*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.*

# D-serine

**Evidence Summary**

Although clinical trials suggest benefit in people with schizophrenia or Parkinson's disease, it may worsen Alzheimer's, peripheral neuropathy, and osteoarthritis by overactivating glutamate NMDA receptors.

**Neuroprotective Benefit:** D-serine has been tested in multiple clinical trials, mostly in schizophrenics, but the evidence is mixed and inconsistent. It may be harmful for dementia patients or older people with excessive glutamate receptor activation.

**Aging and related health concerns:** Although a small clinical trial suggested benefit for Parkinson's patients, preclinical studies suggest potential harm with regards to increasing oxidative damage in the brain and worsening neuropathic and osteoarthritic pain.

**Safety:** Numerous clinical trials have reported that D-serine is well-tolerated with few side effects, though one small study saw higher incidence of proteinuria.

**What is it?** D-serine is categorized as a nootropic. It is an amino acid found in the brain and is produced primarily in astrocytes; the conversion of L-serine to D-serine is catalyzed by the serine racemase enzyme [1]. D-serine acts as a co-agonist of glutamate NMDA receptors and binds at the glycine site [2]. NMDA receptors mediate synaptic plasticity, synaptogenesis, excitotoxicity, memory acquisition, and learning. Schizophrenia is characterized by reduced NMDA receptor signaling and therefore, D-serine supplementation has been tested extensively in patients with schizophrenia. It is thought to improve cognitive symptoms in this population. It is worth noting that in Alzheimer's disease, there is excess glutamate receptor activation. Memantine, one of the drugs used to treat Alzheimer's disease, is an NMDA receptor *antagonist*.

**Neuroprotective Benefit:** D-serine has been tested in multiple clinical trials, mostly in schizophrenics, but the evidence is mixed and inconsistent. It may be harmful for dementia patients or older people with excessive glutamate receptor activation.

*Types of evidence:*

- 9 double-blind randomized controlled trials, 6 in schizophrenics, 1 in people at risk for schizophrenia, and 2 in healthy adults
- 1 open-label trial in schizophrenics
- 3 studies examining levels of D-serine, 2 in the CSF and 1 in the blood
- 2 postmortem studies examining D-serine levels
- Numerous laboratory studies

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

Although most studies with D-serine have been carried out in people with schizophrenia, there have been 2 studies that tested D-serine in healthy people. In a double-blind randomized controlled trial of 35 healthy adults, D-serine (a single dose of 2.1 g) reduced measures of depression and anxiety feelings, improved attention and vigilance, and improved the ability to retain verbal information over interference [3]. These results suggest that in healthy subjects, D-serine reduces subjective feelings of sadness and anxiety and has procognitive effects. However, statistically significant differences between D-serine and placebo were only observed for attention, and for the rest of the measures the differences were with baseline. A different study in 50 older adults also showed that D-serine treatment (30 mg/kg, mixed in orange juice) significantly decreased errors on a spatial memory test, but this effect was not compared to placebo and may have been a practice effect (though in 1 out of 5 test trials, there was a statistically significant difference between D-serine and placebo groups) [4]. Subjects that achieved

higher increases in plasma D-serine levels after administration improved more in test performance, but this was not statistically significant. D-serine did not have any effect on working memory, cognitive flexibility, visual attention, or mood scores.

All other clinical trials have been carried out in people with schizophrenia or those at risk. A few studies (carried out by a single group) showed cognitive benefit with D-serine [5; 6; 7] while others reported no benefit over placebo [8; 9; 10; 11]. The ones that showed benefit reported improvements in negative symptoms [7], positive symptoms [6], and auditory plasticity [5]. In the study that tested multiple doses (30, 60, and 120 mg/kg/day), higher plasma levels of D-serine correlated with better improvement in symptomatic and neuropsychological function [6].

*Human research to suggest benefits to patients with dementia*:
No clinical studies have tested whether D-serine is beneficial for dementia patients.

