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.

Diphenhydramine (e.g., Benadryl)

Evidence Summary

Diphenhydramine may improve sleep but tolerance develops quickly and may disrupt cognitive functions including memory. Long-term use of anticholinergic drugs is associated with increased dementia risk.

Potential harm to the brain: Long-term anticholinergic use has been associated with increased dementia risk; diphenhydramine can impair many cognitive functions including memory.

Aging and related health concerns: Diphenhydramine may improve sleep but it is unlikely to increase slow-wave sleep; because of increased risk for greater adverse effects, it is listed as inappropriate for use in older adults based on the Beer's criteria.

Safety: Second- and third-generation antihistamines are equally efficacious to diphenhydramine while being safer with fewer cognitive side effects.

What is it? Diphenhydramine is a first-generation histamine 1 receptor antagonist discovered in the 1940s [1]. It is used to treat allergy and cold symptoms such as sneezing, runny nose, watery eyes, urticaria (hives), skin rash, and pruritus (itchy skin). In addition, histamine receptors in the brain play a role in the maintenance of wakefulness [2]. Therefore, by blocking these receptors diphenhydramine can help people fall asleep. Diphenhydramine also has affinity for muscarinic and adrenergic receptors and readily penetrates the blood-brain-barrier. Thus side effects such as grogginess, drowsiness, and memory loss are common. Diphenhydramine is also used for motion sickness and extrapyramidal symptoms in Parkinson's disease patients.

Potential harm to the brain: Long-term anticholinergic use has been associated with increased dementia risk; diphenhydramine can impair many cognitive functions including memory.

Types of evidence:

- 1 meta-analysis based on 18 RCTs comparing diphenhydramine to other antihistamines
- 1 systematic review of insomnia treatments based on 34 systematic reviews, RCTs, or observational studies
- 17 randomized controlled clinical trials
- 6 observational studies, 1 specifically of diphenhydramine and others on anticholinergic use
- 1 postmortem study of Parkinson's disease patients' brains
- 1 study of case reports on elderly with mild dementia
- 3 reviews

Human research to suggest diphenhydramine increases dementia risk:
Some observational studies have examined the link between anticholinergic drugs and dementia risk, though none have looked at the effects of diphenhydramine alone. In a prospective cohort study of 3,434 older people, higher cumulative anticholinergic drug use was associated with an increased risk for dementia, with the hazard ratio highest (1.54; 95% CI, 1.21-1.96) in the highest cumulative users [3]. The most common anticholinergic drugs used in this population were tricyclic antidepressants, first-generation antihistamines (including diphenhydramine), and bladder antimuscarinics.

In a large population-based study of 141,740 elderly nursing home residents with depression, use of anticholinergic medications was associated with a 26% increase in dementia risk [4]. This study used Medicare data and therefore the use of OTC medications such as diphenhydramine is not accurately reflected in the findings. Drugs with strong anticholinergic effects that were commonly prescribed in

this study were oxybutynin and tolterodine (overactive bladder medications), promethazine (antihistamine), olanzapine (antipsychotic), meclizine (for vertigo), and amitriptyline (antidepressant).

Human research to suggest diphenhydramine impairs cognitive function:
Many acute or short-term double-blind randomized controlled trials have shown that diphenhydramine impairs cognitive functions such as alertness [5], attention [6], aversive memory [7], working memory [6; 8], executive function [9], reaction time [8], and vigilance [6], These studies also reported that diphenhydramine increased fatigue and sleepiness while decreasing motivation [6].

A cohort study followed 1,627 older adults for 10 years to examine the relationship between sleep medication use and cognitive functions [10]. In non-demented people, diphenhydramine use was significantly associated with higher education (OR=2.2) and lower MMSE scores (OR=6.7). These two associations remained significant even after sleep complaint variables were accounted for. It is unclear why diphenhydramine is associated with higher education, but it is alarming that despite higher education, which typically confers greater cognitive reserve, there is an association between diphenhydramine use and lower cognitive scores.

