

# Breaking News Supporting Role of Anticholinergics

Medscape Medical News > Neurology

## 'Strongest Evidence Yet' Links Anticholinergic Drugs, Dementia

Sue Hughes

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63 comments



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### EDITORS' RECOMMENDATIONS



**Just 2 Months' Exposure to Anticholinergics Affects Cognition**

**Pain Patients at Cognitive Risk From Anticholinergic Burden?**

**Reassuring Findings on Anticholinergics in Dementia**

A new study provides the strongest evidence that anticholinergic drugs may increase the risk for dementia in older adults.

The drugs implicated are commonly used, estimated to be taken by about 20% of the older adult population for many conditions. They include popular antihistamines sold over the counter as sleep aids, such as diphenhydramine (*Benadryl*, McNeil-PPC Inc), or for allergy relief, such as chlorpheniramine; oxybutynin and tolterodine for overactive bladder; and the tricyclic antidepressants, such as doxepin or amitriptyline, even when used at low doses for migraine prevention or neuropathic pain.

66

Original Investigation

## Cumulative Use of Strong Anticholinergics and Incident Dementia A Prospective Cohort Study

**DESIGN, SETTING, AND PARTICIPANTS** Prospective population-based cohort study using data from the Adult Changes in Thought study in Group Health, an integrated health care delivery system in Seattle, Washington. We included 3434 participants 65 years or older with no dementia at study entry. Initial recruitment occurred from 1994 through 1996 and from 2000 through 2003. Beginning in 2004, continuous replacement for deaths occurred. All participants were followed up every 2 years. Data through September 30, 2012, were included in these analyses.

**EXPOSURES** Computerized pharmacy dispensing data were used to ascertain cumulative anticholinergic exposure, which was defined as the total standardized daily doses (TSDDs) 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 updated as participants were followed up over time.

**MAIN OUTCOMES AND MEASURES** Incident dementia and Alzheimer disease using standard diagnostic criteria. Statistical analysis used Cox proportional hazards regression models adjusted for demographic characteristics, health behaviors, and health status, including comorbidities.

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67

# Cumulative Use of Strong Anticholinergics and Incident Dementia

## A Prospective Cohort Study

Characteristic	Participant Group <sup>a</sup>					
	All (N = 3434)	Cumulative Anticholinergic Medication Use in 10 y Before Study Entry, TSDD <sup>b</sup>				
		None (n = 745)	1-90 (n = 1083)	91-365 (n = 701)	366-1095 (n = 347)	>1095 (n = 558)
Age, median (IQR), y	74.4 (70-80)	73.0 (69-78)	74.7 (71-80)	74.5 (70-80)	75.1 (70-80)	74.7 (70-80)
Male sex	1387 (40.4)	384 (51.5)	474 (43.8)	271 (38.7)	116 (33.4)	142 (25.5)
White race	3134 (91.4)	686 (92.1)	982 (90.8)	640 (91.7)	309 (89.1)	517 (92.8)
College education (n = 3433)	2279 (66.4)	544 (73.0)	686 (63.3)	458 (65.4)	228 (65.7)	363 (65.1)
Obese (n = 3359)	853 (25.4)	160 (21.9)	254 (23.8)	177 (25.8)	91 (26.8)	171 (32.0)
Current smoker (n = 3427)	173 (5.0)	35 (4.7)	60 (5.6)	22 (3.2)	19 (5.5)	37 (6.6)
Regular exercise (n = 3426) <sup>c</sup>	2453 (71.6)	563 (75.9)	801 (74.1)	498 (71.1)	235 (67.7)	356 (64.0)
Fair or poor self-reported health (n = 3429)	532 (15.5)	65 (8.8)	136 (12.6)	127 (18.1)	66 (19.0)	138 (24.8)
Treated hypertension (n = 3404) <sup>d</sup>	1662 (48.8)	292 (39.2)	501 (46.3)	367 (52.4)	177 (51.0)	325 (58.2)
Treated diabetes mellitus <sup>e</sup>	272 (7.9)	47 (6.3)	77 (7.1)	63 (9.0)	33 (9.5)	52 (9.3)
History of stroke	221 (6.4)	34 (4.6)	42 (3.9)	51 (7.3)	31 (8.9)	63 (11.3)
Coronary heart disease	633 (18.4)	94 (12.6)	205 (18.9)	135 (19.3)	87 (25.1)	112 (20.1)
Parkinson disease (n = 3427)	24 (0.7)	5 (0.7)	5 (0.5)	7 (1.0)	1 (0.3)	6 (1.1)
High level of depressive symptoms (n = 3378) <sup>f</sup>	336 (9.9)	29 (4.0)	80 (7.5)	79 (11.4)	58 (16.8)	90 (16.5)
Current benzodiazepine use <sup>g</sup>	96 (2.8)	1 (0.1)	20 (1.9)	19 (2.7)	16 (4.6)	40 (7.2)
APOE ε4 genotype (n = 2991)	768 (25.7)	163 (24.6)	234 (24.7)	159 (26.0)	89 (29.6)	123 (26.2)

