

# Anticholinergic Burden and Dementia — summary

An evidence synthesis · Holistic Quality LLC

**Author:** Levi Robey · Holistic Quality LLC · **Contact:** levi@holisticquality.io

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**Diphenhydramine as exemplar · the bottom line for readers who want the headline conclusions**

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**Disclaimer.** This is a research synthesis of the published scientific literature. It is **not medical advice** and is **not peer-reviewed**. It is a faithful compression of the full report, which carries the complete 22-study evidence table, mechanism, causal appraisal, and disclosures. Bibliographic data via PubMed. Associations described are **not** assertions of causation unless a cited source establishes one.

**How this was produced.** AI-assisted literature review and drafting, then **human-verified** — every effect size was extracted from and independently re-verified against its source abstract on PubMed, and every study in the full report is linked by DOI. Where the evidence is contested or null, that is stated.

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## The one-paragraph version

Drugs that block acetylcholine — "anticholinergics" — are among the most commonly used medications in older adults, and a large body of research links long-term cumulative use to a higher risk of dementia. The association is real, dose-responsive, and biologically plausible, and in the best studies it survives attempts to rule out reverse causation. But it is not proven to be causal, it is not uniform across drug types, and the conditions these drugs treat may themselves contribute to the risk. **Diphenhydramine** — the active ingredient in over-the-counter sleep aids (ZzzQuil, Tylenol PM, Unisom) and Benadryl — is the most common *strong* anticholinergic that people buy and take for years without a prescription, and without knowing what it is. That makes it the clearest example of an under-counted exposure worth minimizing, even though no study has shown that diphenhydramine specifically causes dementia. A faithful compression of the [full evidence synthesis](#).

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## What the evidence shows

**A consistent, dose-responsive association.** Across 22 primary studies from the UK, USA, Korea, Taiwan, Canada, France, the Netherlands, and China — several million people in total — higher cumulative anticholinergic exposure is repeatedly associated with more dementia. In the largest and best-designed studies, the increase in risk for the highest-exposure groups is modest, roughly 10% to 50% (adjusted hazard/odds ratios about 1.1 to 1.5):

- **Gray 2015 (US, ACT cohort):** HR 1.54 for the heaviest users, with the most recent year of use excluded to reduce reverse causation.
- **Coupland 2019 (England, 284,000 people):** OR up to 1.49; ~10% of dementia in the population statistically attributable to these drugs; the association held even 5–20 years after exposure.
- **Richardson 2018 (UK):** a smaller overall effect (OR 1.11) that persisted for exposure 15–20 years before diagnosis.
- **Recent biobanks (UK Biobank, All of Us, Korean and Chinese cohorts):** broadly reinforce the pattern.

**A plausible mechanism.** Acetylcholine is central to memory, and the loss of cholinergic neurons is a hallmark of Alzheimer's disease — the very reason the main Alzheimer's drugs work by *boosting* acetylcholine. Anticholinergic drugs do the pharmacological opposite.

**It is well-established that these drugs cause acute, reversible confusion** in older adults; diphenhydramine is specifically flagged as a drug to avoid in the elderly. The open question is whether long-term use contributes to *permanent* dementia.

## What the evidence does NOT show

**It does not prove cause and effect.** No randomized trial has ever tested whether anticholinergic drugs cause dementia, and short trials of memory show no effect. All the dementia evidence is observational.

**The conditions treated may carry the risk, not (only) the drugs.** Depression, insomnia, urinary problems, and Parkinson's symptoms can be early signs of the same brain changes that later become dementia. In one study the association disappeared once antidepressant and antipsychotic users were removed; in the bladder-drug studies, even a *non*-anticholinergic comparison drug was linked to dementia — a strong hint that the underlying condition, not just the medication, is part of the story.

**The signal is not uniform, and it is weakest for diphenhydramine's own drug class.** The clearest long-term signals are for anticholinergic antidepressants, bladder drugs, antiparkinson, and antipsychotic medicines. The two best studies that broke results down by drug type did **not** find the antihistamine class (which includes diphenhydramine) independently significant. So the case for diphenhydramine specifically rests on its being a strong anticholinergic that adds to total burden — not on direct evidence that it causes dementia.

**At least one very large, careful study found no overall link** (Liu 2020, Taiwan, ~790,000 people).

## Why diphenhydramine is the exposure nobody counts

Almost all of this research is built on *prescription* records. But diphenhydramine's biggest use is over the counter — the "PM" in nightly sleep aids, and the active ingredient in Benadryl. Someone taking an OTC sleep aid every night for years builds up exactly the kind of cumulative anticholinergic burden the studies associate with risk, while staying completely invisible to the databases used to study it. Most people have no idea the pill is a strong anticholinergic at all.

## The practical takeaway

The prudent conclusion holds up **even if the dementia link turns out not to be causal**:

- Diphenhydramine is a strong anticholinergic (not in dispute).
- Cumulative anticholinergic burden is associated with dementia risk (this synthesis).
- Long-term OTC sleep-aid and allergy use is a large, unmonitored source of that burden.
- Guidance already recommends minimizing anticholinergic use in older adults on other grounds.

So: it is reasonable to avoid unnecessary long-term use of diphenhydramine and other strong anticholinergics — especially nightly OTC sleep aids — and to ask a clinician or pharmacist about lower-anticholinergic alternatives. **Do not stop any prescribed medication on your own; talk to a clinician first.** This is about reducing avoidable exposure, not a reason for alarm about occasional use.

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## How to cite

This page is the **summary brief**. The citable version of record is the **full evidence synthesis** — please cite that:

Robey, L. (2026). *Anticholinergic Burden and Dementia: Associations, Mechanisms, and the Over-the-Counter Exposure Nobody Counts* (full evidence synthesis, Version 1.0). Holistic Quality LLC. doi:10.5281/zenodo.21242588 ·  
<https://holisticquality.io/research/anticholinergic-burden-and-dementia-full>

The full report — with the complete 22-study evidence table, the Bradford Hill causal appraisal, the mechanism and its evidentiary status, the confounding-by-indication analysis, limitations, and full disclosures — is at [holisticquality.io/research/anticholinergic-burden-and-dementia-full](https://holisticquality.io/research/anticholinergic-burden-and-dementia-full). That citable version carries DOI 10.5281/zenodo.21242588 (concept DOI 10.5281/zenodo.21242587, which always resolves to the latest version).

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## Disclosures

**Competing interests.** The author is the founder and principal of Holistic Quality LLC, the commercial publisher of this brief, which develops regulator-facing safety-data and compliance products in areas that include pharmacological and environmental exposure; a sibling property (the Institute for Cognitive Sovereignty) may cite this work in public advocacy. To mitigate this competing interest, every effect size and citation was independently source-verified against its published PubMed record, the limits of the evidence are stated throughout, and the author retained sole editorial control. **Funding:** none (self-funded). **Data availability:** synthesis of published literature; no new data. **AI use:** AI-assisted review/drafting, human-verified; the named author is responsible for all content. **ORCID:** 0009-0005-6946-3569. **Peer-review status:** self-published working paper; not peer-reviewed. Full disclosures are in the [full report](#).

Questions or corrections: [levi@holisticquality.io](mailto:levi@holisticquality.io). #FTP — For The People, Always.