



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.

Guanfacine

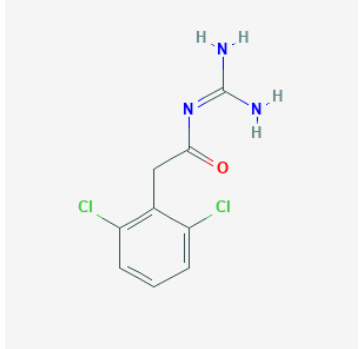
Evidence Summary

Preclinical studies show promise for neuroprotection, but there is little clinical evidence that guanfacine improves cognitive functions. Adverse events are common and there are many drug interactions.

Neuroprotective Benefit: Although there is much preclinical evidence for neuroprotection, there is little clinical evidence that guanfacine promotes cognitive functions except in ADHD patients. A clinical trial for Alzheimer's disease is underway.

Aging and related health concerns: Although guanfacine decreases blood pressure in hypertensive people, it is an old drug and other classes of drugs are used as first-line therapies (diuretics, ACE inhibitors, ARBs, etc.).

Safety: Most people experience adverse events, though many are mild to moderate, including somnolence, thirst, decrease in blood pressure, and postural dizziness. Serious adverse events include syncope. Guanfacine interacts with many drugs.

<p>Availability: Rx</p>	<p>Dose: For ADHD, guanfacine (extended release) dose is started at 1 mg/day and titrated up to a maximum of 4 mg/day.</p>	<p>Chemical formula: C₉H₉Cl₂N₃O MW: 246.09</p>
<p>Half life: 17 hours (range 10-30 hours)(DrugBank.ca)</p>	<p>BBB: penetrant</p>	
<p>Clinical trials: The largest randomized controlled trial included 278 people with hypertension.</p>	<p>Observational studies: An open-label safety study included over 250 children and adolescents with ADHD.</p>	

Source: [PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Guanfacine)

What is it? Guanfacine is a selective α_2A adrenergic receptor agonist originally developed for the treatment of hypertension. Used alone or in combination with other drugs, guanfacine reduces peripheral and renal vascular resistance, and lowers both systolic and diastolic blood pressure and heart rate ([PubChem](https://pubchem.ncbi.nlm.nih.gov/compound/Guanfacine)). Guanfacine is also approved for the treatment of attention deficit hyperactivity disorder (ADHD) in adults and children. The link between guanfacine's mechanism of action and its efficacy for the treatment of ADHD has not been clearly delineated. Guanfacine is currently being tested in a phase 3 study in Alzheimer's patients ([NCT03116126](https://clinicaltrials.gov/ct2/show/study/NCT03116126)).

Neuroprotective Benefit: Although there is much preclinical evidence for neuroprotection, there is little clinical evidence that guanfacine promotes cognitive functions except in ADHD patients. A clinical trial for Alzheimer's disease is underway.

Types of evidence:

- 8 randomized controlled clinical trials
- 1 open-label clinical trial
- Numerous laboratory studies



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

Most studies have been carried out in patients with ADHD. Other studies have included healthy adults as well as patients with stroke, epilepsy, and schizophrenia.

Healthy adults: LITTLE IF ANY BENEFIT.

In a double-blind randomized controlled trial of 123 cognitively normal older adults (over the age of 75), guanfacine treatment (0.5 mg or 0.1 mg daily) for 12 weeks had no effect on working memory and executive functions ([Barcelos et al., 2018](#)). Neither dose of guanfacine improved the prefrontal executive function z-score relative to placebo. Post hoc analyses were performed to evaluate a possible selective treatment effect for participants who were younger or had lower baseline executive function, but these were not significant. Additional post hoc analyses were performed for each of the 6 components of the prefrontal executive function z-score, but no treatment effects emerged. Neither dose of guanfacine improved the quality of life or global function relative to placebo.

