

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.

Latrepirdine

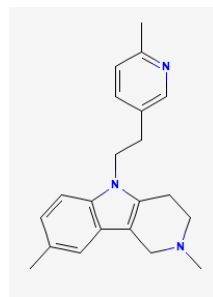
Evidence Summary

While phase 3 trials of latrepirdine in Alzheimer's disease have failed, a new polymorph (DMB-I25) is undergoing a phase 3 study as of 2026, with an estimated completion date in May 2027.

Neuroprotective Benefit: A phase 2 trial in AD showed robust clinical benefits, but phase 3 trials have failed. Meta-analyses of clinical trials have reported a lack of cognitive benefit in AD. A new crystal polymorph (DMB-I25) is in a phase 3 trial.

Aging and related health concerns: Several studies in mice have suggested that latrepirdine treatment may increase their lifespan. There have not been any studies testing latrepirdine for the prevention or treatment of age-related diseases in humans.

Safety: Latrepirdine has been generally well tolerated in clinical trials, with adverse events comparable to those with placebo. Common adverse events include dry mouth, fatigue, and depressed mood.

Availability: Rx in Russia but withdrawn from the market due to newer, more selective compounds; not approved in the US	Dose: Clinical trials in Alzheimer's patients have tested a dose up to 60 mg/day (taken as 20 mg tablets, 3 times daily, orally).	Chemical formula: C ₂₁ H ₂₅ N ₃ MW: 319.4  Source: PubChem
Half-life: elimination half-life of ~6 hours	BBB: penetrant	
Clinical trials: Published meta-analyses of randomized placebo-controlled trials of latrepirdine have included up to 1,697 Alzheimer's disease patients.	Observational studies: none available	

What is it?

Latrepirdine is an antihistamine drug approved in Russia in 1983 but later withdrawn from the market when newer more selective compounds were approved. In addition to antihistamine actions, latrepirdine also weakly inhibits the butyrylcholinesterase and acetylcholinesterase, weakly blocks the glutamate NMDA receptor, inhibits voltage-gated calcium channels, antagonizes the 5-HT₆ and 5-HT₇ receptors, activates AMP kinase, and inhibits mitochondrial permeability transition pore opening ([Bachurin et al., 2001](#); [Doody et al., 2008](#); [Weisova et al., 2013](#); [Kumar and Singh, 2015](#); [Eckert et al., 2018](#); [Nirogi et al., 2023](#); [Dhull et al., 2026](#)). Latrepirdine turned up in a screen as a potential Alzheimer's disease treatment by scientists at the Institute of Physiologically Active Compounds in Russia ([Miller, 2010](#)).

Recent studies suggest that a new crystal structure of latrepirdine, DMB-I25, has better pharmacologic properties, including higher bioavailability in the blood and brain ([Gorin et al., 2023](#); [WO2022160066](#)). This new crystal is undergoing a phase 3 trial in Alzheimer's disease ([NCT07251023](#)).

Neuroprotective Benefit: A phase 2 trial in AD showed robust clinical benefits, but phase 3 trials have failed. Meta-analyses of clinical trials have reported a lack of cognitive benefit in AD. A new crystal polymorph (DMB-I25) is in a phase 3 trial.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 6 clinical trials
- Numerous review articles
- Numerous laboratory studies

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

No clinical or observational studies have evaluated the effects of latrepirdine for preventing dementia or age-related cognitive decline.

Human research to suggest benefits to patients with Alzheimer's dementia:

In a phase 2 double-blind randomized placebo-controlled trial in 155 Russian patients with mild to moderate Alzheimer's disease, latrepirdine treatment (20 mg, 3 times daily, orally) for 26 weeks significantly improved the primary outcome, ADAS-Cog, compared to placebo (mean drug-placebo difference=-4.0; 95% CI, -5.73 to -2.28; $p<0.0001$) ([Doody et al., 2008](#)). Patients in the latrepirdine group also significantly improved ADAS-Cog compared to baseline (mean difference=-1.9; 95% CI, -2.92 to -0.85; $p=0.0005$). Latrepirdine treatment also significantly improved the secondary outcome measure, MMSE, compared to placebo ($p<0.0001$). The mean change from baseline on the activities of daily living scale (ADCS-ADL) significantly favored latrepirdine ($p=0.002$). The neuropsychiatric inventory score (NPI) also showed significant benefit with latrepirdine compared to placebo ($p=0.006$).

