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.

Agmatine

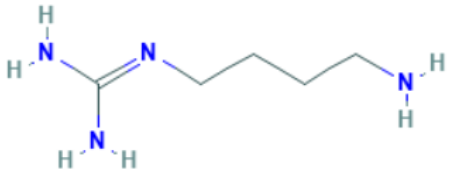
Evidence Summary

Agmatine is a supplement that can modulate many neurotransmitter systems and may be useful for Alzheimer's and other age-related disease, but there is little human data on its use.

Neuroprotective Benefit: Agmatine has some effects in preclinical rodent models of neurodegenerative disease, but human data is lacking.

Aging and related health concerns: Preclinical studies suggest agmatine may have some effects for cardiovascular disease, diabetes, and neuropathy, but there is little human data.

Safety: Some small studies have reported safety outcomes (such as nausea), but they were both funded by a company selling the supplement and are open label.

Availability: Available as a supplement online	**Dose**: 2.67g/day divided in two doses	**Molecular Formula:** $C_5H_{14}N_4$ **Molecular weight:** 130.19g/mol
Half-life: 10 min	**BBB**: Penetrant in animal models	
Clinical trials: One (possibly) ongoing for neuropathy	**Observational studies**: None	Source: Pubchem

What is it?

Agmatine is a polyamine formed by the decarboxylation of L-arginine by arginine decarboxylase. The function of agmatine is complex, and it can have effects on several neurotransmitter systems (e.g. opioid, serotonergic, adrenergic, imidazoline receptors) (Paszcuk et al, 2007). The rationale for agmatine's use in neuropathy lies in its neuromodulatory activities on NMDA receptors and as an inhibitor of nitric oxide synthase (NOS). In cardiovascular disease, it may have an effect on lipid levels or vascular relaxation (El-Awady and Suddek, 2013). In diabetes it may have an effect on imidazoline receptors, either peripherally or in the brain (in the adrenal gland) (Su et al, 2009). It also may activate α_2 adrenergic receptors. As a neurotransmitter, agmatine may also be involved in memory, as it increases memory in rodents after learning (Liu et al, 2008).

Agmatine is extensively used throughout the body. The effect supplementation has for certain individuals could depend on endogenous levels of agmatine. For instance, at higher doses agmatine may block NMDA receptors depending on endogenous levels.

Neuroprotective benefit: Agmatine has some effects in preclinical rodent models of neurodegenerative disease, but human data is lacking.

Types of evidence:

- Several preclinical studies of diabetes-induced cognitive impairment, stroke, TBI, and aging.

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
None

Human research to suggest benefits to patients with dementia:
None

Mechanisms of action for neuroprotection identified from laboratory and clinical research
Agmatine was reported to cross the blood-brain barrier in mice and monkeys (Piletz et al, 2003).Administered intracerebroventricularly (i.c.v.) after i.c.v. injection of Aβ42 or 40, agmatine reduced depression-like symptoms, improved cognition, increased BDNF and neprilysin levels, and decreased TNF-α and IL-6 (at 20µg/animal but not 10 µg/animal), and reduced malondialdehyde (MDA). These results were potentiated with imidazoline I_1 and I_2 agonists and attenuated with imidazoline I_1 and I_2 antagonists (Kotagale et al, 2020; Kotagale et al, 2020; de Souza et al, 2018).

In a type 2 diabetes mouse model (high fat diet + streptozotocin injection, STZ), a two-week treatment with agmatine (100mg/kg i.p. from week 12-14) improved diabetes symptoms (e.g., fasting glucose, insulin levels, insulin and glucose tolerance) and improved insulin signaling in the brain. Agmatine also reduced expression of p-GSK3β, p-tau, amyloid beta, and improved cognition (Kang et al, 2017). In another type 2 diabetes mouse model (i.c.v. injection of STZ) a 10-day treatment with agmatine (40 or 80mg/kg, i.p.) improved cognition, reduced cell death, and reduced p-GSK3β in the 80mg group (Moosavi et al, 2014).

