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.

Igmesine

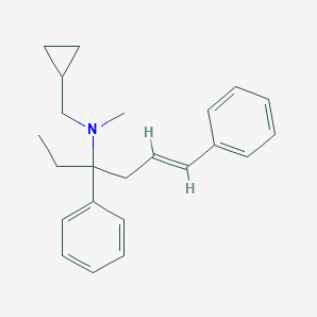
Evidence Summary

Igmesine showed cognitive protection in preclinical models and anti-depressant effects in early clinical trials in major depressive disorder, but clinical development has since been discontinued.

Neuroprotective Benefit: Numerous preclinical studies have shown cognitive benefits with igmesine; however, clinical development of igmesine for depression and other indications was discontinued many years ago.

Aging and related health concerns: Igmesine may protect against cell death in cerebral ischemia and inhibit cancer cell growth and migration, but the evidence is limited to very few preclinical studies.

Safety: Although igmesine has been tested in phase II and phase III trials, types and frequencies of adverse events have not been published.

Availability: research-grade only	**Dose**: Optimal dose is unknown. Doses tested in clinical studies ranged from 25 to 200 mg/day.	**Chemical formula:** $C_{23}H_{29}N$ **MW**: 319.492 g/mol  Source: PubChem
Half life: not reported	**BBB**: not reported	
Clinical trials: Largest study was a double-blind randomized controlled trial in patients with major depressive disorder (n=348).	**Observational studies**: none	

What is it? Igmesine is an agonist for the sigma-1 receptor, an endoplasmic reticulum (ER) chaperone protein (Maurice et al., 2019). Sigma-1 receptor expression is the highest in the spinal cord, pons, medulla, cerebellum, and hippocampus; they are also expressed in the cerebral cortex (Jin et al., 2015). Peripherally, it is highly expressed in the liver and adrenal gland (Hayashi and Su, 2004). Neurosteroids such as pregnenolone, testosterone, and DHEA are endogenous ligands of sigma-1 receptors (Takebayashi et al., 2004). Activation of sigma-1 receptors triggers physiological responses to ER stress and modulate calcium mobilization in mitochondria. Sigma-1 receptors form a trimeric complex with the inositol triphosphate (IP3) receptor and the ankyrin isomer 220, a cytoskeletal adaptor protein linking spectrin to F-actin (Phan et al., 2005). Upon stimulation, sigma-1 receptors dissociate from the IP3 receptor and translocates to the plasma membrane and nucleus, which leads to calcium mobilization from IP3 receptor-gated ER calcium pools. Sigma-1 receptors also interact with glutamate NMDA receptors, dopamine receptors, and ion channels, thereby influencing the TCA cycle, oxidative stress, mitochondrial function, neuronal plasticity, neuronal firing, and neurotransmitter release (e.g., 5-HT, glutamate, dopamine, norepinephrine, acetylcholine, and GABA).

Sigma-1 agonist molecules are thought to act as antidepressant, anti-amnesic, and neuroprotective agents. Igmesine has also been tested for its potential anti-diarrheal properties (Roze et al., 1998). There were a number of preclinical studies on igmesine that were published between 1991 and 2006, but since then, very few studies have been published. Clinical development for igmesine, led by Pfizer, was discontinued some time before 2004 due to marketing considerations (Fischer et al., 2004; Volz and Stoll, 2004).

Neuroprotective Benefit: Numerous preclinical studies have shown cognitive benefits with igmesine; however, clinical development of igmesine for depression and other indications was discontinued many years ago.

Types of evidence:

- No clinical trials testing igmesine effects on cognitive functions
- 1 double-blind randomized controlled trial in patients with major depressive disorder
- Numerous laboratory studies and reviews

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?
No studies have evaluated the effects of igmesine on cognitive outcomes.

In a double-blind randomized controlled trial of 348 patients with major depressive disorder, igmesine treatment (25 mg/day) significantly improved depression rating scale (HAM-D score) compared to placebo during the interim analysis, but by the end of the 6 weeks treatment, the effects were no longer statistically significant (Pande et al., 1999). Although in the UK subset of patients (n=263), igmesine (25 mg) was significantly superior to placebo. Also, in the outpatient subset, igmesine (25 mg) was significantly superior to placebo. No benefits were seen at the higher 100 mg dose of igmesine, though the authors speculated that because this group had a smaller sample size (n=50) compared to the 25 mg dose group (n=100), there may have been a lack of statistical power.

Human research to suggest benefits to patients with dementia: None available.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:
Numerous laboratory studies have explored the potential neuroprotective effects of igmesine, though most studies were published before 2006.

Igmesine treatment has been shown to improve cognitive functions in a rat model of scopolamine-induced amnesia (at 0.25-16 mg/kg, i.p.)(Earley et al., 1991), in a mouse model of accelerated aging (SAMP8 mice; at 0.1-3 mg/kg, s.c.)(Maurice et al., 1996), in rats prenatally exposed to cocaine (Meunier and Maurice, 2004), and in a mouse model of chronic alcohol consumption (Meunier et al., 2006). In rats intracerebroventricularly injected with Aβ40 or Aβ25-35, igmesine treatment (30 mg/kg) showed antidepressant effects by reducing stress-induced immobility (Urani et al., 2002; 2004).