A prospective cohort study of 426 older hospitalized patients reported that diphenhydramine treatment was associated with a significantly increased risk for delirium symptoms (RR=1.7; 95% CI, 1.3-2.3), including inattention (RR,=3.0; 95% CI, 1.5-5.9), disorganized speech (RR=5.5; 95% CI, 1.0-29.8), and altered consciousness (RR=3.1; 95% CI, 1.6-6.1)[11].

Other observational studies have been carried out, but these examined the links between anticholinergic drug use and cognitive functions and do not evaluate diphenhydramine specifically.

In a population-based longitudinal study of 1,473 older adults without dementia, anticholinergic medication users declined more on episodic memory over 6 years compared to nonusers with a medium effect size (Cohen's d=0.42)[12]. These results were independent of age, sex, education, overall drug intake, physical activity, depression, cardiovascular risk burden, and cardiovascular disease. In this study, anticholinergic drug use was not associated with performance in processing speed, semantic memory, short-term memory, verbal fluency, and global cognition as measured by the MMSE.

In a cross-sectional study of 473 patients with subjective cognitive decline or neurocognitive disorders, anticholinergic medication use was associated with lower cognitive and functional scores, as measured by MMSE and IADL [13].

In a retrospective cohort study of 274 Taiwanese older men, over 50% had exposure to anticholinergic drugs at baseline and these people had significantly higher risk for cognitive decline (MMSE) than the unexposed (OR 2.69, 95% CI 1.36-5.31)[14]. In this study, the most frequently used anticholinergic drugs were cardiovascular drugs (48.2%), antipsychotics (21.6%), theophylline (20.1%), antidepressants (12.2%), gastrointestinal drugs (11.5%), and antihistamines (8.6%). The effects on MMSE remained after excluding people who were taking antipsychotics.

Human research to suggest harm to patients with dementia:
Case reports from 1994 suggest that elderly with mild dementia are especially prone to delirium following diphenhydramine use [15]. Of the 65 patients who were prescribed diphenhydramine (25 mg for difficulty sleeping) in the hospital, 15% of those over 70 and 5% of those 69 and under experienced short-term delirium.

In a cross-sectional study of 2359 older people in a memory clinic, about half of whom (1127) with Alzheimer's disease, use of anticholinergic drugs was associated with functional impairment, as measured by the activities of daily living (ADL)[16]. In male subjects with mild cognitive impairment, anticholinergic medication use was associated with significant impairment in shopping and drug management. Because the full text was inaccessible, the study could not be fully reviewed.

First-generation antihistamines such as diphenhydramine are listed as inappropriate for use in older adults, because they can cause many side effects including confusion, dizziness, drowsiness, blurred vision, sedation, difficulty urinating, constipation, and hypotension [17; 18].

Mechanisms of action of how decreasing diphenhydramine use might reduce risk of cognitive decline and/or AD:
Diphenhydramine readily penetrates the blood-brain-barrier and blocks muscarinic receptors, thus interfering with acetylcholine-regulated functions such as memory formation, learning, and attention. A study of 2 longitudinal cohorts reported that anticholinergic use (not diphenhydramine specifically) was associated with poorer memory, lower executive function, reduced cerebral glucose metabolism and increased brain atrophy (reduced total cortical volume and temporal lobe cortical thickness, and greater lateral ventricle volumes) compared to nonusers [19]. Common anticholinergics taken by this population were atropine (to treat heart rhythm problems), diphenhydramine, paroxetine (SSRI), and many overactive bladder medications (e.g., oxybutynin, tolterodine, solifenacin, darifenacin).

Anticholinergic/antimuscarinic drugs have also been associated with increased Alzheimer's disease-related pathology. A postmortem study of 120 Parkinson's disease patients' brains revealed that amyloid plaque densities were more than 2.5-fold higher in cases treated with antimuscarinic medication in the long-term (2-18 years) compared with untreated or short-term treated (under 2 years) cases [20]. Neurofibrillary tangle densities were also highest in the long-term antimuscarinic-treated compared to untreated and short-term treated groups.