There have been several studies examining cerebral spinal fluid (CSF) levels of D-serine in people with Alzheimer's, but the evidence is mixed and not compelling. One study in 2015 showed that D-serine levels were higher in the CSF of probable Alzheimer's patients than in cognitively healthy subjects [12]. They also found that combining D-serine levels to the amyloid/tau index remarkably increased the sensitivity and specificity of diagnosis of probable Alzheimer's in the cohort. CSF D-serine levels also discriminated between non-demented and Alzheimer's patients. However, a newer and larger study in 2016 showed that CSF D-serine levels were only slightly increased (by 13%) in Alzheimer's patients compared with controls [13]. After accounting for age, the difference between Alzheimer's patients and controls was not significant. CSF D-serine levels in Alzheimer's patients did not differ from other types of dementia and was also not correlated to cognitive function as measured by MMSE scores. Also, L-serine levels in CSF were not significantly different between diagnostic groups and no correlations with MMSE scores were found. This study concluded that the large overlap of CSF D-serine levels across groups made it an unsuitable biomarker for Alzheimer's and for cognitive decline. Older studies looking at serum levels of D-serine also reported no significant differences between Alzheimer's disease patients and controls [14].

Postmortem studies have also shown that L- and D-serine concentrations in the brain were comparable between Alzheimer's disease patients and normal controls [15; 16].

*Mechanisms of action for neuroprotection identified from laboratory and clinical research*:
Despite poor blood-brain-barrier diffusion, D-serine administration significantly increases extra- and intracellular D-serine concentrations in the rat brain [17].

Numerous rodent studies have suggested that D-serine has neuroprotective properties. In normal mice, D-serine treatment (50 mg/kg/day, systemic) enhanced memory consolidation, object recognition, and working memory [18]. In APP knock-out mice, chronic D-serine treatment (in drinking water) restored cognitive deficits, improved spine dynamics, and normalized D-serine levels [19]. Also, D-serine treatment (1 g/kg, i.p.) prevented impairments in memory consolidation in a mouse model of acute stress [20]. D-serine treatment also enhanced synaptic plasticity in aged rats [21] as well as in a mouse model of accelerated aging (SAMP8 mice) [22]. These studies suggest that while D-serine levels are decreased with aging, the affinity of D-serine binding to NMDA receptors is not affected [21].

*APOE4 interactions:* Unknown

**Aging and related health concerns:** Although a small clinical trial suggested benefit for Parkinson's patients, preclinical studies suggest potential harm with regards to increasing oxidative damage in the brain and worsening neuropathic and osteoarthritic pain.

*Types of evidence:*

- 1 randomized controlled trial in Parkinson's disease patients
- 1 study examining levels of D- and L-serine in the CSF of people with osteoarthritis and neuralgia
- Several laboratory studies

***Parkinson's disease***: POTENTIAL BENEFIT. One small double-blind randomized controlled trial of 13 Parkinson's disease patients reported that D-serine treatment (30 mg/kg/day) for 6 weeks resulted in significantly reduced symptoms of extrapyramidal and abnormal involuntary movement compared to placebo [23]. These preliminary findings suggest that D-serine treatment may be beneficial in Parkinson's disease, but larger-sized studies with optimized dosages are warranted.

***Oxidative damage***: POTENTIAL HARM. In a study in rats, a single D-serine treatment (50-200 mg/kg, i.p.) significantly increased the levels of lipid peroxidation, protein carbonyls, and DNA damage in whole-brain samples [24]. In addition, D-serine treatment disrupted the cellular antioxidant status by

decreasing levels of antioxidant enzymes (catalase, glutathione peroxidase, superoxide dismutase), glutathione, and mitochondrial function.

***Neuropathic and osteoarthritic pain***: POTENTIAL HARM. A mouse model of neuropathic pain reported that spinal D-serine may contribute to the induction of mechanical allodynia (pain sensitization) after peripheral nerve injury and that reducing D-serine may alleviate nerve injury-induced chronic neuropathic pain [25]. The authors suggested that the study provides a rationale for using D-serine *antagonists* to treat peripheral nerve injury-induced neuropathy.

In a study examining levels of D-serine in the CSF, people with knee osteoarthritis (3.97 μM/L) had significantly higher levels compared to people with no pain (2.72 μM/L)[26]. Oddly, D-serine levels in people with postherpetic neuralgia (1.85 μM/L) were lower than those with no pain, an unexpected finding, though this difference was not statistically significant. Based on this and the preclinical work, there is a possibility that NMDA receptor stimulation by D-serine worsens pain arising from osteoarthritis.