The majority of participants (86%) opted to enroll in the blinded extension phase of the trial. At 52 weeks, mean changes from baseline scores significantly favored latrepirdine for all 5 clinical outcome measures (ADAS-Cog, MMSE, ADCS-ADL, NPI, CIBIC-plus) ([Doody et al., 2008](#)). For ADAS-Cog, the latrepirdine group showed a significant difference compared to placebo, with a between-group difference of -6.9 ($p<0.0001$). The latrepirdine-placebo difference on the ADCS-ADL and CIBIC-plus continued to widen between week 26 and week 52.

The phase 3 CONNECTION study was co-sponsored by Pfizer, which had entered a global collaboration with Medivation Inc. for the development of latrepirdine. The trial enrolled 598 patients with mild-to-moderate Alzheimer's disease at 63 sites in North America, Europe, and South America ([Pfizer press release, 2010](#)). Patients were randomized to either latrepirdine 20 mg, 3 times daily, latrepirdine 5 mg, 3 times daily, or placebo. After 6 months of treatment, there were no significant differences across the 3 groups in the co-primary endpoints (ADAS-Cog and Clinician's Interview-based Impression of Change plus Caregiver Input). Secondary endpoints were also negative, including the MMSE, in which the placebo group performed numerically (but not statistically) better.

Several editorials and publications have delved into the potential reasons for why the phase 2 and 3 trials showed such discrepant results ([Jones 2010](#); [Doody et al., 2008](#)). The patients in the phase 2 study were younger (mean age, 68.1 years old) than the phase 3 trial (mean age, 74.4 years old). The phase 2 study in Russia had a mean baseline MMSE score of 18.7 versus the mean baseline MMSE score was 17.7 for the phase 3 trial. The phase 2 trial showed an improvement with latrepirdine concomitant with a worsening in the placebo group. In the phase 3 trial, neither the latrepirdine nor the placebo group deteriorated significantly. The participants in the phase 2 trial in Russia had low use of concomitant drugs. There were also comments about the latrepirdine formulation used in the phase 2 study being potentially different from that of the phase 3 trial, based on different side effect profiles. For example, the original medication has a bitter taste and a numbing effect on the tongue, which could lead to unblinding, while the phase 3 trial used tablets that were film-coated.

In a 2015 Cochrane meta-analysis of 6 double-blind randomized placebo-controlled trials, including a total of 1,697 Alzheimer's patients, there did not appear to be a significant effect of latrepirdine on cognition or function in mild-to-moderate Alzheimer's patients ([Chau et al., 2015](#)). Clinical global impression of change was assessed in 4 trials using Clinician's Interview - Based Impression of Change Plus Caregiver Input (CIBIC-Plus), but only results from [Doody et al., 2008](#) could be extracted, which showed small but significant improvements favoring latrepirdine. Due to the publication bias and imprecision, the authors considered this to be low quality of evidence. With regards to cognitive function (ADAS-Cog and MMSE), 3 trials ([Doody et al., 2008](#), CONCERT, and CONNECTION) were included, totaling 1,243 patients. The meta-analysis showed a lack of significant effect of latrepirdine on ADAS-Cog (MD=-1.49; 95% CI, -3.47 to 0.49; p=0.14). There was considerable between-study heterogeneity, and the quality of evidence was rated as "low" due to the imprecision and high inconsistency across studies.

Similarly, meta-analysis of the 3 trials (1,243 patients) found that there was no significant effect of latrepirdine on MMSE (MD=0.59; 95% CI, -0.94 to 2.11; $p=0.45$). Due to the imprecision and high heterogeneity across studies, the quality of evidence was rated as “low” ([Chau et al., 2015](#)).

