

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.

Allopregnanolone

Evidence Summary

Although allopregnanolone (allo) has neuroprotective and regenerative properties in the brain based on preclinical studies, dosing may be tricky due to its sedative effects.

Neuroprotective Benefit: Allo promotes neurogenesis, reduces inflammation, and lowers A β burden in preclinical models, but produces sedative effects at high doses. No human data available yet, though a clinical trial is underway.

Aging and related health concerns: Preclinical studies suggest that allo may offer regenerative properties in Parkinson's disease, peripheral neuropathy, ischemia, and traumatic brain injury, but no studies have confirmed these effects in humans yet.

Safety: Acute dosing has not caused serious adverse effects, but long-term effects are unknown; allopregnanolone significantly increases sedation so dosage and dosing schedule are important considerations.

What is it? Allopregnanolone (Allo) is a neurosteroid that is a metabolite of progesterone and is synthesized in the central nervous system, adrenal cortex, and gonads ([Irwin et al., 2014](#)). It directly binds to and modulates GABA-A receptors ([Locci and Pinna, 2017](#)). Allo has been shown to modulate anxiety, depression, seizure activity, sedative activity, cholesterol homeostasis, and the immune system ([Chen et al., 2011](#); [Irwin et al., 2014](#)). Based on some preclinical evidence, therapeutic efficacy of Allo has been suggested for Alzheimer's disease, Parkinson's disease, multiple sclerosis, Niemann-Pick, diabetic neuropathy, epilepsy, and traumatic brain injury.

Neuroprotective Benefit: Allo promotes neurogenesis, reduces inflammation, and lowers A β burden in preclinical models, but produces sedative effects at high doses. No human data available yet, though a clinical trial is underway.

Types of evidence:

- 1 double-blind RCT testing acute effects of allo in healthy women
- 2 observational studies showing lower levels of allo in dementia patients
- Numerous laboratory studies

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

No clinical studies so far have suggested cognitive protection. A double-blind RCT of 28 healthy women tested the effects of a single dose of allo (0.07 mg/kg) that produced serum concentrations of allo equivalent to those in third-trimester pregnant women ([Kask et al., 2008](#)). Women receiving this dose of allo had impaired episodic memory when compared to those receiving placebo. However, there were no effects of allo on semantic memory or working memory with this dose. There was also no correlation between the change in episodic memory task performance and serum concentration of allo. The negative effect of allo on episodic memory may have been due to its sedative effects. Physiological levels of allo are highest in the third trimester of pregnancy ([Luisi et al., 2000](#)).

Human research to suggest benefits to patients with dementia: A phase I/II clinical trial is underway.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Postmortem studies have shown that allopregnanolone levels are reduced on average by over 50% in the prefrontal cortex ([Marx et al., 2006](#)) and temporal cortex ([Naylor et al., 2010](#)) of Alzheimer's disease patients compared to control subjects, though there is a high level of variability within each group. In both studies, low allopregnanolone levels correlated with worse Braak neuropathological disease stage.

Blood levels of allopregnanolone are also reduced in both Alzheimer's and vascular dementia patients compared to controls ([Bernardi et al., 2000](#)).

Allo is blood-brain-barrier penetrant ([Irwin et al., 2015](#)). There have been many studies examining the effects of allo in preclinical models of Alzheimer's. In the 3xTgAD mouse model, allo increases neurogenesis (by inducing CREB and neuronal differentiation factor NeuroD) and the survival of newly generated neurons, restores cognitive function, and reduces A β generation in the hippocampus, cortex, and amygdala ([Wang et al., 2005](#); [Wang et al., 2010](#); [Chen et al., 2011](#); [Singh et al., 2012](#); [Irwin et al., 2015](#)). Allo also reduces microglia activation (expression of OX42) and increases CNPase, an oligodendrocyte myelin marker ([Chen et al., 2011](#)). In a hippocampal neuronal culture, allo significantly increases dendritic spine density ([Shimizu et al., 2015](#)). Administration of allo prior to and during the early stages of AD pathology was optimal in increasing regenerative responses and reducing AD pathology, while allo treatment initiated at or after the point of A β plaque generation was not protective ([Chen et al., 2011](#)). Thus, for translation to human patients, targeting the early stages of the disease is likely optimal.