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68

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## A Prospective Cohort Study

Table 2. Any and Cumulative Anticholinergic Use During the Study Period

Medication Class	All Participants, No. (%) (N = 3434) <sup>a</sup>	Total TSDDs Filled (% of All TSDDs) <sup>b</sup>
Antihistamines	2224 (64.8)	1 158 404 (17.2)
Gastrointestinal tract antispasmodics	1566 (45.6)	365 141 (5.4)
Antivertigo agents/antiemetics	1433 (41.7)	154 488 (2.3)
Antidepressants	1352 (39.4)	4 241 590 (63.1)
Bladder antimuscarinics	668 (19.5)	702 825 (10.5)
Skeletal muscle relaxants	175 (5.1)	20 274 (0.3)
Antipsychotics	38 (1.1)	45 888 (0.7)
Antiarrhythmics	22 (0.6)	31 249 (0.5)
Antiparkinsonians	12 (0.3)	1615 (0.02)
<b>Total</b>		<b>6 721 473 (100)</b>

Abbreviation: TSDD, total standardized daily dose.

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69



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## A Prospective Cohort Study

Table 3. Association of Incident Dementia and AD With 10-Year Cumulative Anticholinergic Use<sup>a</sup>

Diagnosis, TSDD <sup>b</sup>	Follow-up Time, Person-years	No. of Events	%	HR (95% CI)	
				Unadjusted <sup>c,d</sup>	Adjusted <sup>d,e</sup>
<b>Dementia</b>					
0	5618	136	2.42	1 [Reference]	1 [Reference]
1-90	7704	203	2.63	0.96 (0.77-1.20)	0.92 (0.74-1.16)
91-365	5051	172	3.41	1.31 (1.04-1.65)	1.19 (0.94-1.51)
366-1095	2626	102	3.88	1.39 (1.07-1.82)	1.23 (0.94-1.62)
>1095	4022	<b>NNH 47</b>	4.57	1.77 (1.40-2.23)	1.54 (1.21-1.96)
<b>AD</b>					
0	5618	112	1.99	1 [Reference]	1 [Reference]
1-90	7704	168	2.18	0.96 (0.75-1.24)	0.95 (0.74-1.23)
91-365	5051	128	2.53	1.21 (0.93-1.58)	1.15 (0.88-1.51)
366-1095	2626	83	3.16	1.38 (1.03-1.85)	1.30 (0.96-1.76)
>1095	4022	<b>NNH 60</b>	3.63	1.73 (1.34-2.24)	1.63 (1.24-2.14)

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70

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### Conclusions

An increased risk for dementia was seen in people with higher use of anticholinergics. Our findings suggest that a person taking an anticholinergic, such as oxybutynin chloride, 5 mg/d, or doxepin hydrochloride, 10 mg/d, for more than 3 years would have a greater risk for dementia. Prescribers should be aware of this potential association when considering anticholinergics for their older patients and should consider alternatives when possible. For conditions with no therapeutic alternatives, prescribers should use the lowest effective dose and discontinue therapy if ineffective. These findings also have public health implications for the education of older adults about potential safety risks because some anticholinergics are available as over-the-counter products. Given the devastating consequences of dementia, informing older adults about this potentially modifiable risk would allow them to choose alternative products and collaborate with their health care professionals to minimize overall anticholinergic use. Additional studies are needed to confirm these findings and to understand the underlying mechanisms.

71