A meta-analysis of 3 trials (1,243 patients) found that there was no clear evidence of benefit from latrepirdine on function, assessed by an activities of daily living score (ADCS-ADL)(MD=1.00; 95% CI, -1.15 to 3.15; $p=0.36$)([Chau et al., 2015](#)). The quality of evidence was rated as low due to imprecision and serious inconsistency across the studies.

The authors considered the evidence provided on these outcomes to be of overall low quality. They did find some high quality evidence showing a small benefit of latrepirdine on the Neuropsychiatric Inventory score (NPI) (mean difference=-1.77; 95% CI, -3.09 to -.045; $p=0.009$). Overall, the authors noted that the meta-analysis was limited by the small number of studies, imprecision, and inconsistencies across studies, and some likelihood of bias.

The most recent published Alzheimer’s trial of latrepirdine used a specific crystal structure of latrepirdine, DMB-I25. In a double-blind randomized placebo-controlled trial of 135 patients with probable mild to moderate Alzheimer’s disease, treatment with latrepirdine (DMB-I25, 60 mg daily, orally), for 26 weeks resulted in a significantly improved cognitive score (ADAS-Cog) compared to placebo (one-sided p -value of 0.006)([Gorin et al., 2026](#)). Participants did not have confirmed diagnosis of Alzheimer’s with CSF or PET analysis of amyloid or tau. All participants received memantine in addition to the study medication. The lower dose of DMB-I25 (30 mg daily, orally) also showed numeric improvement but was not statistically different from placebo. With regards to Clinical Global Impressions (CGI) Efficacy index score, both doses of DMB-I25 (30 mg and 60 mg daily) showed significant improvement compared to the placebo group ($p=0.0016$ and $p=0.0006$, respectively). With regards to CGI Improvement index score (CGI-I), DMB-I25 60 mg-dose group showed statistically significant improvements both relative to its own baseline ($p=0.0235$) and compared to placebo ($p=0.0468$). There were no significant effects of DMB-I25 on the quality of life questionnaire (QOL-AD). Based on the findings, the 60 mg daily dose was determined to be the optimal dose for future studies.

Human research to suggest benefits to patients with Huntington’s disease:

There have been 2 randomized controlled trials that have tested the effects of latrepirdine in patients with Huntington’s disease.

A double-blind randomized placebo-controlled trial of 91 patients with mild to moderate Huntington's disease reported that latrepirdine treatment (20 mg, 3 times daily, orally) for 90 days significantly improved mean cognitive scores, measured by MMSE, compared to placebo (treatment effect of 0.97 points, 95% CI, 0.10 to 1.85; $p=0.03$) ([Kiebert et al., 2010](#)). However, no significant effects of latrepirdine were seen on the Unified Huntington's Disease Rating Scale (UHDRS) cognitive tests (verbal fluency, symbol digit modalities, and Stroop interference) or the ADAS-Cog measure used in Alzheimer's disease. There were also no significant effects of latrepirdine on motor or functional subscales of UHDRS.

In a larger, longer, double-blind randomized placebo-controlled trial of 403 patients with mild to moderate Huntington's disease, latrepirdine treatment (20 mg, 3 times daily, orally) for 26 weeks did not significantly affect cognitive function, measured by MMSE (1.5-point) compared to placebo (1.3-point; $p=0.39$) ([HORIZON investigators, 2013](#)). Similarly, the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) was also not significantly different between latrepirdine-treated vs placebo-treated patients. There were also no significant treatment effects on secondary efficacy outcome measures, including behavior, daily function, and motor function.

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

In preclinical studies, various potential neuroprotective mechanisms of latrepirdine have been reported, including induction of autophagy to clear protein aggregates, partial prevention of tauopathy, improvement of cellular energy balance, enhancement of mitochondrial functions, an increase in calcium retention capacity of mitochondria, and an increase in the threshold for mitochondrial transition pore opening (reviewed in [Ustyugov et al., 2015](#); [Ustyugov et al., 2018](#)). Latrepirdine has pleiotropic effects, including inhibition of the butyrylcholinesterase, acetylcholinesterase, the glutamate NMDA receptor, voltage-gated calcium channels, and 5-HT_{6/7} receptors, activation of AMP kinase, and inhibition of the mitochondrial permeability transition pore opening ([Bachurin et al., 2001](#); [Doody et al., 2008](#); [Weisova et al., 2013](#); [Kumar and Singh, 2015](#); [Eckert et al., 2018](#); [Nirogi et al., 2023](#); [Dhull et al., 2026](#)).