**Safety:** Numerous clinical trials have reported that D-serine is well-tolerated with few side effects, though one small study saw higher incidence of proteinuria.

*Types of evidence:*

- 6 double-blind randomized controlled trials; 4 in schizophrenics, 1 in people at risk for schizophrenia, and 1 in Parkinson's patients
- Several laboratory studies

D-serine has been tested in numerous randomized controlled trials and most have reported that it is well-tolerated with few side effects [9; 11; 23; 27]. The largest double-blind randomized controlled study was in 195 schizophrenia patients who received D-serine (2g/day) for 16 weeks as an add-on treatment [11]. This study reported that D-Serine was well- tolerated, differing from placebo in only 3 adverse effects, 2 of which were higher in the placebo group. Mouth sores were more prevalent in the D-serine group (4.1% with D-serine, 0% with placebo), while dizziness (11.3% with D-serine, 22.4% with placebo) and headache (13.4% in D-serine, 29.6% in placebo) were more common in the placebo group. The second largest study was a randomized partially-double-blind placebo-controlled trial with 104 schizophrenia patients, which reported no differences in side effects between D-serine (30 mg/kg) and placebo after 12 weeks of treatment [8]. Lab tests also did not show any clinically significant differences. A smaller study in 60 schizophrenia patients also reported no differences in adverse events

with D-serine when compared to placebo [9]. They also reported that blood cell count, chemistry, and EKG remained unchanged and were within normal ranges.

One small double-blind randomized controlled trial of 35 people at risk for schizophrenia reported a few adverse effects [7]. One participant in the D-serine group expressed suicidal thoughts at week 11 and was admitted to the hospital but permitted to remain in the study. Two participants in the D-serine group (and none in the placebo group) were withdrawn because of out of range renal values that were regarded as possibly related to treatment. Of the 17 individuals with trace or greater proteinuria, 11 (64.7%) had been randomly assigned to D-serine and 6 (35.4%) had been randomly assigned to placebo. All abnormalities were resolved during continued treatment.

*Drug interactions*: Information on drug interactions is unavailable. Because D-serine is an agonist of NMDA receptors, it is likely to interfere with actions of other drugs targeting NMDA receptors, such as memantine, ketamine, dextromethorphan, and nitrous oxide (all of which are NMDA receptor antagonists).

**Sources and dosing:** D-serine is available as dietary supplements in the form of capsules. One clinical trial in healthy adults that showed cognitive benefits used a dose of 2.1 g (single dose) [3] and the other one used a dose of 30 mg/kg (mixed in orange juice)[4]. The most commonly tested dose has been 30 mg/kg (e.g., 2.7 g for someone weighing 200 lb), but higher doses (60-120 mg/kg) have been used in schizophrenics [5; 6; 7].

**Research underway:** Based on ClinicalTrials.gov, only one clinical trial testing D-serine is currently ongoing. A double-blind randomized placebo-controlled phase II/III trial is testing whether D-serine is effective for treating tardive dyskinesia (involuntary movements), a common side effect of antipsychotic medications [28]. This study is scheduled to be completed in January 2018. There is one phase IIa randomized double-blind placebo-controlled trial testing L-serine in people with early stage Alzheimer's disease [29]. No rationale is provided for the use of L-serine in this population. The study is currently recruiting participants and was scheduled to be completed in July 2018. Results are not published yet.