Notably, regenerative properties of allo in rodents are achieved with a once per month or once per week regimen at 10 mg/kg, per i.v. injection, whereas a constant infusion treatment regimen is anti-regenerative ([Chen et al., 2011](#)). Chronic allo treatment results in cognitive dysfunction and decreased hippocampal weight in wild-type mice ([Bengtsson et al., 2016](#)). In mouse models of Alzheimer's disease, chronic allo treatment also resulted in impaired learning and memory and increased levels of soluble (toxic) A β in the brain ([Bengtsson et al., 2012, 2013](#)).

APOE4 interactions: Patients carrying the APOE4 allele have reduced allopregnanolone levels in the temporal cortex compared to non-carriers ([Naylor et al., 2010](#)). Although allo treatment may be more effective in APOE4 carriers than non-carriers, this possibility has not been tested yet.

Aging and related health concerns: Preclinical studies suggest that allo may offer regenerative properties in Parkinson's disease, peripheral neuropathy, ischemia, and traumatic brain injury, but no studies have confirmed these effects in humans yet.

Types of evidence:

- o clinical trials
- Numerous laboratory studies

Parkinson's disease: POTENTIAL BENEFIT. In two rodent models of Parkinson's disease, allo treatment (5 and 20 mg/kg, oral gavage or 10 mg/kg, s.c. once per week for 2 weeks) significantly restored cognitive dysfunction ([Nezhadi et al., 2016](#); [Adeosun et al., 2012](#)). Allo treatment (10 mg/kg, s.c., once per week for 2 weeks) also promoted neurogenesis and restored the number of dopaminergic neurons in the substantia nigra in these mice ([Adeosun et al., 2012](#)). These neuroprotective effects have not been confirmed in Parkinson's disease patients yet.

Peripheral neuropathy: POTENTIAL BENEFIT. In a rat model of chemotherapy (oxaliplatin)-induced peripheral neuropathy, prophylactic or corrective allo treatment (4 mg/kg, every other day) prevented/abolished biochemical and functional alterations in peripheral nerves ([Meyer et al., 2011](#)). Allo restored sciatic nerve conduction velocity and action potential peak amplitude that were drastically reduced by chemotherapy. Protective effects of allo have also been demonstrated in a rat and cell culture model of diabetic neuropathy. Allo reduced sensitivity to pain (hyperalgesia) and decreased markers of apoptosis (caspase 3 and Bax) ([Afrazi et al., 2014](#)). No studies have confirmed these protective effects of allo in neuropathy patients yet.

Traumatic brain injury: POTENTIAL BENEFIT. In a rat model of traumatic brain injury, allo treatment (4 mg/kg/day, i.p.) for 5 days improved memory performance, reduced neuronal death, and reduced inflammation (levels of IL-1 β , TNF α) ([He et al., 2004a, 2004b](#)). Dose and treatment regimens that are recommended are immediate and continuous exposure, given the high levels of glutamate excitotoxicity present during an acute injury. A phase II double-blind, placebo-controlled RCT of allo in treating traumatic brain injury was conducted but its results have yet to be published ([NCT01673828](#)). In this trial, allo was started within 8 hours after injury and given i.v. continuously for a 4-day treatment period, followed by a one-day dose de-escalation.

Cerebral ischemia: POTENTIAL BENEFIT. In a rat model of ischemia, allo treatment (8 mg/kg, i.v.) significantly reduced the impairment in spatial learning and memory, as well as in reference and working memory, and prevented the narrowing of the hippocampus, otherwise induced by ischemia ([Morali et al., 2011](#)). This better performance of allo-treated rats compared to the vehicle group occurred in spite of a loss of pyramidal neurons in the hippocampus. No studies have tested allo in ischemia/stroke patients.

Cholesterol homeostasis: POTENTIAL BENEFIT. Preclinical studies have shown that allo regulates cholesterol homeostasis via increasing liver-X-receptor (LXR) and pregnane-X-receptor (PXR). LXR activation increases cholesterol efflux through increased ABCA1 and ApoE expression, and prevents

overactivation of gamma secretase and overproduction of A β ([Whitney et al., 2002](#); [Shenoy et al., 2004](#)). No studies have confirmed these effects in humans yet.

