW**: 291.37 g/mol  Source: PubChem
Half-life: 5.5 hours	**BBB**: Penetrant.	
Clinical trials: A review of fasudil indicated over 500 patients have been enrolled in RCTs involving fasudil.	**Observational studies**: No observational studies have been published on fasudil.	

What is it?

Fasudil (also known as HA-1077 or AT877) is perhaps best known for its vasodilatory activity, particularly in blood vessels serving the brain (Ono-Saito & Hidaka, 1999; Killick et al., 2023). Fasudil is an inhibitor of Rho-associated protein kinases (ROCKs), which are serine/threonine kinases that are downstream effectors of the small GTPase Rho. There are two ROCKs: ROCK1 and ROCK2. Both ROCK1 and ROCK2 are inhibited by fasudil. ROCK regulates the cytoskeleton through phosphorylating a variety of targets. Through its modulation of the cytoskeleton, ROCK is involved in a number of cell events such as actin cytoskeleton organization, cell migration, smooth muscle contraction, chemotaxis, cell adhesion, neurite outgrowth, autophagy, and apoptosis (Lee et al., 2022; Guan et al., 2023). ROCK has also been implicated in ROS formation and tau phosphorylation, and can contribute to inflammatory responses (Lee et al., 2022). Clinical trials for fasudil started in the early 1990's, before the discovery of ROCK (1996) and was initially reported as an intracellular Ca2+ channel blocker; further research indicated that the drug acted on ROCK1 and ROCK2, leading to modulation of vasodilation. At higher doses, fasudil may inhibit other kinases including PKA, PKG and PKC, possibly limiting some of its applications. Fasudil is currently approved for treatment of cerebral vasospasm in Japan and China; it is being explored for other cardiovascular applications, as well as use in neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and rare tauopathies.

Asahi Kasei Pharma Corporation received approval for fasudil in Japan in 1995 for the treatment of cerebral vasospasm, and injectable fasudil is currently available in Japan and China for treatment of

cerebral vasospasm and associated symptoms following surgery for subarachnoid hemorrhage. In 2006, Asahi entered into a licensing agreeing with CoTherix to develop fasudil in the United States and Europe. Actelion then bought CoTherix and shuttered the fasudil program. Asahi sued Actelion, and Asahi ultimately was awarded more than $300M in damages. While Actelion appealed the judgement, the judgment was upheld (Article in Forbes; press release). In 2019, Asahi entered into a licensing agreement with Woolsey Pharmaceuticals to develop and commercialize any non-ophthalmic and non-intravenous formulation of fasudil in all territories outside of Japan, China, South Korea, and Taiwan (press release).

Neuroprotective Benefit: A few small case reports or clinical trials have hinted at potential benefit of fasudil. However, larger, more rigorous studies are needed to determine biological efficacy. Ongoing studies may provide more insight and clarity.

Types of evidence:

- 1 randomized controlled trial
- 2 case studies or case reports
- Human Alzheimer's disease post-mortem data for increased ROCK expression
- Numerous reviews
- 1 meta-analysis of animal data
- Numerous laboratory studies

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

No studies have been performed to assess whether fasudil may prevent dementia.

Human research to suggest benefits to patients with dementia:

In one case study of two dementia patients with wandering symptoms, periodic treatment with fasudil with 30-60 mg/day improved wandering symptoms and increased MMSE scores by about 3 points. The study was published in 1996, of relatively poor quality, and is confounded by other drugs (Kamei et al., 1996). Another study of fasudil in patients with dementia and wandering behavior was completed in 2022; results are not yet available. The study enrolled 24 patients. All enrolled patients first underwent a

6-week open-label period #1 in which participants received 30 mg of oral fasudil three times daily for a total of 90 mg per day. Participants were then assessed for whether they appeared to be responding to treatment; the assessment was based on the extent of change of score on the Global Impression of Wandering scale. Non-responders entered an open-label period #2, in which they received 60 mg of oral fasudil three times daily for a total of 180 mg per day. Non-responders to this second open-label phase would move to the final post-treatment visit. Patients who responded to treatment in either open-label period advanced to the double-blind crossover phase. In this phase, participants would receive either placebo or fasudil at their responding dose (either 90 or 180 mg daily) for 6 weeks, at which point the patient would crossover to the other treatment group. The primary outcome measure was change in wandering behavior; other outcome measures included assessments of cognition, safety, and neuropsychiatric symptoms. This study was sponsored by Woolsey Pharmaceuticals (Woolsey Pharmaceuticals resource on the FOUND Study; NCT04793659).