In aged rodents, agmatine (40mg/kg) improved spatial working memory and object recognition but had no effect on spatial reference learning and memory. It also suppressed elevated NOS activity (Rushaidhi et al, 2012; Rushaidhi et al, 2013).

On the other hand, agmatine treatment impaired fear memory acquisition in middle aged rodents (Stewart and McKay, 2000; McKay et al, 2002). These results suggest that the effect of agmatine on cognition likely depends on the dose, the levels of agmatine present endogenously, and the specific type of memory.

Stroke
In a rat model of stroke (middle cerebral artery occlusion – MCAO), post-stroke treatment with agmatine reduced brain edema, gliosis, and blood brain barrier disruption. It improved motor function

and also reduced the expression of AQP1, AQP4, and AQP9 (Kim et al, 2010; Wang et al, 2010; Ahn et al, 2014; Huang et al, 2013). Agmatine also reduced infarct size in an ischemia-reperfusion model (MCAO) when given before, right after, and two hours after ischemia-reperfusion, but not when treatment was delayed five hours after. Agmatine also reduced iNOS positive neurons when given before or at the onset of MCAO (Kim et al, 2004).

In a gerbil model of stroke (MCAO) agmatine also reduced infarct size (measured 48 hours after MCAO), improved neurological functioning, increased the levels of antioxidant proteins, and reduced lipid peroxidation (Selakovic et al, 2019).

Traumatic Brain Injury (TBI)
In a model of TBI (fluid percussion injury), agmatine given directly after TBI and for an additional three days reduced injury size, improved motor function, and reduced cell death and gliosis. It also increased neurogenesis and angiogenesis (Kuo et al, 2011). In another rodent model of TBI (cold-induced TBI), agmatine reduced brain edema, cell death, blood brain barrier disruption, and improved neurological outcomes (Kim et al, 2015).

APOE4 Interactions:
None reported

Aging and related health concerns: Preclinical studies suggest agmatine may have some effects for cardiovascular disease, diabetes, and neuropathy, but there is little human data.

Types of evidence:

- One placebo-controlled trial for lumbar disc-associated radiculopathy
- One open-label trial for peripheral neuropathy
- Several preclinical studies in cardiovascular disease, diabetes, and neuropathy

Cardiovascular disease
In a rabbit model of hypercholesterolemia, three-week treatment with agmatine (10mg/kg/day) improved levels of LDL-c, triglycerides, HDL-c, and improved endothelium-dependent (but not independent) relaxation. It also reduced a marker of oxidative stress, malondialdehyde (MDA), and atherosclerotic plaque size (El-Awady and Suddek, 2013). In a rabbit model of vascular endothelial dysfunction (nicotine-induced vascular dysfunction), agmatine treatment over six weeks mostly

improved lipid profiles (reduced LDL-c, increased HDL-c, but increased triglycerides). It also reduced subendothelial vascular fat accumulation and reduced expression of an inflammatory marker (NF-κB) (Nader et al, 2016).

In a mouse model of atherosclerosis (ApoE KO mice), agmatine (20mg/kg) reduced atherosclerotic lesion size and increased HDL-c. It also increased IL-12 and MCP-1 (an inflammatory marker) (Wisniewska et al, 2017).

In a rat model of hypertension, agmatine reduced blood pressure when injected intravenously. Interesting, however, it increased blood pressure when injected intracerebroventricularly (i.c.v.) (Schafer et al, 1999).

Diabetes

In an STZ-induced rodent diabetes model, agmatine reduced blood glucose levels and improved memory function (Bhutada, et al, 2012). In other models of diabetes (high fructose diet, or STZ-injection), agmatine improved insulin sensitivity and glucose levels, possibly through its effect on peripheral or central I_2-imidazoline receptors or stimulation of the adrenal gland to enhance β-endorphin secretion (Su et al, 2009; Huang et al, 2005; Jou et al, 2004). Agmatine also improved endothelium-dependent vascular relaxation in STZ diabetic rodents (Ozyazgan et al, 2003).