In aged (20-month-old) mice, a single dose of latrepirdine (1.0 mg/kg, i.p.) significantly increased cerebral glucose utilization (frontal cortex, hippocampus, and cerebellum), measured by FDG-PET ([Day et al., 2011](#)). This effect of latrepirdine was not observed in young (5-month-old) mice.

In a mouse model of tauopathy (TauP301S Tg mice), chronic treatment of latrepirdine in the drinking water started at 5 weeks of age partially protected against the progressive decline in motor function



(measured by accelerating rotarod test) and accumulation of tau-positive dystrophic neurons ([Peters et al., 2013](#)). While latrepirdine treatment reduced the accumulation of hyperphosphorylated tau in the spinal cord, there were no significant effects of the drug on the total number of neurons or neuroinflammation (measured by GFAP immunoreactivity).

In a mouse model of Alzheimer's disease (TgCRND8 mice), latrepirdine treatment (3.5 mg/kg/day, i.p.) for 31 days improved learning behavior (measured by contextual fear conditioning) and reduced the accumulation of A β 42 and α -synuclein in the brain ([Steele et al., 2013](#)). In mouse neuroblastoma cells, latrepirdine enhanced mTOR- and Atg5-dependent autophagy ([Steele et al., 2013](#)).

In a mouse model of amyotrophic lateral sclerosis (ALS; SOD1G93A mice) that has strong activation of AMPK (a master regulator of energy balance), preconditioning with an AMPK activator, latrepirdine (1 μ g/kg/day, intraperitoneal) from postnatal day 70 to 120 significantly increased AMPK activity in the spinal cord, increased lifespan ($p < 0.01$), and delayed the onset of motor function deficits, measured by the rotarod test and stride length test ([Coughlan et al., 2015](#)). Male SOD1G93A mice showed a more significant increase in lifespan (171 days in the latrepirdine group compared to 158 days in the vehicle control). The difference was not significant in female SOD1G93A mice (166 days in the latrepirdine group vs 159 days in the vehicle control).

In another mouse model of ALS (S-FUS[1-359] tg mice), treatment with a bioisostere of latrepirdine (DF402, 70 μ g/ml in drinking water; equivalent to 12 mg/kg/day) started on postnatal day 42 (before onset of pathology) delayed the disease onset and slowed the progression of pathology ([Chaprov et al., 2021](#)). In the spinal cord of S-FUS[1-359] mice, DF402 treatment reverses gene expression changes seen in these mice that are not observed in wild-type mice.

In isolated rat brain mitochondria, latrepirdine administration prevents A β -induced mitochondrial swelling ([Shevtsov et al., 2014](#)).

In primary neurons, latrepirdine treatment at subnanomolar concentrations activated the AMP kinase, increased intracellular ATP levels, and protected against glutamate-induced excitotoxicity ([Weisova et al., 2013](#)).

In both primary mouse cortical neurons and human neuroblastoma cells (SH-SY5Y cells), latrepirdine administration increased mitochondrial membrane potential and mitochondrial ATP levels without

affecting mitochondrial biogenesis, suggesting that latrepirdine improves the function of existing mitochondria ([Zhang et al., 2010](#)).

Recent studies in rats have shown that the pharmacokinetics and bioavailability are different across 6 polymorphs of latrepirdine ([Gorin et al., 2023](#)). One of the polymorphs showed the highest bioavailability as well as cognitive benefits, measured by conditioned passive avoidance, in a rat model of scopolamine-induced cognitive impairment. Other polymorphs did not exhibit these effects in rats. The most recent published trial along with the ongoing phase 3 trial is testing the new crystal structure of latrepirdine, DMB-I25 ([Gorin et al., 2026](#); [NCT07251023](#)).