Human autopsy data suggests that ROCK1 protein is elevated in patients with asymptomatic Alzheimer's, MCI, and Alzheimer's disease (Henderson et al., 2016). In addition, human autopsy data suggests that ROCK1 and ROCK2 protein levels are elevated in patients with two tau neurodegenerative diseases (progressive supranuclear palsy and corticobasal degeneration) (Gentry et al., 2016).

A study of 106 male patients with MCI compared the effects of 2 months of treatment with placebo and nimodipine, a calcium channel blocker used for treatment of hypertension, with 30 mg of intravenous fasudil daily and nimodipine combination treatment. The authors reported that the combination treatment was associated with improved verbal fluency, Mini-Mental State Examination (MMSE) scores, and daily functioning. The full study by Yan et al., 2011, has not been published in English; the above details have been reported in a review article from Ballard et al., 2020.

Fasudil has and is also being tested in patients with amyotrophic lateral sclerosis (ALS). There is very preliminary data on fasudil in ALS patients from three compassionate use cases. Three patients with probably or definite ALS were given 30 mg fasudil intravenously twice daily for 20 days. While no conclusions can be drawn from such a small sample size with open-label treatment, the authors did note that one patient had an improvement in slow vital capacity and another had improvements in a measure of muscle units. All three patients had attenuated decline on the ALS Functional Rating Scale during fasudil treatment and at 1 month after fasudil infusions (Koch et al., 2020). A randomized controlled trial of 120 patients with ALS named ROCK-ALS was completed in November 2023; results are not yet available. NCT05218668 is an ongoing open-label study of fasudil in ALS patients described in the

"Research Underway" section. Information from these two studies will hopefully help shed some light on the potential use of fasudil in ALS.

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

As reviewed by several groups, including Koch et al., 2018, Ballard et al., 2020, and Lee et al., 2022, there are several mechanisms of action through which the inhibition of ROCK by fasudil is thought to be neuroprotective. ROCK has many cellular functions, and can promote production and deposition of Aβ, tau phosphorylation, neuritic and synaptic loss, apoptosis, and inflammation. The Parkin-dependent mitophagy pathway may be negatively regulated by ROCK (Mani et al., 2022). Fasudil inhibition of ROCK may decrease neuroinflammation, Aβ production, tau phosphorylation, ROS production, and synaptic loss; and increase neurite outgrowth and neuronal survival. ROCK may also modulate autophagy, and fasudil may therefore affect aggregate load (Koch et al., 2018).

One potential mechanism for fasudil's improvements in Alzheimer's animal models may be due to its anti-inflammatory effects. In microglia cell cultures exposed to advanced glycation end products (which activate the ROCK pathway), fasudil decreased ROS production, NLRP3 expression, NFkB nuclear localization, iNOS expression, COX expression, and promoted an M2 (anti-inflammatory) phenotype (Chen et al., 2017). Fasudil treatment has attenuated astrogliosis and microgliosis in both ALS and AD animal models (Guo et al., 2020). Another potential mechanism by which fasudil might be beneficial in Alzheimer's disease is its ability to induce autophagy. In a transcriptional network analysis looking for drugs that might be repurposed, Iorio et al., 2010 reported that fasudil induces a transcriptional response similar to other autophagy inducing drugs and was confirmed to induce autophagy in human fibroblasts. In preclinical cell and animal models of AD, fasudil treatment can mitigate impaired dendritic arborization and reduce synaptic dysfunction and loss, the latter through the Dkk1-driven Wnt-PCP pathway (reviewed in Koch et al., 2018). As the regulation of the actin cytoskeleton by ROCK is involved in neurite outgrowth as well as synaptic functions such as synaptic vesicle cycling, ROCK inhibitors may have other synaptic functions (Koch et al., 2018, Martín-Cámara et al., 2021)