Though in the accelerated aging mouse model, chronic igmesine administration for 10 days appeared less effective on long-term memory retrieval than acute treatment (Maurice et al., 1996), suggesting the possibility that igmesine may be more beneficial as a cognitive enhancer rather than a treatment for a chronic neurodegenerative condition.

In most behavioral studies, sigma-1 receptor ligands did not facilitate or impede the learning ability in control groups, suggesting that it is under pathological conditions that sigma-1 receptors are activated (Jin et al., 2015). Anti-amnesic effects of sigma-1 receptor ligands appear to occur only when cognitive functions are impaired due to deficits in neural transmission (Hayashi and Su, 2004).

Mechanisms: Igmesine appears to exert its neuroprotective effects by increasing acetylcholine release (Junien et al., 1991), modulating NMDA receptor-induced neuronal firing in the hippocampus (Hayashi and Su, 2004), and modulating plasma membrane potentials and intracellular calcium signaling. Sigma-1 receptor ligands act in a modulatory way, such that they do not cause calcium mobilization, neuronal firing, or neurotransmitter release by themselves; their actions occur when the IP_3 receptors, potassium channels, or the NMDA receptors were activated (Hayashi and Su, 2004). Thus sigma-1 receptor ligands may act as a modulator or amplifier of signal transduction that is related to NMDA receptor activity and/or calcium signaling.

Caveats: Sigma-1 receptor activation may be a double-edged sword with regards to Alzheimer's. It may facilitate cognitive functions through modulating NMDA receptor-dependent learning and memory, but it may also aggravate Aβ-mediated neurotoxicity and apoptosis via NR2B subunit-containing NMDA receptors (Jin et al., 2015).

APOE4 interactions: Unknown.

Aging and related health concerns: Igmesine may protect against cell death in cerebral ischemia and inhibit cancer cell growth and migration, but the evidence is limited to very few preclinical studies.

Types of evidence:

- A few laboratory studies

Only a few preclinical studies have explored the effects of igmesine on age-related conditions.

In a gerbil model of global cerebral ischemia, igmesine treatment (50, 75, and 100 mg/kg) provided significant protection against cell death while also attenuating ischemia-induced hyperactivity and the increase in nitric oxide synthase activities (O'Neill et al., 1995).

In cell culture studies, igmesine treatment significantly inhibited voltage-activated K+ currents in both small cell lung cancer and leukemic cell lines (Renaudo et al., 2004). They also showed that sigma ligands inhibit cell growth through a cell cycle arrest in the G1 phase but not via an apoptotic mechanism. In a more recent cell culture study, igmesine inhibited breast and colorectal cancer cell migration by dissociating the complex formed by SK3 (a calcium-activated K+ channel) and Orai (a voltage-independent calcium channel)(Gueguinou et al., 2017).

Safety: Although igmesine has been tested in phase II and phase III trials, types and frequencies of adverse events have not been published.

Types of evidence:

- A few clinical trials in major depressive disorder

Igmesine has been tested in clinical trials of functional diarrhea and depression (Hayashi et al., 2011). The trial for depression moved further into phase III but failed to show efficacy (Pande et al., 1999). The authors noted that adverse events at the 100 mg dose was higher than those at the 25 mg dose, but no patients dropped out of the trial due to adverse events. No information on the frequencies or types of adverse events were included in the publication.

In a small double-blind crossover study in 16 healthy volunteers, a single dose of 200 mg igmesine inhibited the PGE2-induced intestinal secretion, though this effect was not observed with 25 mg igmesine (Roze et al., 1998). Authors suggested that igmesine may have anti-diarrheal effects; however it is not clear whether this also means that igmesine may worsen constipation.

Sources and dosing: Only research-grade igmesine is available. In clinical studies in patients with major depression, doses that were tested included 25 mg/day and 100 mg/day. In a clinical study in healthy volunteers, a dose up to 200 mg was tested (Roze et al., 1998).

Drug interactions: Drug interactions with igmesine have not been well-studied. Based on its mechanism of action, it likely interacts with other drugs that bind to sigma-1 receptors, such as dextromethorphan, neuroleptics (e.g., haloperidol), antidepressants (e.g., imipramine, desipramine,

clomipramine, opipramol, trazodone, fluvoxamine, sertraline, fluoxetine, citalopram, paroxetine, clorgyline, moclobemide, etc.), anti-convunsants (phenytoin), and steroid hormones (Takebayashi et al., 2004).

Research underway: No ongoing clinical trials are testing the efficacy of igmesine based on ClinicalTrials.gov. A sigma-1 receptor-selective radioligand [^{11}C]SA4503 can map sigma-1 receptors in the CNS of living people (Kawamura et al., 2000). This and other sigma-1 receptor PET ligands may be important tools for evaluating the role of this receptor in neurodegenerative and psychiatric disorders.

Patents: An international application (WO2017137600A1) titled "Igmesine for use in the treatment of neurodegenerative diseases" was published on August 18, 2017. The inventors are Francois Roman and Johann Meunier.

Search terms:
Pubmed, Google: igmesine, JO-1784

Websites visited for igmesine:

- Clinicaltrials.gov (0)
- Examine.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem
- DrugBank.ca (0)
- Labdoor.com (0)
- ConsumerLab.com (0)
- Cafepharma (0)
- Pharmapro.com (0)

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