



Cumulative Use of Strong Anticholinergic Medications and Incident Dementia

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Abstract

IMPORTANCE—Many medications have anticholinergic effects. The general view is that anticholinergic-induced cognitive impairment is reversible upon medication discontinuation. However, a few studies suggest that anticholinergic medications may be associated with increased dementia risk.

OBJECTIVE—To examine whether cumulative anticholinergic medication use is associated with a higher risk of incident dementia.

DESIGN—Prospective population-based cohort study using data from the Adult Changes in Thought Study.

SETTING—Group Health, an integrated health-care delivery system, Seattle, Washington

PARTICIPANTS—3,434 participants aged 65 and older with no dementia at study entry. Initial recruitment occurred between 1994 and 1996 or 2000 and 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants received follow-up every two years.

EXPOSURE—Using computerized pharmacy dispensing data, cumulative anticholinergic exposure was defined as the total standardized daily doses (TSDD) dispensed in the past 10 years. The most recent 12 months of use was excluded to avoid use related to prodromal symptoms. Cumulative exposure was time-varying.

MAIN OUTCOMES AND MEASURES—Incident dementia and Alzheimer's disease using standard diagnostic criteria. Statistical analyses used Cox proportional hazards models, adjusted for demographic, health behaviors and health status including comorbidities.

RESULTS—The most common anticholinergic drug classes used were tricyclic antidepressants, first generation antihistamines and bladder antimuscarinics. Over a mean follow-up of 7.3 years, 797 participants (23%) developed dementia (637 developed Alzheimer's). A 10-year cumulative dose-response relationship was observed for both dementia and Alzheimer's disease (test for trend, $p < 0.001$). For dementia, adjusted hazard ratios (HRs) and 95% confidence interval (CI) for cumulative anticholinergic use was 0.92 (95% CI, 0.74-1.16) for 1-90 TSDD; 1.19 (CI, 0.94-1.51) for 91-365 TSDD; 1.23 (CI, 0.94-1.62) for 366-1095 TSDD; and 1.54 (95% CI, 1.21-1.96) for >1095 TSDD, compared to non-use. A similar pattern of results was noted for Alzheimer's disease. Results were robust to secondary, sensitivity and post-hoc analyses.

CONCLUSION AND RELEVANCE—Higher cumulative anticholinergic medication use is associated with an increased risk for dementia. Efforts to increase awareness among health professionals and older adults about this potential medication-related risk are important to minimize anticholinergic use over time.

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eTable 1. List of anticholinergics and minimum effective daily dose^a

Antihistamines <ul style="list-style-type: none"> • Azatadine (2 mg)^b • Bromodiphenhydramine • Brompheniramine (12 mg) • Carbinoxamine • Chlorpheniramine (4 mg) • Clemastine (2 mg) • Cyproheptadine (4 mg) • Dexbrompheniramine • Dexchlorpheniramine • Dimethindene • Diphenhydramine (50 mg) • Doxylamine (5 mg) • Hydroxyzine (75 mg) • Phenindamine • Phenyltoloxamine • Trimeprazine (10 mg)^b • Triprolidine (10 mg) 	Antiparkinson agents <ul style="list-style-type: none"> • Benzotropine (0.5 mg) • Biperiden • Chlorphenoxamine • Cycrimine • Ethopropazine • Procyclidine (7.5 mg)^b • Trihexyphenidyl (6 mg) Antipsychotics <ul style="list-style-type: none"> • Chlorpromazine (10 mg) • Chlorprothixene • Clozapine (20 mg) • Loxapine • Mesoridazine (100 mg)^b • Olanzapine (2.5 mg) • Pimozide (1 mg) • Piperacetazine • Thioridazine (10 mg) • Trifluoperazine (0.5 mg) 	Gastrointestinal antispasmodics <ul style="list-style-type: none"> • Adiphenine • Alverine • Anisotropine • Atropine products (0.0582 mg) • Belladonna alkaloids • Clidinium (7.5 mg)^b • Dicyclomine (40 mg) • Diphemanil • Glycopyrrolate (0.6 mg) • Hexocyclium • Homatropine (6 mg) • Hyoscyamine (0.31 mg)^b • Isopropamide (10 mg)^b • Mepenzolate • Methantheline (100 mg)^b • Methixene • Methscopolamine (10 mg) • Methyldatropine • Oxyphencyclimium • Oxyphenonium • Pipenazole • Poldine • Tridihexethyl • Piperidolate • Propantheline (22.5 mg) • Scopolamine <ul style="list-style-type: none"> o Patch (0.33 mg) o Oral (0.0195 mg) • Thiphenamil
Antidepressants <ul style="list-style-type: none"> • Amitriptyline (10 mg) • Amoxapine (50 mg) • Clomipramine (25 mg) • Desipramine (10 mg) • Doxepin (10 mg) • Imipramine (10 mg) • Nortriptyline (10 mg) • Paroxetine (10 mg) • Protriptyline (5 mg) • Trimipramine (50 mg) 	Bladder antimuscarinics <ul style="list-style-type: none"> • Darifenacin (7.5 mg) • Fesoterodine • Flavoxate (300 mg) • Oxybutynin <ul style="list-style-type: none"> o Patch (3.9 mg) o Oral (5 mg) • Solifenacin (5 mg) • Tolterodine (2 mg) • Trospium (20 mg) 	Antiarrhythmic <ul style="list-style-type: none"> • Disopyramide (400 mg)
Antivertigo/antiemetic <ul style="list-style-type: none"> • Buclizine • Cyclizine (50 mg) • Dimenhydrinate (200 mg) • Meclizine (25 mg) • Prochlorperazine (15 mg) • Promethazine (50 mg) • Promazine • Triflupromazine 	Skeletal muscle relaxants <ul style="list-style-type: none"> • Cyclobenzaprine • Orphenadrine (200 mg) 	

^aMinimum effective doses are only given for medications used by participants

^bMedications used by participants but no longer on the market; mesoridazine and clidinium were on the Beers list for highly anticholinergic medications