In an animal model of Alzheimer's disease, high-dose fasudil (10 mg/kg) improved cognition, decreased hippocampal neuron death, and decreased inflammatory markers in the hippocampus (IL-1B, TNFα, NFkB) (Song et al., 2013). Wei et al., 2021 also reports improvements in cognitive function, reduced hippocampal neuronal loss, and mitigated oxidative stress in their animal model of AD after fasudil treatment. In an animal model of cognitive dysfunction (cerebral Streptozotocin injection), fasudil

treatment over 4 weeks reversed cognitive decline and increased the number of synapses in the hippocampus (Hou et al., 2012); other groups have also reported improvements in memory of streptozotocin models after treatment with fasudil (Kumar & Bansal, 2018). In an aged rat model, 4 daily injections of fasudil were associated with dose-dependent improvements in cognition (Huentelman et al., 2009).

APOE4 interactions:

It is not known whether fasudil has any differential effects based on an individual's APOE status.

Aging and related health concerns: Fasudil has clinical utility for certain specific cardiovascular conditions such as subarachnoid hemorrhage. Fasudil is being studied for other indications, cardiovascular and otherwise.

Types of evidence:

- 4 systematic reviews and meta-analyses of human data
- 9 randomized controlled trials
- 2 reviews
- 1 systematic review and meta-analysis of animal data
- Numerous preclinical studies

Fasudil is approved in Japan and China to treat cerebral vasospasm and delayed cerebral ischemic symptoms. It has also been tested for a number of other cardiovascular indications.

Subarachnoid Hemorrhage: BENEFIT

Fasudil was approved in Japan for surgical treatment of subarachnoid hemorrhage. In a double blinded RCT in 267 patients undergoing surgery for subarachnoid hemorrhage, treatment with fasudil (30 mg/day IV within 24 hours of surgery for 14 days) reduced angiographically demonstrable vasospasm by 38%, symptomatic vasospasm by 30%, and the number of patients with poor clinical outcome associated with vasospasm by 54% compared to placebo. There were no serious adverse events associated with fasudil (Shibuya et al., 1992).

Two randomized open trials compared fasudil (30 mg 3x/day IV for 14 days) to nimodipine (a calcium channel blocker) after subarachnoid hemorrhage surgery and reported similar efficacy or better clinical outcomes with fasudil treatment. Adverse events between drugs were similar (Zhao et al., 2006; Zhao et al, 2011). Multiple systematic reviews and meta-analyses have found benefits of fasudil (Liu et al., 2012), though some of these studies have found greater benefit with other drugs such as nimodipine, nicardipine, or cilostazol (Mishra et al., 2021; Dayyani et al., 2022).

Pulmonary Hypertension: PROBABLE BENEFIT

Several studies have investigated the efficacy of fasudil for pulmonary hypertension. A 2023 meta-analysis and systematic review of 12 studies with a total of 575 patients found that treatment with fasudil is associated with a statistically significant improvement in multiple hemodynamic parameters. One trial found that fasudil significantly decreased rehospitalization and mortality in patients with pulmonary hypertension. The authors caution that these studies were only short-term or midterm, and that longer RCTs are necessary to confirm these benefits. The full text of this paper was not accessible and specific details could not be reviewed; the above information was reported in the abstract of the paper (Abedi et al., 2023).

Stroke: POTENTIAL BENEFIT

160 patients with acute ischemic stroke received either placebo or fasudil (60mg 2xday for 14 days). Fasudil improved neurological function and clinical outcome compared to placebo (Shibuya et al., 2005).