Safety: Acute dosing has not caused serious adverse effects, but long-term effects are unknown; allopregnanolone significantly increases sedation so dosage and dosing schedule are important considerations.

Types of evidence:

- 4 clinical studies testing acute effects of allopregnanolone
- Numerous laboratory studies

All clinical studies on allopregnanolone have only tested its acute effects. In a double-blind RCT of 16 women with premenstrual dysphoric disorder (and 12 healthy controls), a single injection of allo (0.05 mg/kg, i.v.) significantly increased self-rated sedation ([Kask et al., 2009](#)).

A pharmacokinetic study in 10 healthy women reported that allo given in a cumulative dose of 0.09 mg/kg (three i.v. injections of 0.015, 0.03, and 0.045 mg/kg) did not have any adverse effects other than fatigue, mild nausea, and sedation ([Timby et al., 2006](#)). Self-rated sedation was affected until 55 min after the last dose. Three women reported mild feelings of alcohol-like intoxication, 3 women experienced mild nausea, and 1 woman reported flushing. One woman reported an anxiety attack 24 hours after the allo injection.

In a clinical study of 9 men and 9 women (on oral contraceptives), allo (three i.v. injections of 0.015, 0.03, and 0.045 mg/kg) did not result in serious adverse effects, but 3 men and 2 women reported sleepiness and tiredness, 3 men and 4 women reported feeling as if they had taken alcohol, 1 man reported flushing, and 1 woman complained of a mild frontal headache. ([van Broekhoven et al., 2007](#)). Also, men scored higher on “sedation” than women after allo.

In a recent study, 120 hours of continuous infusion of allo effectively treated 2 super-refractory status epilepticus patients ([Vaitkevicius et al., 2017](#)), though the full text was inaccessible and therefore details of this study could not be evaluated.

Drug interactions are unknown. However, due to its actions on the GABA-A receptor, the risk of serious side effects may be increased when taken with benzodiazepines, barbiturates, alcohol, and sleep or anxiety medications.

Sources and dosing: Allo is not available on the market in the US. Dosing is tricky with allo due to its actions on the GABA-A receptor, producing sedative effects. Like other neurosteroids, allo has an inverted U-shaped dose-response profile, where too high or too low of an allo dose leads to suboptimal responses ([Wang et al., 2005](#)). In aged and Alzheimer's model mice, treatment once per week at sub-sedative doses (10 mg/kg, i.v.) was optimal for regeneration and reduction in Alzheimer's pathology ([Chen et al., 2011](#); [Irwin et al., 2014](#)). Doses being tested for a phase I study in MCI and mild Alzheimer's patients are 2 mg, 4 mg, and 6-18 mg once per week (i.v.) for 12 weeks ([NCT02221622](#)). In clinical trials, the maximally tolerated dose is established as the dose inducing sedation.

Research underway: ADDF is funding Roberta Diaz Brinton at University of Arizona to accelerate advancement of allopregnanolone from phase I to phase II clinical trial in MCI and mild AD ([NCT02221622](#)). Other clinical trials are testing whether allopregnanolone is effective in treating chronic low back pain in veterans ([NCT01898013](#)), treatment-resistant depression ([NCT02900092](#)), and Fragile-X associated tremor/ataxia syndrome ([NCT02603926](#)). These studies are currently recruiting participants.

A recent study investigated the effectiveness of an allo analog. In a cell culture model, BR297 exhibited advantages over allo with regards to both protection of mitochondrial functions and reduction of oxidative stress ([Lejri et al., 2017](#)). Under conditions of high oxidative stress, BR297 decreased reactive oxygen species, improved mitochondrial respiration, and promoted cell survival in ways that appeared more robust compared to allo. However, these studies in cell culture are still preliminary and it is not known whether BR297 or other analogs of allo will be more neuroprotective.

Search terms:

Pubmed, Google: allopregnanolone

- + clinical trial, + Alzheimer's, + cognitive, + meta-analysis, + safety, + lifespan, + neuropathy, + Parkinson's

Clinicaltrials.gov: allopregnanolone, ganaxolone

Treato.com, Examine.com, DrugAge, Geroprotectors: No results



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