APOE4 interactions:

No studies have evaluated whether latrepirdine affects APOE4 carriers differently from non-carriers.

Aging and related health concerns: Several studies in mice have suggested that latrepirdine treatment may increase their lifespan. There have not been any studies testing latrepirdine for the prevention or treatment of age-related diseases in humans.

Types of evidence:

- A few laboratory studies

***Lifespan:* INCREASED IN MOUSE MODELS**

Based on a review article, the maximum and average lifespan of wild-type C57Bl/6 mice was increased with latrepirdine treatment compared to the control cohort (reviewed in [Ustyugov et al., 2018](#)). The average lifespans of 2 amyotrophic lateral sclerosis (ALS) transgenic mice (γ -syn-TG and Fus-TG) were also increased when latrepirdine treatment (1.5 mg/kg/day) was started at the presymptomatic stage.

In another mouse model of ALS (SOD1G93A mice), latrepirdine treatment (1 μ g/kg/day, intraperitoneal) from postnatal day 70 to 120 significantly increased lifespan compared to vehicle control ($p < 0.01$), with male mice showing a significant effect (but not females) ([Coughlan et al., 2015](#)).

Safety: Latrepirdine has been generally well tolerated in clinical trials, with adverse events comparable to those with placebo. Common adverse events include dry mouth, fatigue, and depressed mood.

Types of evidence:

- 2 meta-analyses or systematic reviews
- 5 clinical trials

In a 2015 Cochrane meta-analysis of 4 double-blind randomized placebo-controlled trials, including a total of 1,034 Alzheimer's patients, latrepirdine and placebo were comparable in adverse events (RR=1.03), serious adverse events (RR=0.86), dropouts (RR=0.91), and dropouts due to adverse events (RR=0.98)([Chau et al., 2015](#)).

In a 2014 meta-analysis of 5 randomized controlled trials across various neurological conditions (Alzheimer's, Huntington's, schizophrenia), latrepirdine was generally well tolerated when given alone or in combination with a variety of other drugs (e.g., donepezil, warfarin)([Cano-Cuenca et al., 2014](#)). The most common adverse event was dry mouth, which exceeded 6%. Fatigue was the second most frequent adverse event with latrepirdine and was experienced by 3% of patients.

In a phase 2 double-blind randomized placebo-controlled trial in 155 Russian patients with mild to moderate Alzheimer's disease, latrepirdine treatment (20 mg, 3 times daily, orally) for 26 weeks was well tolerated, with dry mouth and depressed mood or depression the most common adverse events associated with latrepirdine ([Doody et al., 2008](#)). There were no significant differences in the percentage of patients who had adverse events in the latrepirdine group versus the placebo group. Although depression or depressed mood was recorded more commonly in the latrepirdine group than in the placebo group, the change in the NPI depression score from baseline to week 26 was not different between the two groups. Hyperhidrosis, insomnia, angina pectoris, asthenia, hyperkalemia, motor dysfunction (repetitive activity), polyuria, atrial flutter, raised blood bilirubin, dyspnea, and musculoskeletal pain all occurred at least twice as frequently in the latrepirdine group, but overall frequencies were low. There were no significant differences between the two treatment groups in blood pressure, weight, temperature, or changes in electrocardiogram, including QT interval prolongation. There were numerically more serious adverse events in the placebo group than the latrepirdine group at week 52 (p=0.03). Two patients died during the study in each group: 1 patient in the latrepirdine group froze to death after wandering outside, 1 patient in the latrepirdine group died of unknown causes, 1 patient in the placebo group died of a hemorrhagic stroke, and 1 patient in the placebo group died after being hit by a car.