**Search terms:**
Pubmed, Google: D-serine

- + meta-analysis, + systematic review, + cognitive, + dementia, + clinical trial, + ApoE, + lifespan, + cardiovascular, + diabetes, + atherosclerosis, + neuropathy

Websites visited for D-serine:

- Clinicaltrials.gov
- Examine.com
- Treato.com (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com (0)
- WebMD.com (0)

**References**:

1. Wolosker H, Blackshaw S, Snyder SH (1999) Serine racemase: a glial enzyme synthesizing D-serine to regulate glutamate-N-methyl-D-aspartate neurotransmission. *Proc Natl Acad Sci U S A* 96, 13409-13414.https://www.ncbi.nlm.nih.gov/pubmed/10557334

2. Monahan JB, Corpus VM, Hood WF *et al.* (1989) Characterization of a [3H]glycine recognition site as a modulatory site of the N-methyl-D-aspartate receptor complex. *J Neurochem* 53, 370-375.https://www.ncbi.nlm.nih.gov/pubmed/2545816

3. Levin R, Dor-Abarbanel AE, Edelman S *et al.* (2015) Behavioral and cognitive effects of the N-methyl-D-aspartate receptor co-agonist D-serine in healthy humans: initial findings. *J Psychiatr Res* 61, 188-195.https://www.ncbi.nlm.nih.gov/pubmed/25554623

4. Avellar M, Scoriels L, Madeira C *et al.* (2016) The effect of D-serine administration on cognition and mood in older adults. *Oncotarget* 7, 11881-11888.https://www.ncbi.nlm.nih.gov/pubmed/26933803

5. Kantrowitz JT, Epstein ML, Beggel O *et al.* (2016) Neurophysiological mechanisms of cortical plasticity impairments in schizophrenia and modulation by the NMDA receptor agonist D-serine. *Brain* 139, 3281-3295.https://www.ncbi.nlm.nih.gov/pubmed/27913408

6. Kantrowitz JT, Malhotra AK, Cornblatt B *et al.* (2010) High dose D-serine in the treatment of schizophrenia. *Schizophr Res* 121, 125-130.https://www.ncbi.nlm.nih.gov/pubmed/20541910

7. Kantrowitz JT, Woods SW, Petkova E *et al.* (2015) D-serine for the treatment of negative symptoms in individuals at clinical high risk of schizophrenia: a pilot, double-blind, placebo-controlled, randomised parallel group mechanistic proof-of-concept trial. *Lancet Psychiatry* 2, 403-412.https://www.ncbi.nlm.nih.gov/pubmed/26360284

8. D'Souza DC, Radhakrishnan R, Perry E *et al.* (2013) Feasibility, safety, and efficacy of the combination of D-serine and computerized cognitive retraining in schizophrenia: an international collaborative pilot study. *Neuropsychopharmacology* 38, 492-503.https://www.ncbi.nlm.nih.gov/pubmed/23093223

9. Lane HY, Lin CH, Huang YJ *et al.* (2010) A randomized, double-blind, placebo-controlled comparison study of sarcosine (N-methylglycine) and D-serine add-on treatment for schizophrenia. *Int J Neuropsychopharmacol* 13, 451-460.https://www.ncbi.nlm.nih.gov/pubmed/19887019

10. Tsai GE, Yang P, Chung LC *et al.* (1999) D-serine added to clozapine for the treatment of schizophrenia. *Am J Psychiatry* 156, 1822-1825.https://www.ncbi.nlm.nih.gov/pubmed/10553752

11. Weiser M, Heresco-Levy U, Davidson M *et al.* (2012) A multicenter, add-on randomized controlled trial of low-dose d-serine for negative and cognitive symptoms of schizophrenia. *J Clin Psychiatry* 73, e728-734.https://www.ncbi.nlm.nih.gov/pubmed/22795211

12. Madeira C, Lourenco MV, Vargas-Lopes C *et al.* (2015) d-serine levels in Alzheimer's disease: implications for novel biomarker development. *Transl Psychiatry* 5, e561.https://www.ncbi.nlm.nih.gov/pubmed/25942042

13. Biemans EA, Verhoeven-Duif NM, Gerrits J *et al.* (2016) CSF d-serine concentrations are similar in Alzheimer's disease, other dementias, and elderly controls. *Neurobiol Aging* 42, 213-216.https://www.ncbi.nlm.nih.gov/pubmed/27143438

14. Hashimoto K, Fukushima T, Shimizu E *et al.* (2004) Possible role of D-serine in the pathophysiology of Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 28, 385-388.https://www.ncbi.nlm.nih.gov/pubmed/14751437