In a double-blind randomized controlled trial of 60 healthy male volunteers, a single dose of guanfacine (1 or 2 mg) showed no statistically significant effects on any of the cognitive measures tested ([Muller et al., 2005](#)). Different cognitive domains were tested, such as verbal and non-verbal declarative memory, verbal and non-verbal working memory, and executive functions. Two trends were observed with poorer performance on digit span backward and slower 'Go' reaction times after guanfacine. Thus, no improvements of prefrontal memory or executive functions were seen after guanfacine. The negative trends on digit span backward and go reaction time suggested a mild sedative effect of guanfacine at these doses, possibly via mechanisms of autoreceptor down-regulation.

In a double-blind randomized controlled trial of 55 healthy young college-educated volunteers, a single dose of guanfacine (29 µg/kg) improved spatial working memory, as measured by decreased between-search errors in the two most difficult settings of the task (t-test: $p < 0.01$; for both comparisons) ([Jakala et al., 1999](#)). However, no statistical corrections were made for multiple comparisons and a lower dose of guanfacine (7 µg/kg) had no effect on between-search errors. Guanfacine had no effect on attentional set-shifting. The authors speculated that performance in cognitive tests that are dependent on distinct prefrontal areas may be differentially sensitive to guanfacine.

In another double-blind randomized controlled trial of 43 young healthy volunteers reported that a single dose of guanfacine (29 µg/kg) improved performance on paired associates learning only at the



most difficult stage; no improvement was seen for visual short-term recognition memory (measured by delayed matching-to-sample test)([Jakala et al., 1999](#)). Similar to the study above, no statistical corrections were made for multiple comparisons, and a lower dose of guanfacine had no effect on any of the cognitive tasks.

ADHD: IMPROVED SYMPTOMS AND ATTENTION

Weaker prefrontal cortex function is a hallmark of ADHD. Specifically, decreased activities are seen in the right inferior prefrontal cortex, a brain area critical for inhibiting inappropriate actions ([Rubia et al., 1999](#)). This prefrontal subregion normally grows with maturity but fails to do so in people with ADHD ([Shaw et al., 2009](#)). Guanfacine helps ADHD patients control inappropriate behavior and impulses, including inappropriate aggressive impulses. In a phase 3 double-blind randomized controlled trial of 201 adults with ADHD, guanfacine treatment (titrated from 2 mg/day to 4-6 mg/day, oral, extended release) for 12 weeks significantly improved ADHD rating scale (ADHD-RS-IV) total score (guanfacine, -11.55 ± 1.10 ; placebo, -7.27 ± 1.07 ; $p=0.0005$; effect size 0.52)([Iwanami et al., 2020](#)). There were significantly greater improvements in guanfacine treatment for inattention (-7.39 ± 0.79 vs -4.89 ± 0.76 ; $p=0.0032$) and hyperactivity-impulsivity (-3.84 ± 0.54 vs -2.10 ± 0.52 ; $p=0.0021$) subscale scores, clinical global impression scores (48.1% vs 22.6%; $p=0.0007$), and patient global impression-improvement scores (25.3% vs 11.8%; $p=0.0283$).

In a phase 2 double-blind randomized controlled trial in 182 children and adolescents with ADHD, guanfacine treatment (1, 2, and 3 mg/day, extended release, oral) for 45 days did not result in significant improvements compared to placebo on measures of psychomotor functioning or alertness ([Kollins et al., 2011](#)). However, guanfacine extended release treatment was associated with significant improvement in ADHD symptoms based on the ADHD Rating Scale IV total scores.

In a pilot MRI study in 25 children and adolescents with ADHD, guanfacine treatment (started at 1 mg/day and titrated up to a maximum of 4 mg/day) significantly improved scores on the clinical global impression improvement scale ([Bedard et al., 2015](#)). Although the response inhibition-related activation in mid-cingulate cortex did not differ between guanfacine and placebo treatment, clinical improvement was differentially associated with reductions in midcingulate activation for guanfacine compared with activation gains for placebo.

Epilepsy: POTENTIAL BENEFIT BUT REQUIRES FURTHER STUDY

In an open-label clinical study of 14 patients with frontal lobe epilepsy, 14 patients with temporal lobe epilepsy, and 10 healthy controls, a single dose of guanfacine (2 or 3 mg, oral) improved recognition



memory as measured by accuracy on the delayed match-to-sample task ([Swartz et al., 2008](#)). Greater benefits for healthy controls and frontal lobe epilepsy groups were observed compared to the temporal lobe epilepsy patients. Increased accuracy was not associated with slower performances in any group, suggesting that the cognitive benefits of guanfacine were not hampered by increased sedation. A future placebo-controlled trial is necessary to confirm the potential benefits of guanfacine in epilepsy patients.