In a double-blind randomized placebo-controlled trial of 135 patients with probable mild to moderate Alzheimer's disease, treatment with the new polymorph of latrepirdine, DMB-I25 (30 or 60 mg daily, orally), for 26 weeks resulted in adverse event incidence that was similar to the placebo group ([Gorin et al., 2026](#)). Adverse events included dizziness, somnolence, lethargy, and asthenia. There were no severe or life-threatening adverse events or deaths recorded in the study. An association with DMB-I intake was noted for 31 adverse event episodes (in 18 patients), most of which were mild in severity, normalized without additional therapy, and did not require study discontinuation.

A double-blind randomized placebo-controlled trial of 91 patients with mild to moderate Huntington's disease reported that latrepirdine treatment (20 mg, 3 times daily, orally) for 90 days resulted in adverse event rates that were similar between the latrepirdine group (68.5%) and the placebo group (68.0%) ([Kiebertz et al., 2010](#)). The most common adverse events in the study were falls, worsening chorea, and somnolence. Only fatigue and dry mouth occurred more frequently in the latrepirdine group compared to the placebo group.

In a double-blind randomized placebo-controlled trial of 403 patients with mild to moderate Huntington's disease, latrepirdine treatment (20 mg, 3 times daily, orally) for 26 weeks was well tolerated and adverse event rates were comparable to placebo (70% in the latrepirdine group and 80% in the placebo group)([HORIZON investigators, 2013](#)).

Drug interactions: Latrepirdine is rapidly and extensively metabolized in the liver, primarily by cytochrome P450 CYP2D6 (and to a lesser extent by CYP2C19 and CYP3A4). Higher latrepirdine plasma concentrations have been observed in CYP2D6 poor metabolizers and in people taking a potent CYP2D6 inhibitor relative to CYP2D6 extensive metabolizers ([Chew et al., 2016](#)).

In a 2014 meta-analysis of 5 randomized controlled trials across various neurological conditions (Alzheimer's, Huntington's, schizophrenia), latrepirdine was well tolerated when given in combination with donepezil or warfarin ([Cano-Cuenca et al., 2014](#)).

Sources and dosing:

Latrepirdine was approved in Russia but withdrawn from the market due to newer, more selective compounds. It is not approved in the US. Clinical trials in Alzheimer's patients have tested a dose up to 60 mg/day (taken as 20 mg tablets, 3 times daily, orally)([Doody et al., 2008](#); [Gorin et al., 2026](#)).

Recent studies suggest that a new crystal structure of latrepirdine, DMB-I25, has better pharmacologic properties, including higher bioavailability in the brain and pro-cognitive effects in animal models ([Gorin et al., 2023](#); [WO2022160066](#)). This new crystal is undergoing a phase 3 trial in Alzheimer's disease ([NCT07251023](#)).

Research underway:

A phase 3 randomized double-blind placebo- and active comparator-controlled trial in 450 patients with mild to moderate Alzheimer's disease is testing the efficacy and safety of DMB-I (Dimebon®, INN: latrepirdine) ([NCT07251023](#)). Patients will be randomized to 1 of 3 treatment groups: 1) DMB-I (10 mg, 2 tablets, 3 times per day) + Akatinol Memantine® (20 mg once daily), 2) placebo (2 tablets 3 times daily) + Akatinol Memantine® (20 mg once daily), and 3) DMB-I (10 mg, 2 tablets, 3 times per day). The randomized phase is 26 weeks, which is followed by an open-label extension of the study for another 26 weeks. During the open-label extension, patients in group 1 and 3 will continue their therapy unchanged, while group 2 will replace placebo with DMB-I while continuing to take Akatinol Memantine®. The primary outcome is change in ADAS-Cog overall score at week 26 compared to baseline. Other outcomes include changes in ADAS-Cog component scores, Neuropsychiatric Inventory (NPI) behavioral symptom frequency and severity, activities of daily living (IADL), and clinical global impression scores. This study is estimated to be completed in May 2027.

Search terms:

Pubmed, Google: latrepirdine, dimebon

Websites visited for latrepirdine:

- [Clinicaltrials.gov](#)
- Examine.com (0)
- DrugAge (0)
- Drugs.com (0)
- WebMD.com (0)
- [PubChem](#)
- [DrugBank.com](#)
- Cafepharm (0)
- Pharmapro.com (0)



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