APOE4 interactions: Unknown.

Aging and related health concerns: Diphenhydramine may improve sleep but it is unlikely to increase slow-wave sleep; because of increased risk for greater adverse effects, it is listed as inappropriate for use in older adults based on the Beer's criteria.

Types of evidence:

- List of potentially inappropriate medication use in older adults from 2015
- 1 systematic review of insomnia treatments based on 34 systematic reviews, RCTs, or observational studies
- 1 review on the safety and efficacy of sleep medicines

No evidence of lifespan-extension or reduction was found in DrugAge, Geroprotectors, or PubMed.

Sleep: Although some studies suggest that diphenhydramine improves overall sleep parameters, the effects are moderate and tolerance develops after 1-2 weeks of uninterrupted use [1]. A systematic review of insomnia treatments reported that there is insufficient evidence for diphenhydramine in effectively treating insomnia [21]. Diphenhydramine is not on the list of drugs that may enhance slow-wave sleep, the non-REM sleep phase associated with restoration, recuperation, and clearance of toxins from the brain [22].

Safety: Second- and third-generation antihistamines are equally efficacious to diphenhydramine while producing fewer cognitive side effects.

Types of evidence:

- List of potentially inappropriate medication use in older adults from 2015
- 1 meta-analysis based on 18 RCTs
- 1 double-blind randomized controlled trial in healthy adults

- 3 double-blind randomized controlled trial testing acute effects of diphenhydramine versus second-generation antihistamines
- 1 review on the safety and efficacy of sleep medicines
- 2 reviews comparing first- and second-generation antihistamine drugs

First-generation antihistamines: First-generation antihistamines such as diphenhydramine can cause many side effects in older adults, such as confusion, dizziness, drowsiness, blurred vision, sedation, difficulty urinating, constipation, and hypotension [17]. Older adults with renal and hepatic impairment are especially prone to these adverse effects [1]. Thus, diphenhydramine is listed as inappropriate for use in older adults based on the Beer's criteria [18]. Second- and third-generation antihistamines such as loratadine (Claritin), fexofenadine (Allegra), cetirizine (Zyrtec), and desloratadine (Clarinex) are not considered "drugs to avoid" by older adults. Serious adverse events appear to be uncommon in young adults. In a double-blind randomized controlled trial of 59 healthy adults, diphenhydramine did not cause any significant effects on vital sign values or clinical laboratory values [5].

Second- and third-generation antihistamines: Second- and third-generation antihistamines were developed to minimize adverse events common to diphenhydramine and older-generation antihistamines [23]. Therefore, these newer antihistamines are likely safer while equally efficacious to diphenhydramine. A meta-analysis based on 18 randomized controlled trials reported that diphenhydramine was associated with significantly worse performance in cognitive measures (effect size, 0.31) compared to second-generation antihistamines (including acrivastine, astemizole, cetirizine, fexofenadine, loratadine, or terfenadine) [24]. Significant mean effect sizes emerged on 3 out of 6 measures, including self-report, attention, and evoked brain potential. Effect size of 0.21 for memory approached significance (p=0.050).

Diphenhydramine versus desloratadine (Clarinex): In a double-blind randomized controlled trial of 204 people, a single dose of diphenhydramine (50 mg) significantly impaired working memory, psychomotor speed, reasoning/computation, and divided attention compared to desloratadine (5 mg; Clarinex) or placebo [25]. Diphenhydramine also significantly increased sleepiness compared to desloratadine or placebo. No statistically significant differences were seen between desloratadine and placebo in any of these cognitive or sleepiness measures.

Diphenhydramine versus loratadine (Claritin): In a double-blind placebo-controlled trial of 98 healthy volunteers, subjects taking diphenhydramine demonstrated poorer cognitive performance than subjects taking loratadine or placebo on tasks of divided attention, working memory, speed, and

vigilance [6]. Subjects taking diphenhydramine also reported greater fatigue and sleepiness and lower levels of motivation, and rated the quality of their performance as lower than subjects taking loratadine or placebo. In contrast, there were no differences between loratadine and placebo in any measure of cognitive or psychomotor test performance, mood, or sedation.