Stroke: POTENTIAL BENEFIT BUT REQUIRES FURTHER STUDY

In a double-blind randomized controlled cross-over trial in 13 patients with unilateral neglect following a right hemisphere stroke, a single dose of guanfacine showed statistically significant improvement in neglect compared to placebo, measured by the total number of targets found in a time-limited cancellation paradigm (mean improvement of 5, out of a possible 64)([Dalmaijer et al., 2018](#)). However, there was no evidence of a change in neglect patients' directional attention bias. In other words, guanfacine improved search in neglect by boosting the number of targets found but had no effects on directional bias or search organization, nor did it improve sustained attention or working memory on independent tasks. Further studies are necessary to determine whether longer term guanfacine treatment may be effective for neglect patients and whether it affects functional outcome measures.

Schizophrenia: NO BENEFIT

In a double-blind randomized controlled trial of 40 schizophrenia patients, guanfacine treatment (titrated from 0.5 mg daily to 2 mg daily) for 4 weeks failed to improve any of the cognitive measures tested when compared to placebo ([Friedman et al., 2001](#)). However, exploratory non-parametric statistics revealed some significant differences and some trends between guanfacine and placebo on spatial working memory test performance and reaction time in subjects treated with atypical neuroleptics (e.g., risperidone). The combination of risperidone and guanfacine produced improvement in spatial working memory performance, reaction time, and task-switching (Trails B test) performance. However, no corrections for multiple comparisons were carried out so the differences could be due to chance. The authors speculated that the differential effects in patients treated with the combination is due to the differential effects on catecholamine release in the prefrontal cortex.

Human research to suggest benefits to patients with dementia:

None currently available. Guanfacine is currently being tested in a phase 3 clinical trial in Alzheimer's patients ([NCT03116126](#)).

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

Numerous studies have tested the efficacy of guanfacine in animal models including monkeys and rodents.

In primates, cognitive abilities arise from highly evolved glutamate NMDA receptor circuits in layer III of the dorsolateral prefrontal cortex ([Arnsten and Wang, 2016](#)). Norepinephrine has a high affinity for $\alpha 2A$ -adrenergic receptors compared to other adrenergic receptors, and data from monkeys suggest that these adrenergic receptors are the ones activated under optimal arousal conditions. In the primate dorsolateral prefrontal cortex, $\alpha 2A$ receptors are colocalized with voltage-gated cation HCN channels in layer III dendritic spines near the synapse and in the spine neck. Stimulation of $\alpha 2A$ receptors with guanfacine increases information-specific neuronal firing, important for working memory, thus enhancing mental representations. In contrast, $\alpha 2A$ receptor blockade with an antagonist (yohimbine) causes a complete collapse of prefrontal network firing that can be restored by blocking HCN channels.

Infusion of guanfacine into the dorsolateral cortex improves working memory in monkeys and systemic administration of guanfacine improves a variety of prefrontal cognitive functions. For example, a high dose of guanfacine (0.5 mg/kg) significantly improved spatial working memory, as measured by the delayed response test ([Arnsten et al., 1988](#)). In a different study, guanfacine treatment (0.0015 mg/kg, i.m.) in aged rhesus monkeys significantly improved performance on a sustained attention task (i.e. decreased omission errors by $50.8 \pm 4.3\%$ without an effect on commission errors) although failed to improve performance on the spatial working memory task ([Decamp et al., 2011](#)). In this study, a higher dose of guanfacine (0.5 mg/kg, i.m.) had no benefits on either sustained attention or spatial working memory. Guanfacine also improves impulse control, allowing monkeys to inhibit responses to immediate, small rewards and instead, waited longer for a larger reward ([Kim et al., 2012](#)). In young adult rhesus monkeys, guanfacine treatment (0.7 mg/kg, i.m.) significantly improved performance on a working memory task and significantly increased regional cerebral blood flow values in the dorsolateral prefrontal cortex, the brain region most tightly associated with working memory performance ([Avery et al., 2000](#)).