Neuropathy

In an open-label study with 11 patients with painful small fiber neuropathy (eight with diabetic neuropathy, two with idiopathic neuropathy, and one with inflammatory neuropathy), treatment with agmatine (2.67g/day, AgmaSet) over a period of two months reduced neuropathic pain intensity. The average reduction in pain was 46.4% and it reduced several painful sensations (e.g., burning, oversensitivity to touch, shooting pain, etc.). The authors also note that there are hundreds of unpublished observations from individuals that use agmatine for neuropathic pain. Note that the study was conducted by individuals who sell AgmaSet (Rosenberg et al, 2020).

In another placebo-controlled study (again run by individuals who sell AgmaSet) in 99 patients with lumbar disc-associated radiculopathy, patients were treated with 2.67g/day of AgmaSet for two weeks. Only 61 patients were examined in the final analysis (19 dropped out of the study – relatively balanced between groups, 17 patients were excluded from the analysis due to unreliable data or surgery). Both groups reported improvements in pain scores and general health with the agmatine group reporting

quicker improvement in pain scores. Agmatine was reported to also improve on a physical health score 60 days after treatment stopped (Kenyan et al, 2010).

In a rodent model of inflammation-related nerve injury, treatment with agmatine reduced hyperalgesia and neuropathic pain. It also reduced sensitivity to chemical and thermal stimuli and reduced lesion size in a model of spinal cord injury (Fairbanks et al, 2000). Treatment also reduced pain sensitivity in several other models of hypersensitivity to pain (injection of Complete Freund's Adjuvant – CFA – into the mouse paw, partial sciatic nerve ligation). However, it had no effect on pathologies (e.g., paw edema caused by injection of CFA into the paw) (Paszcuk et al, 2007). Agmatine was also reported to prevent axon degeneration in a model of sciatic nerve injury in rats (article in Turkish, cannot access, Sezer et al, 2014). Agmatine was also reported to attenuate cisplatin-induced neuropathy in rats (Donertas et al, 2018).

Safety: Some small studies have reported safety outcomes (such as nausea), but they were both funded by a company selling the supplement and are open label.

Types of evidence:

- Two open-label studies and one case study in two individuals

In small two open-label studies (n=11 and 34), agmatine was relatively safe with the most common side effects being nausea and mild-to-moderate diarrhea at higher doses (3.6g/day) which improved following cessation of treatment. (Rosenberg et al, 2020; Kenyan et al, 2010). A case study (from two individuals affiliated with the company that sells agmatine) reported that five-year treatment was not associated with side effects on blood or urine laboratory measures (Gilad and Gilad, 2014).

Drug interactions:
Agmatine may interact with drugs that target α_2 adrenergic receptors. For instance, in a rodent model of hypertension, it potentiated the hypotensive effects of clonidine (an α_2 adrenergic receptor agonist) (Schafer et al, 1999). It binds to many receptors and likely has many other potential interactions. Drugbank list almost 700 potential interactions. However, there is not much clinical data on safety. Due to its role in the arginine pathway, agmatine may interact with either L-arginine or L-citrulline supplements.

Sources and dosing:
The dose used in clinical studies was 2.67g/day in a divided dose with three capsules taken in the morning and three in the evening (Kenyan et al, 2010). Agmatine can be purchased from many sources online. The source used in the clinical trials was AgmaSet (link).

Research underway:
One trial is reported to be underway in small fiber peripheral neuropathy. The trial was listed in 2018, but its current status is unknown (NCT01524666).

Search terms:

- Agmatine + Alzheimer, stroke, aging, lifespan, neuropathy, cardiovascular, [clinical trial], diabetes, cancer

Websites visited:

- Clinicaltrials.gov
- Pubmed