Diphenhydramine versus fexofenadine (Allegra): In a double-blind randomized controlled trial of 42 healthy people, a single dose of diphenhydramine (50 mg) significantly increased response time, omission errors, and drowsiness compared with placebo [26]. In contrast, fexofenadine (180 mg) treatment did not cause significant changes in any attention or drowsiness measures compared with baseline or with placebo. Another double-blind RCT in 42 aviation personnel found that a single fexofenadine treatment (180 mg) resulted in faster reaction time, fewer omission and commission errors, and better delayed recall accuracy compared to diphenhydramine treatment (50 mg) [27]. The study also found that diphenhydramine resulted in significantly more drowsiness than fexofenadine. Effects of fexofenadine were similar to placebo.

Comparisons across antihistamines: In a review from 2006 that compared the effects of new and old antihistamines, clinical evidence confirmed that desloratadine, cetirizine and fexofenadine are effective at managing the symptoms of seasonal allergies in adults and children; however, cetirizine is more likely to cause sedation [23]. Another similar review from 2007 stated that diphenhydramine impairs psychomotor performance and cognitive function but newer drugs had less or no sedating effects [28]. For example, loratadine and desloratadine are non-sedating but less efficacious than cetirizine or fexofenadine. Cetirizine has the fastest onset of action among the newer antihistamines, and while the incidence of sedation is less than that of first-generation antihistamines, it is greater than placebo. Fexofenadine does not impair psychomotor or cognitive skills and shows no dose-related increase in sedation but has a slower onset of action than diphenhydramine and cetirizine. In summary, newer antihistamines provide similar efficacy as first-generation antihistamines but with less or no sedation.

Contraindications: People with bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension should exercise caution when taking diphenhydramine due to its atropine (antimuscarinic)-like action (e.g., drowsiness, dry mouth, blurred vision, flushing, and gastrointestinal symptoms) [17].

Drug interactions: A total of 802 drugs (4779 brand and generic names) are known to interact with diphenhydramine [29]. Diphenhydramine has additive effects with alcohol and drugs for sleep and anxiety (such as zolpidem, lorazepam, and alprazolam) [17]. Diphenhydramine also interacts with

muscle relaxants (e.g., carisoprodol, cyclobenzaprine), tamoxifen, and other antihistamines (e.g., cetirizine, chlorpheniramine). MAO inhibitors prolong and intensify the drying effects of diphenhydramine.

Sources and dosing: Diphenhydramine is available OTC and brand names include, but are not limited to, Benadryl, Allergy Relief, Banophen, Diphedryl, Q-Tryl, Siladryl Allergy, Simply Sleep, Sleepinal, Sominex, Tranquil, Twilite, ZzzQuil, and Z-sleep. Doses commonly used for insomnia are 50 mg of diphenhydramine hydrochloride orally once a day at bedtime (or 76 mg diphenhydramine citrate) [30]. For allergies or cold symptoms, typical doses are 25-50 mg of diphenhydramine hydrochloride orally every 4-6 hours (or 38-76 mg of diphenhydramine citrate every 4-6 hours).

Research underway: There are many clinical trials underway to test diphenhydramine but most of these are testing novel drugs against diphenhydramine.

Search terms:

Pubmed, Google: Diphenhydramine, Benadryl, or anticholinergic

- + cognitive, + dementia, + ApoE/apolipoprotein, + meta-analysis, + systematic review, + aging, + cardiovascular, + lifespan

Websites visited for Diphenhydramine / Benadryl:

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

References:

1. Schroeck JL, Ford J, Conway EL *et al.* (2016) Review of Safety and Efficacy of Sleep Medicines in Older Adults. *Clin Ther* 38, 2340-2372.https://www.ncbi.nlm.nih.gov/pubmed/27751669