In mice, the guanfacine effects on working memory are much less robust than those in monkeys, consistent with the very small number of layer II/III prefrontal cortex neurons in mice ([Arnsten and Wang, 2016](#)). Repeated guanfacine administration may increase the number of dendritic spines on layer II/III neurons under basal conditions and enhance prefrontal cortex dendritic spine maturation *in vitro*.



Chronic stress: In a rat model of chronic stress (exposed to restraint stress), guanfacine treatment (0.1 mg/kg, s.c.) for 21 days restored the stress-induced atrophy seen in dendrites and dendritic spines of layer III pyramidal neurons in the prefrontal cortex ([Hains et al., 2015](#)). Acute stress exposure impairs prefrontal cortex-mediated cognition by activating feedforward cAMP-calcium-K⁺ channel signaling, which weakens synaptic inputs and reduces neuronal firing. Guanfacine treatment also protected working memory performance, and cognitive performance correlated with dendritic spine density.

Hypoxia: In a rat model of high-altitude hypobaric hypoxia (rats exposed to simulated altitude of 7620 m), prefrontal cognitive and executive functions are negatively impacted. Guanfacine treatment (1 mg/kg) for 7 days ameliorated the neurological outcomes of high-altitude exposure and associated prefrontal neurodegeneration ([Kausser et al., 2016](#)). Guanfacine treatment significantly increased the expression of BDNF in layer II of the medial prefrontal cortex during normoxia and hypoxia. There was also an inverse correlation of BDNF levels with neurodegeneration of pyramidal cells present in layer II of medial prefrontal cortex. There was a significant decrease in apoptotic proteins, caspase3 and Bax, while a significant increase in the anti-apoptotic protein Bcl2 with guanfacine treatment during hypoxia. Guanfacine treatment also significantly increased MAP2 and spinophilin expression in dendritic arbors and spines, respectively, which were accompanied by changes in morphological parameters of dendrites.

APOE4 interactions: Unknown.

Ageing and related health concerns: Although guanfacine decreases blood pressure in hypertensive people, it is an old drug and other classes of drugs are used as first-line therapies (diuretics, ACE inhibitors, ARBs, etc.).

Types of evidence:

- Numerous clinical trials for hypertension
- Several laboratory studies

Lifespan: EXTENDS LIFESPAN IN WORMS

In a library screening of compounds that increase longevity in *C. elegans*, guanfacine was one of the 60 compounds identified ([Ye et al., 2014](#)). Guanfacine treatment increased lifespan of *C. elegans* by 15%, though its ability to protect them from oxidative stress was not statistically significant.



Hypertension: DECREASES BLOOD PRESSURE

Although guanfacine is effective in treating hypertension, it is an older drug and is not included in the list of first-line therapies (e.g., diuretics, ARBs, ACE inhibitors) when treating hypertension ([2017 Guideline for High Blood Pressure in Adults](#)).

A double-blind randomized controlled trial of 278 patients with mild-to-moderate hypertension reported that guanfacine treatment (1 mg/day, oral) for 12 weeks significantly reduced blood pressure ([Materson et al., 1986](#)). Systolic blood pressure was decreased by 14 mmHg and diastolic blood pressure was decreased by 13 mmHg. Doses of guanfacine at 2 and 3 mg/day were not more effective than the 1 mg/day dose; 0.5 mg/day was not better than placebo.

In a comparative effectiveness double-blind randomized controlled trial of 102 patients with mild-to-moderate hypertension, 8 weeks of guanfacine (1 mg/day) reduced systolic blood pressure by 11 mmHg and diastolic blood pressure by 9 mmHg ([Lewin et al., 1990](#)). Guanfacine and prazosin (1 mg/day) appeared to be equally effective.

In a small double-blind randomized controlled trial of 16 elderly patients with hypertension, guanfacine treatment (2 mg/day) for 4 weeks significantly reduced heart rate and systolic and diastolic ambulatory blood pressure ([Dupont et al., 1987](#)). The antihypertensive effect was maintained over the duration of the study. Guanfacine did not cause bradycardia in any of the patients but did induce a small but statistically significant reduction in heart rate. The mean baseline office (standing) blood pressure was 181.6/107.3 mmHg. Guanfacine treatment for 4 weeks lowered mean office (standing) blood pressure to 152.4/92.1 mmHg.