Atherosclerosis: POTENTIAL FOR BENEFIT

In a cross-over trial with healthy individuals or patients with coronary artery disease (n total = 29), oral fasudil (40 mg 3x/day) for 30 days improved flow-mediated dilation (a measure of endothelial function) and decreased Rho-kinase activity in lymphocytes in coronary artery disease (CAD) patients but had no effect on controls. There was no effect on endothelium-independent vasodilation in any group (suggesting that fasudil affects endothelial cells). Rho-kinase activity in lymphocytes was lower in healthy subjects than in CAD patients, suggesting that fasudil did not decrease activity below a healthy baseline. Additionally, the percent change in Rho kinase activity was correlated with the percent improvement in flow-mediated dilation suggesting that it might be beneficial to measure Rho-kinase

activity to see if the drug would be beneficial (Nohria et al., 2006). Fasudil was also reported to reduce lesion size in a mouse model of atherosclerosis (Wu et al., 2009)

Age-related impairments in physiological response to exercise: POTENTIAL BENEFIT

There are age-related impairments in the physiological response to exercise and hypoxia, such as changes in blood flow to skeletal muscle and vascular tone. A small study of 12 young (average age: 25) and 13 older adults (average age: 65), all healthy, investigated the effects of fasudil on some aspects of hemodynamic response to exercise. The study was a double-blinded randomized controlled crossover design; participants were randomized to an infusion of either 60 mg fasudil or placebo for their first study visit, and then received the opposite treatment at their second study visit. The study found that fasudil administration mitigated the age-related impairments, improving hemodynamic aspects such as blood flow in the older adults. The authors hypothesize that this benefit may be due in part to increased circulating ATP responses in older adults when they received fasudil. This is a small study that looked at handgrip exercises to model exercise conditions; future larger studies examining different muscle groups would be useful. They did not observe the same effect in the younger adults (Racine et al., 2022).

Angina: NEITHER BENEFIT NOR HARM

A randomized controlled trial enrolled 84 patients with stable angina, who received either oral fasudil (titrated up to 80 mg b.i.d.) or placebo for 8 weeks. Exercise duration was non-significantly improved compared to placebo, and angina score significantly improved (a score of the severity of angina). There were no differences in time to or frequency of angina. Fasudil did not affect heart rate or blood pressure (Vicari et al., 2005).

Preclinically, fasudil has also been explored for a variety of indications, including longevity (Spindler et al., 2012), diabetic cardiomyopathy (Guan et al., 2012), diabetic nephropathy (Komers et al., 2011), multiple sclerosis (reviewed by Yan et al., 2019), and cancer (Barcelo et al., 2023). Preclinical evidence also supports potential benefits of fasudil for other cardiovascular conditions. A meta-analysis and systematic review of preclinical animal studies found that fasudil appears to improve several measures of cardiovascular health, including size of myocardial infarct, levels of cardiac enzymes, and systolic and diastolic functions (Huang et al., 2018).

Safety: Short-term use of fasudil appears to be well-tolerated, with few adverse events reported. Little is known about long-term use of fasudil. Larger, longer studies with rigorous adverse event reporting are needed to fully understand the safety profile.

Types of evidence:

- 1 postmarketing surveillance study
- 4 randomized controlled trials
- 1 case report

Suzuki et al., 2007 conducted a post-marketing survey of 1462 patients receiving fasudil after undergoing surgery for subarachnoid hemorrhage. Adverse events (AEs) were similar between the post-marketing survey analysis and the phase 3 trial from Shibuya et al.,1992 with the most common AEs including hemorrhage (1.7% of patients), blood and lymphatic system disorders (0.8%), and hepatic disorders (0.5%). Overall, fewer adverse events were reported in the post-marketing survey than in the placebo group from the phase 3 trial (3.8% vs. 5.7%), so it is difficult to tell whether any adverse events were drug-related rather than surgery-related. Since fasudil causes vasodilation, higher doses may lower blood pressure, especially in dehydrated patients (Shibuya et al., 1992).