2. Monti JM (1993) Involvement of histamine in the control of the waking state. *Life Sci* 53, 1331-1338.https://www.ncbi.nlm.nih.gov/pubmed/8412498

3. Gray SL, Anderson ML, Dublin S *et al.* (2015) Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 175, 401-407.https://www.ncbi.nlm.nih.gov/pubmed/25621434

4. Chatterjee S, Bali V, Carnahan RM *et al.* (2016) Anticholinergic Medication Use and Risk of Dementia Among Elderly Nursing Home Residents with Depression. *Am J Geriatr Psychiatry* 24, 485-495.https://www.ncbi.nlm.nih.gov/pubmed/26976294

5. Kay GG, Schwartz HI, Wingertzahn MA *et al.* (2016) Next-day residual effects of gabapentin, diphenhydramine, and triazolam on simulated driving performance in healthy volunteers: a phase 3, randomized, double-blind, placebo-controlled, crossover trial. *Hum Psychopharmacol* 31, 217-226.https://www.ncbi.nlm.nih.gov/pubmed/27018419

6. Kay GG, Berman B, Mockoviak SH *et al.* (1997) Initial and steady-state effects of diphenhydramine and loratadine on sedation, cognition, mood, and psychomotor performance. *Arch Intern Med* 157, 2350-2356.https://www.ncbi.nlm.nih.gov/pubmed/9361576

7. Papassotiropoulos A, Gerhards C, Heck A *et al.* (2013) Human genome-guided identification of memory-modulating drugs. *Proc Natl Acad Sci U S A* 110, E4369-4374.https://www.ncbi.nlm.nih.gov/pubmed/24145423

8. Katz IR, Sands LP, Bilker W *et al.* (1998) Identification of medications that cause cognitive impairment in older people: the case of oxybutynin chloride. *J Am Geriatr Soc* 46, 8-13.https://www.ncbi.nlm.nih.gov/pubmed/9434659

9. Sands L, Katz IR, DiFilippo S *et al.* (1997) Identification of drug-related cognitive impairment in older individuals. Challenge studies with diphenhydramine. *Am J Geriatr Psychiatry* 5, 156-166.https://www.ncbi.nlm.nih.gov/pubmed/9106379

10. Basu R, Dodge H, Stoehr GP *et al.* (2003) Sedative-hypnotic use of diphenhydramine in a rural, older adult, community-based cohort: effects on cognition. *Am J Geriatr Psychiatry* 11, 205-213.https://www.ncbi.nlm.nih.gov/pubmed/12611750

11. Agostini JV, Leo-Summers LS, Inouye SK (2001) Cognitive and other adverse effects of diphenhydramine use in hospitalized older patients. *Arch Intern Med* 161, 2091-2097.https://www.ncbi.nlm.nih.gov/pubmed/11570937

12. Papenberg G, Backman L, Fratiglioni L *et al.* (2017) Anticholinergic drug use is associated with episodic memory decline in older adults without dementia. *Neurobiol Aging* 55, 27-32.https://www.ncbi.nlm.nih.gov/pubmed/28407520

13. Dauphinot V, Mouchoux C, Veillard S *et al.* (2017) Anticholinergic drugs and functional, cognitive impairment and behavioral disturbances in patients from a memory clinic with subjective cognitive decline or neurocognitive disorders. *Alzheimers Res Ther* 9, 58.https://www.ncbi.nlm.nih.gov/pubmed/28764796

14. Wu YH, Wang CJ, Hung CH *et al.* (2017) Association between using medications with anticholinergic properties and short-term cognitive decline among older men: A retrospective cohort study in Taiwan. *Geriatr Gerontol Int* 17 Suppl 1, 57-64.https://www.ncbi.nlm.nih.gov/pubmed/28436193

15. Tejera CA, Saravay SM, Goldman E *et al.* (1994) Diphenhydramine-induced delirium in elderly hospitalized patients with mild dementia. *Psychosomatics* 35, 399-402.https://www.ncbi.nlm.nih.gov/pubmed/8084991