Diabetes: MAY DECREASE GLUCOSE LEVELS

In a small uncontrolled clinical study of 18 people with hypertension and type 2 diabetes, guanfacine treatment for 1 year produced a marked improvement in the oral glucose tolerance test and serum glucose levels ([Hauger-Klevene et al., 1985](#)).



Safety: Most people experience adverse events, though many are mild to moderate, including somnolence, thirst, decrease in blood pressure, and postural dizziness. Serious adverse events include syncope. Guanfacine interacts with many drugs.

Types of evidence:

- 1 meta-analysis
- 7 double-blind randomized controlled clinical trials
- 2 open-label clinical studies
- 1 review
- Numerous laboratory studies

In the multiple clinical trials of guanfacine in adolescents and children with ADHD, there have not been reports of serum enzyme elevations or clinically apparent liver injury ([PubChem](#)). Similarly, despite widescale use of guanfacine for both hypertension and ADHD, there have been no reports of clinically apparent liver injury attributable to guanfacine.

Healthy adults: In a double-blind randomized controlled trial of 123 cognitively normal older adults (over the age of 75), guanfacine treatment (0.5 mg or 0.1 mg daily) for 12 weeks was well-tolerated ([Barcelos et al., 2018](#)). The only event that was statistically more common with guanfacine treatment was dry mouth, which occurred in 0 participants receiving placebo, 3 participants receiving guanfacine 0.1 mg, and 7 participants receiving guanfacine 0.5 mg. A total of 6 serious adverse events occurred during the trial, including 1 prior to randomization (pneumonia), 2 in the placebo group (myocardial infarction, subarachnoid hemorrhage), 2 in the guanfacine 0.1 mg group (stroke, pneumonia), and 1 in the guanfacine 0.5 mg group (hyponatremia due to adrenal insufficiency). The effect of guanfacine on blood pressure changed over time. At week 1, there was a significant effect of guanfacine 0.5 mg treatment compared to placebo on change in standing systolic (−8.1 mmHg on 0.5 mg compared to placebo, corrected for covariates) and diastolic (−5.8 mmHg), supine systolic (−8.9 mmHg), and diastolic (−4.1 mmHg), but not on orthostatic systolic blood pressure. At the 0.1 mg dose, the only significant effect was on change in supine diastolic blood pressure (−3.4 mmHg). At week 12, the only effect that remained significant was for the 0.5 mg dose in supine diastolic BP (−4.6 mmHg compared to placebo). There was no overall effect of guanfacine treatment on sedation as measured by the Epworth Sleepiness Scale.



In a double-blind randomized controlled trial of 60 healthy male volunteers, a single dose of guanfacine (1 or 2 mg, immediate release) was well-tolerated without side effects or complications ([Muller et al., 2005](#)).

ADHD patients: In a meta-analysis of double-blind randomized controlled trials in children, adolescents, and adults with ADHD that compared across multiple treatments, tolerability was lower for guanfacine compared to placebo ([Cortese et al., 2018](#)).

In a phase 3 double-blind randomized controlled trial of 201 adult ADHD patients, guanfacine treatment (titrated from 2 mg/day to 4-6 mg/day) for 12 weeks resulted in more treatment-emergent adverse events (81.2%) compared to placebo (62.0%) and greater discontinuation due to treatment-emergent adverse events (19.8% vs 3.0%) ([Iwanami et al., 2020](#)). The main adverse events for the guanfacine group were somnolence, thirst, blood pressure decrease, nasopharyngitis, postural dizziness, and constipation; most adverse events were mild to moderate in severity.