15. Chouinard ML, Gaitan D, Wood PL (1993) Presence of the N-methyl-D-aspartate-associated glycine receptor agonist, D-serine, in human temporal cortex: comparison of normal, Parkinson, and Alzheimer tissues. *J Neurochem* 61, 1561-1564.https://www.ncbi.nlm.nih.gov/pubmed/8397299

16. Nagata Y, Borghi M, Fisher GH *et al.* (1995) Free D-serine concentration in normal and Alzheimer human brain. *Brain Res Bull* 38, 181-183.https://www.ncbi.nlm.nih.gov/pubmed/7583345

17. Pernot P, Maucler C, Tholance Y *et al.* (2012) d-Serine diffusion through the blood-brain barrier: effect on d-serine compartmentalization and storage. *Neurochem Int* 60, 837-845.https://www.ncbi.nlm.nih.gov/pubmed/22465696

18. Bado P, Madeira C, Vargas-Lopes C *et al.* (2011) Effects of low-dose D-serine on recognition and working memory in mice. *Psychopharmacology (Berl)* 218, 461-470.https://www.ncbi.nlm.nih.gov/pubmed/21556803

19. Zou C, Crux S, Marinesco S *et al.* (2016) Amyloid precursor protein maintains constitutive and adaptive plasticity of dendritic spines in adult brain by regulating D-serine homeostasis. *EMBO J* 35, 2213-2222.https://www.ncbi.nlm.nih.gov/pubmed/27572463

20. Guercio GD, Bevictori L, Vargas-Lopes C *et al.* (2014) D-serine prevents cognitive deficits induced by acute stress. *Neuropharmacology* 86, 1-8.https://www.ncbi.nlm.nih.gov/pubmed/24978104

21. Potier B, Turpin FR, Sinet PM *et al.* (2010) Contribution of the d-Serine-Dependent Pathway to the Cellular Mechanisms Underlying Cognitive Aging. *Front Aging Neurosci* 2, 1.https://www.ncbi.nlm.nih.gov/pubmed/20552041

22. Yang S, Qiao H, Wen L *et al.* (2005) D-serine enhances impaired long-term potentiation in CA1 subfield of hippocampal slices from aged senescence-accelerated mouse prone/8. *Neurosci Lett* 379, 7-12.https://www.ncbi.nlm.nih.gov/pubmed/15814189

23. Gelfin E, Kaufman Y, Korn-Lubetzki I *et al.* (2012) D-serine adjuvant treatment alleviates behavioural and motor symptoms in Parkinson's disease. *Int J Neuropsychopharmacol* 15, 543-549.https://www.ncbi.nlm.nih.gov/pubmed/21733283

24. Armagan G, Kanit L, Yalcin A (2011) D-serine treatment induces oxidative stress in rat brain. *Drug Chem Toxicol* 34, 129-138.https://www.ncbi.nlm.nih.gov/pubmed/21314463

25. Choi SR, Moon JY, Roh DH *et al.* (2017) Spinal D-Serine Increases PKC-Dependent GluN1 Phosphorylation Contributing to the Sigma-1 Receptor-Induced Development of Mechanical Allodynia in a Mouse Model of Neuropathic Pain. *J Pain* 18, 415-427.https://www.ncbi.nlm.nih.gov/pubmed/27986591

26. Sethuraman R, Krishnamoorthy MG, Lee TL *et al.* (2007) Simultaneous analysis of D- and L-serine in cerebrospinal fluid by use of HPLC. *Clin Chem* 53, 1489-1494.https://www.ncbi.nlm.nih.gov/pubmed/17586591

27. Ermilov M, Gelfin E, Levin R *et al.* (2013) A pilot double-blind comparison of d-serine and high-dose olanzapine in treatment-resistant patients with schizophrenia. *Schizophr Res* 150, 604-605.https://www.ncbi.nlm.nih.gov/pubmed/24094884

28. Heresco-Levy U (2013) D-Serine treatment for tardive dyskinesia. *ClinicalTrialsgov.*https://clinicaltrials.gov/ct2/show/study/NCT01804920

29. Stark AC (2017) Phase IIa L-serine Trial for eAD (LSPI-2). *ClinicalTrialsgov.*https://clinicaltrials.gov/ct2/show/NCT03062449