16. Boccardi V, Baroni M, Paolacci L *et al.* (2017) Anticholinergic Burden and Functional Status in Older People with Cognitive Impairment: Results from the Regal Project. *J Nutr Health Aging* 21, 389-396.https://www.ncbi.nlm.nih.gov/pubmed/28346565

17. Manaye KF, Allard JS, Kalifa S *et al.* (2011) 17alpha-estradiol attenuates neuron loss in ovariectomized Dtg AbetaPP/PS1 mice. *J Alzheimers Dis* 23, 629-639.https://www.ncbi.nlm.nih.gov/pubmed/21157032

18. (2015) Potentially Inappropriate Medication Use in Older Adults 2015. *HealthAgingorg*.http://www.healthinaging.org/resources/resource:potentially-inappropriate-medication-use-in-older-adults-2015/

19. Risacher SL, McDonald BC, Tallman EF *et al.* (2016) Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults. *JAMA Neurol* 73, 721-732.https://www.ncbi.nlm.nih.gov/pubmed/27088965

20. Perry EK, Kilford L, Lees AJ *et al.* (2003) Increased Alzheimer pathology in Parkinson's disease related to antimuscarinic drugs. *Ann Neurol* 54, 235-238.https://www.ncbi.nlm.nih.gov/pubmed/12891676

21. Alessi C, Vitiello MV (2011) Insomnia (primary) in older people. *BMJ Clin Evid* 2011.https://www.ncbi.nlm.nih.gov/pubmed/22030082

22. Walsh JK (2009) Enhancement of slow wave sleep: implications for insomnia. *J Clin Sleep Med* 5, S27-32.https://www.ncbi.nlm.nih.gov/pubmed/19998872

23. Spangler DL, Brunton S (2006) Efficacy and central nervous system impairment of newer-generation prescription antihistamines in seasonal allergic rhinitis. *South Med J* 99, 593-599.https://www.ncbi.nlm.nih.gov/pubmed/16800414

24. Bender BG, Berning S, Dudden R *et al.* (2003) Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J Allergy Clin Immunol* 111, 770-776.https://www.ncbi.nlm.nih.gov/pubmed/12704356

25. Wilken JA, Kane RL, Ellis AK *et al.* (2003) A comparison of the effect of diphenhydramine and desloratadine on vigilance and cognitive function during treatment of ragweed-induced allergic rhinitis. *Ann Allergy Asthma Immunol* 91, 375-385.https://www.ncbi.nlm.nih.gov/pubmed/14582817

26. Mansfield L, Mendoza C, Flores J *et al.* (2003) Effects of fexofenadine, diphenhydramine, and placebo on performance of the test of variables of attention (TOVA). *Ann Allergy Asthma Immunol* 90, 554-559.https://www.ncbi.nlm.nih.gov/pubmed/12775138

27. Bower EA, Moore JL, Moss M *et al.* (2003) The effects of single-dose fexofenadine, diphenhydramine, and placebo on cognitive performance in flight personnel. *Aviat Space Environ Med* 74, 145-152.https://www.ncbi.nlm.nih.gov/pubmed/12602446

28. Banerji A, Long AA, Camargo CA, Jr. (2007) Diphenhydramine versus nonsedating antihistamines for acute allergic reactions: a literature review. *Allergy Asthma Proc* 28, 418-426.https://www.ncbi.nlm.nih.gov/pubmed/17883909

29. Simpkins JW, Rajakumar G, Zhang YQ *et al.* (1997) Estrogens may reduce mortality and ischemic damage caused by middle cerebral artery occlusion in the female rat. *J Neurosurg* 87, 724-730.https://www.ncbi.nlm.nih.gov/pubmed/9347981

30. Levin-Allerhand JA, Lominska CE, Wang J *et al.* (2002) 17Alpha-estradiol and 17beta-estradiol treatments are effective in lowering cerebral amyloid-beta levels in AbetaPPSWE transgenic mice. *J Alzheimers Dis* 4, 449-457.https://www.ncbi.nlm.nih.gov/pubmed/12515896

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.