In an open-label phase 3 extension study of 133 children and adolescents with ADHD, guanfacine treatment (extended release, 1-7 mg/day, oral) for up to 2 years resulted in most participants (82.7%) experiencing treatment-emergent adverse events ([Huss et al., 2018](#)). Adverse events reported in at least 10% of participants were somnolence (36.0%), headache (28.5%), fatigue (20.1%), and nasopharyngitis (11.7%). Serious treatment-emergent adverse events were reported in 4.7% of participants and those leading to discontinuation were reported in 3.3% of participants. The incidence of sedative adverse events (e.g., somnolence, sedation, and hypersomnia) peaked during week 3, lasted a median duration of 11.0 days, and decreased thereafter. Small changes from baseline to the final assessment in mean supine pulse (- 5.5 bpm, SD=12.98) and blood pressure (systolic, -0.6 mmHg, SD=9.32; diastolic, -0.2 mmHg SD=9.17) were reported. Nine participants (4.2%) reported 10 incidences of aggression. Changes in electrocardiogram parameters from baseline to the final assessment included a decrease in mean heart rate of - 7.6 bpm (SD=13.76), an increase in mean PR interval of + 3.4 ms (SD=12.48), and an increase in mean QTcF interval of + 0.7 ms (SD=16.01). The proportion of participants with a clinically important electrocardiogram result was below 6% for all parameters except for low heart rate (11.8% of participants). No participant had a clinically important QTcF interval while on treatment. Treatment-emergent adverse events that led to early termination (7 participants, 3.3%) were somnolence (2 participants), aggression, first-degree atrioventricular block, dizziness, drug abuse and increased weight. All of these, except drug abuse, were considered by the investigator to be related to guanfacine extended release treatment and resolved either during dose tapering or after drug discontinuation.



In another open-label extension study of 257 children and adolescents with ADHD (of whom 60 completed the study), guanfacine treatment (1-4 mg/day) for 2 years resulted in 87.3% of subjects experiencing treatment-emergent adverse events ([Sallee et al., 2009](#)). Withdrawal of consent was the most frequent reason for discontinuation, followed by loss to follow up (13.5%; 28 of 208 subjects), adverse event (13.5%; 28 of 208 subjects), and lack of efficacy (12.5%; 26 of 208 subjects). The majority of somnolence, sedation, or fatigue events were moderate or mild in severity and resolved by end of treatment. Of 206 patients receiving guanfacine monotherapy, 37.9% experienced somnolence, 24.8% experienced headaches, 15.0% experienced fatigue, and 12.6% experienced sedation. Although not among the most common, hypotension was reported in 13 subjects (5.0%), decreased diastolic blood pressure was found in 9 subjects (3.5%), decreased blood pressure in 7 subjects (2.7%), and decreased systolic blood pressure in 6 subjects (2.3%). Mean changes from baseline of the antecedent study to end point in systolic and diastolic blood pressure were -6.6 mmHg (SD=11.3) and -4.6 mmHg (9.9). Twenty-two treatment-emergent serious adverse events occurred in 16 (6.2%) subjects. No electrocardiogram abnormality was considered by investigators as a serious adverse event. Syncope (fainting) occurred in 5 subjects and was categorized as a serious adverse event possibly or probably related to guanfacine.

A phase 2 double-blind randomized controlled trial of 182 children and adolescents with ADHD reported that guanfacine (extended release, 1-3 mg/day) for 45 days resulted in some treatment-emergent adverse events that occurred higher than with placebo, including somnolence (41.3% vs. 22.8%), headache (24.8% vs. 19.3%), upper abdominal pain (8.3% vs. 3.5%), and sedation (7.4% vs. 5.3%) ([Kollins et al., 2011](#)). Most sedative adverse events were mild to moderate, occurred during dose titration, decreased with dose maintenance, and resolved during the study period. One subject in the guanfacine group discontinued due to fatigue and somnolence. An incidence of severe adverse events was 5.8% for the guanfacine group and 1.8% for the placebo group. Treatment-emergent adverse events led to study discontinuation in 5 subjects: 4 in the guanfacine group (3.3%) and 1 in the placebo group (1.8%). Of the 4 discontinuations due to adverse events in the guanfacine group, 3 were deemed unrelated to the study medication. One subject discontinued due to a drug-related adverse event with symptoms of fatigue, somnolence, and increased difficulty focusing. Clinical laboratory values (i.e., hematology, clinical chemistry, and urinalysis) and physical examinations showed no clinically significant mean changes from baseline or treatment-group differences.

