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'Strongest Evidence Yet' Links Anticholinergic Drugs, Dementia

Sue Hughes | January 27, 2015

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.

The study, published online in *JAMA Internal Medicine* on January 26, was conducted by a team led by Shelly Gray, PharmD, University of Washington, Seattle.

"We found an obvious dose-response relationship between anticholinergic drug use and risk of developing dementia: the higher the usage, the greater the risk," Dr Gray commented to *Medscape Medical News*.

Even Low Doses Implicated

But people taking just the minimum effective dose of these agents for prolonged periods qualified as having high use and were found to be at greater risk for dementia compared with those not taking such medicines.

"This is not excessive use," Dr Gray said. "Many of these agents are used chronically, and chronic use — even at low doses — would put you in the highest risk category."

She said that although previous studies have linked anticholinergic agents to cognitive problems, the general population and even most doctors were unaware of the issue.

"Anticholinergic drugs do have other more recognized side effects, such as dry mouth, constipation, and urinary retention, and there has been a movement away from using them, but they are still very commonly prescribed and bought in over-the-counter products."

While this study extends previous findings on the link between anticholinergic drugs and cognition problems, it does not prove causality because it is still based on observational data.

"It isn't possible to prove causation with observational data," Dr Gray added. "I would say that we haven't proven that these drugs cause dementia, but our results certainly reinforce concerns about this issue."

While there is awareness that these drugs may cause short-term drowsiness or confusion, which is included in the prescribing information, there is no mention of long-term effects on cognition, and generally awareness of this issue is very low, Dr Gray said. "The pharmacist or doctor may not even know. Education on this issue is key, and both the public and doctors need to be encouraged to use alternative treatments where possible."

Dr Gray noted that all studies of this issue have been conducted in older individuals. "There is no data on how these drugs may affect younger people, but I personally will avoid taking anticholinergic agents," she added.

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The current population study involved 3434 older adults (average age, 73 years). Their medication use over the past 10 years was tracked from pharmacy records, and they were followed for an average of another 7.3 years with dementia screening every 2 years during this follow-up period.

About 20% of the population were using anticholinergic drugs. The researchers worked out a minimum effective dose of each anticholinergic medication and then calculated cumulative exposure, which was defined as the total standardized daily doses (TSDD) dispensed in the past 10 years.

Over the follow-up period, 797 participants (23.2%) developed dementia, and 637 of these (79.9%) developed Alzheimer's disease.

A 10-year cumulative dose-response relationship was observed for dementia. A similar pattern of results was noted for Alzheimer's disease.

TSDD of Anticholinergic Drug and Risk for Dementia (vs No Use)

TSDD	Hazard Ratio (95% Confidence Interval)
1 - 90	0.92 (0.74 - 1.16)
91 - 365	1.19 (0.94 - 1.51)
366 - 1095	1.23 (0.94 - 1.62)
>1095	1.54 (1.21 - 1.96)

Dr Gray explained that taking the minimum daily effective dose of one the anticholinergic agents every day for 3 years would put people in the highest risk category. "You could also get into this highest category by taking this dose sporadically over a longer period, or by taking a higher dose for a shorter period."

"Very Credible Data"

Coauthor of an accompanying editorial, Noll L. Campbell, PharmD, Purdue University College of Pharmacy, West Lafayette, Indiana, told *Medscape Medical News* that this study provided "the strongest evidence to date that anticholinergic drugs cause dementia." His coathor is Malaz A. Boustani, MD, MPH, from the Regenstrief Institute and Indiana University School of Medicine, Indianapolis, Indiana.

Dr Campbell, who has also authored some studies showing similar findings, explained that the current study had the longest record of medication history. This history was measured from dispensing records and so provided "very credible data," which is "probably the best that can be done in an observational study."

"Even low doses of the drugs included in this study increased the risk of dementia when taken long term. It looks as though it could be a cumulative effect. The more you use the higher your risk," he noted.

"We have several studies now all suggesting that these anticholinergic medications are associated with cognitive problems. But while many geriatricians and psychiatrists may be aware of these data, these medicines are often prescribed by family doctors who may not be aware of this issue. Publishing this study in *JAMA Internal Medicine* is a good idea as it will reach more family doctors that way," he said.

Dr Campbell added: "Maybe the best group to try to make aware of this issue is the patients themselves. Dementia is a much-feared condition. It would definitely be a priority for me not to take any medication that might increase my risk of this condition."

Dr. Gray noted that future studies would focus on understanding the biochemical mechanism that might underlie this association, adding that a subset of patients from the current study have given permission for their brain tissue to be studied on autopsy, which could help shed light on this.

Dr Campbell suggested that the next step could be a randomized study looking at the risk for dementia in patients who have been taking these drugs and are assigned to continue or stop their medication. His group is applying for funding for such a study.

The study was supported by grants from the National Institutes of Health's National Institute on Aging and the Branta Foundation. Dr Gray has disclosed no relevant financial relationships. Dr Campbell receives grant support from the National Institutes of Health and Astellas Pharma US.

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