In an RCT in 84 patients with stable angina, fasudil and placebo had similar numbers of side effects (Vicari et al., 2005). An RCT with a cross-over design in 12 young adults and 13 older adults, all healthy, randomized participants to an infusion of either placebo or 60 mg fasudil at their first study visit; participants received the opposite treatment at their second visit. The study reported that there were no adverse events (Racine et al., 2022). A 2019 paper details the results of a randomized controlled trial of acute administration of either 30 mg or 60 mg of intravenous fasudil in 60 patients with congenital heart defects and severe pulmonary arterial hypertension. Hemodynamic measurements were taken before and after fasudil administration. Peripheral blood pressure decreased slightly. There were no serious adverse events. Two patients in the 30 mg group had dizziness and nausea; one patient in the 60 mg group had abdominal pain that resolved on its own (Ruan et al., 2019).

Koch et al., 2020 details case reports of three ALS patients who received compassionate use of 30 mg of intravenous fasudil twice daily for 20 days. It is difficult to draw conclusions from three patients using an open label drug, but the authors report no side effects or significant changes in blood pressure, heart rate, or any laboratory parameter across the three patients.

While the effects of short-term use of fasudil are relatively well-understood, the long-term use of fasudil has yet to be fully explored. Ongoing clinical trials may shed more light on whether fasudil is appropriate for long-term use.

Drug interactions:
The drug interactions of fasudil have not yet been fully elucidated. Drugbank.ca lists approximately 300 drugs that might or do interact with fasudil.

Research underway:

There are three ongoing trials of fasudil registered on clinicaltrials.gov; all are studying the effects of fasudil in neurodegenerative diseases.

NCT04734379 is a currently active Phase 2a study of oral fasudil in patients with one of two specific 4-repeat tauopathies: progressive supranuclear palsy or corticobasal syndrome. The study plans to enroll 15 patients, all of whom will receive 180 mg oral fasudil daily for 48 weeks. At the end of the trial, participants will have the option to continue open-label treatment for up to an additional 12 months. The primary outcome measure of the trial is incidence of adverse events. Secondary outcome measures focus on biomarker levels, including changes in tau and phosphorylated tau levels and imaging biomarkers such as changes in brain volume and white matter tract integrity. This study is sponsored by Woolsey Pharmaceuticals.

NCT05218668 is an ongoing study of fasudil in patients with ALS. This open label study plans to enroll 30 participants. The initial participants will receive 180 mg of oral fasudil daily. After at least 10 patients have been enrolled and treated with 180 mg daily of fasudil for 4 weeks, subsequent participants may receive up to 240 mg daily of fasudil. Dosing will continue for 24 weeks; participants will then have the option to join a 12-month extension phase. The primary outcome of the study is incidence of adverse events and serious adverse events. Secondary outcomes include different measurements of ALS disease progression, such as change in decline of slow vital capacity, muscle strength, and the Revised ALS Functional Rating Scale. This study is sponsored by Woolsey Pharmaceuticals.

NCT05931575 is a randomized controlled trial of fasudil in patients with Parkinson's disease (PD). The trial aims to enroll 75 patients who will receive study medication by mouth twice daily. Participants will

be randomized to either low dose fasudil (two daily doses of 22 mg each), high dose fasudil (two daily doses of 44 mg each), or placebo. Patients will receive treatment for 3 weeks; efficacy endpoints will be measured at 4 weeks. The primary outcome of the study is incidence and occurrence of adverse events, including study termination due to adverse events. Secondary outcome measures include a variety of assessments of disease progression, including motor symptoms, cognitive function, depression symptoms, and both clinician and patient global impression of improvement. This study is being run by the Technical University of Munich in Munich, Germany.

The ADDF is also sponsoring a randomized controlled double-blinded study examining the efficacy of fasudil in patients with MCI run by Dr. Clive Ballard. The study is nested in a multi-arm clinical trial platform, and plans to enroll 200 individuals and randomize them to either placebo or fasudil. The primary outcome measures will be safety and changes in cognitive function as measured by computer-based assessments. Secondary outcomes include changes in daily functioning and PET scan measures. See the ADDF portfolio page for more details.

Search terms:

Pubmed, Google: Fasudil

- Dementia, neurodegeneration, ALS, PD, multiple sclerosis, hypertension, stroke, diabetes

Websites visited for fasudil:

- Clinicaltrials.gov
- Geroprotectors
- PubChem
- DrugBank.ca

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