Hypertensive patients: In a comparative effectiveness double-blind randomized controlled trial of 102 patients with mild-to-moderate hypertension, 8 weeks of guanfacine (1 mg/day) resulted in very few adverse effects ([Lewin et al., 1990](#)). Adverse effects with an incidence of 5% or greater for guanfacine were dizziness (6%) and dry mouth (6%). One patient in the guanfacine group was discontinued from the

study due to adverse laboratory findings: BUN (increased from 33 to 56 mg%), creatine (increased from 1.8 to 2.5 mg%), hyperuricemia, and eosinophilia. A second guanfacine patient already had elevated BUN and creatinine levels and they persisted; the patient discontinued from the study even though the levels did not rise during treatment.

In a double-blind randomized controlled trial of 278 patients with mild-to-moderate hypertension, guanfacine treatment (0.5-3 mg/day, oral) for 12 weeks resulted in an increase in the frequency of side effects at the higher 2 and 3 mg/day doses ([Materson et al., 1986](#)). Only 3.2% of the patients in the 1 mg/day group dropped out of the study because of side effects. The most common complaint was fatigue or somnolence followed by dry mouth, dizziness, headache, and impotence. There was a trend toward more complaints of fatigue, somnolence, and dry mouth at the 2 and 3-mg dose levels. There were no clinically relevant changes in the mean values for any of the 44 laboratory tests performed. There were no changes on electrocardiogram measures except for the slight decrease in heart rate. There were no adverse effects of guanfacine on intraocular pressure, the cornea, or retina.

Overdose: Patients experiencing guanfacine overdose may present with hypotension, drowsiness, lethargy, and bradycardia ([DrugBank.ca](#)). Overdose should be managed by first calling the local poison control. An intravenous saline treatment may be required to maintain blood pressure.

Drug interactions: Guanfacine is oxidized by CYP3A4 to its main metabolite, 3-hydroxyguanfacine, which is then glucuronicated or sulphated ([DrugBank.ca](#)). Based on [Drugs.com](#), guanfacine has [126 major drug interactions](#) and [608 moderate drug interactions](#). Taking guanfacine with CYP3A4 inducers would decrease the serum concentration of guanfacine, while taking it with CYP3A4 inhibitors would increase the serum guanfacine concentration; in both cases, the guanfacine dose should be modified ([Drugs.com](#)).

Sources and dosing: Guanfacine is a prescription medication approved for the treatment of ADHD and hypertension. For ADHD, guanfacine (extended release) dose is started at 1 mg/day orally and titrated up to a maximum of 4 mg/day. An ongoing phase 3 study in Alzheimer's patients is testing a dose of 2 mg extended release oral tablet per day ([NCT03116126](#)).

Research underway: Based on [ClinicalTrials.gov](#), there are currently 20 ongoing studies testing the efficacy of guanfacine ([ClinicalTrials.gov](#)). The phase 3 study in Alzheimer's patients is testing guanfacine add-on therapy (2 mg extended release oral daily tablet) versus placebo in 160 patients with Alzheimer's disease ([NCT03116126](#)). This study is scheduled to be completed in March 2021. Other clinical trials are



testing guanfacine for other indications, such as alcohol abstinence, smoking cessation, chronic pain, ADHD, trigeminal neuralgia, and major depressive disorder.

Search terms:

Pubmed, Google: guanfacine

- + cognitive, + Alzheimer, + ApoE, + meta-analysis, + Cochrane, + mortality, + lifespan, + clinical trial, + blood pressure, + cancer

Websites visited for guanfacine:

- [Clinicaltrials.gov](https://clinicaltrials.gov)
- [DrugAge](https://DrugAge.com)
- [Geroprotectors](https://Geroprotectors.com)
- Drugs.com
- WebMD.com
- [PubChem](https://PubChem.ncbi.nlm.nih.gov)
- DrugBank.ca
- [Cafepharma](https://Cafepharma.com)
- Pharmapro.com (0)

Disclaimer: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the [Terms & Conditions](#).

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit [Cognitive Vitality's Rating page](#).