EDITORIAL

Delaying dementia

Can antihypertensives prevent Alzheimer dementia?

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Oliver Wendell Holmes, Sr., a 19th-century physician, Dean of Harvard Medical School, and poet, described an enchanting thought experiment in his poem, "The Deacon's Wonderful One-Hoss Shay." This carriage was crafted to be equally strong in every part, letting it run in perfect condition for 100 years before, one fine day, it disintegrated like a "bubble burst." For many geriatric neurologists and their patients, that would be a worthy goal: to address all the "weak links," the most vulnerable and fixable aspects of brain aging, thus compressing morbidity due to cognitive decline into a brief flicker prior to death. The emerging realization that dementia is a clinical syndrome with multiple etiologies lends urgency to the argument for a multipronged therapeutic approach more akin to that used in the prevention of coronary artery disease or stroke.

One treatable, putative risk factor for dementia is hypertension. The lifetime risk of hypertension has been estimated at a startling 90%.[1] Several observational studies have shown an adverse effect of elevated blood pressures (BP) on cognitive performance.[2] This appears to be true for contemporaneous BP, measured at the time of cognitive assessment, as well as for midlife BP measured 1–4 decades earlier.[3,4] These observations suggest that all methods effective in lowering BP, be they lifestyle changes or drugs, should help retain or improve cognitive function and reduce the risk of dementia.

Does effective BP lowering in late life reduce the risk of cognitive decline and Alzheimer-type dementia among persons with hypertension as defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)? The Systolic Hypertension in Europe (SYST-EUR) trial suggested that BP lowering with antihypertensive drugs reduced the risk of incident dementia,[5] although other studies failed to corroborate this.[6] Further, whereas a high BP increases the risk of developing stroke, and hence vascular dementia, whether late-life hypertension independently increases the risk of developing dementia remains unclear. One explanation for this uncertainty could be that while hypertension is associated with an increased risk of dementia, it is also associated with the use of antihypertensives that might lower the risk of dementia, through lowering BP or through other independent mechanisms.

If antihypertensive medications reduce the risk of dementia, is this a reflection of the degree of BP lowering, or a class effect associated with one or more specific groups of antihypertensives? Since antihypertensives such as diuretics and β-blockers are already widely used in older persons and have a favorable safety profile, an additional benefit on cognition would have substantial public health implications. In this issue of *Neurology*®, 2 groups of investigators have utilized observational data from a cohort study and a drug trial, respectively, to examine such class-specific drug effects. Gelber et al.[7] analyzed prospectively collected data on 2,197 participants from the Honolulu-Asia Aging Study (HAAS) and observed that persons on β-blockers had a 31% lower risk of developing new cognitive impairment compared to persons not on antihypertensives and to persons on other antihypertensive medications. This was contingent on effective BP lowering with no benefit among persons in whom the BP remained high despite antihypertensive treatment. Yasar et al.[8] conducted a secondary analysis on 1,928 cognitively normal adults and 320 persons with mild cognitive impairment (MCI) who had enrolled in the Ginkgo Evaluation in Memory Study (GEMS) and observed that cognitively normal persons on diuretics, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin II receptor blockers (ARBs) and persons with MCI on diuretics had a 42%–59% reduction in risk of developing dementia compared to persons not on these medications.

Both studies describe class-specific beneficial effects (which would need to be confirmed in additional observational studies and clinical trials), but it remains unclear which groups of antihypertensive medications are most effective. HAAS suggests that β-blockers are most beneficial (although the data also suggest a benefit from use of vasodilators) and the study by Yasar et al. is consistent with this; although the effect of β-blockers was not significant, it was only slightly smaller than the effect of ACEI, ARB, and diuretics. GEMS also found a lower risk of Alzheimer disease (AD) in persons on ARB, and as data on ARB usage were not available in the HAAS cohort, these results could neither be

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Table Samples, study designs, and outcome

	Honolulu-Asia Aging Study	Gingko Evaluation in Memory Study
Sample		
Race/ethnicity	Japanese ancestry	European ancestry
Sex	Men only	Men and women
Recruitment	Community-based	Volunteers enrolled in drug trial
Hypertensive status	All had hypertension	Only 43% had hypertension
Other vascular risk factors	Higher prevalence (e.g., 26% had diabetes)	Relatively healthy sample (e.g., 9% had diabetes)
Cognitive status	Persons with normal cognition only	Persons with normal cognition and mild cognitive impairment
Study design	Cross-sectional (logistic) analysis	Time-to-event (Cox) analysis
Outcome studied	Drop in cognitive test score below specified threshold	Clinical Alzheimer dementia

confirmed nor refuted. However, the association of ACEI and diuretics with risk of cognitive decline and dementia differed in the 2 studies. Neither study noted a specific benefit with use of calcium channel blockers.

How do we reconcile these differing results? There are differences in samples, study designs, and outcome (table). It is possible that ACEI and diuretics reduce the risk of developing dementia in relatively healthy older adults and persons with MCI, while β-blockers have a more general beneficial effect on age-related cognitive decline in a typical older population with a high burden of vascular disease. However, another parsimonious explanation may be that the reported associations are random findings that will not be reproducible in other cohorts. These 2 studies do not report, but likely had limited power to detect, differences between drug classes; indeed, they did not find a significant difference in overall dementia risk among persons on different classes of antihypertensive medications. Large meta-analyses will likely be required to confirm class-specific effects. As a comparison, a recent meta-analysis of 147 trials including 958,000 persons could find no major differences between the different classes of antihypertensive medications in reducing stroke risk.[9]

Some other caveats also need to be considered. The apparent protective effect on AD risk could be due to a greater proportion of the dementia in persons on antihypertensive medications being diagnosed as vascular dementia. The lower risk of AD could also be due to a higher competing risk of cardiovascular mortality among persons on antihypertensive medications. Further, low BP in late life might be associated with an increased risk of dementia, although this may be an instance of reverse causality, with the pathologic process causing cognitive decline resulting in biological and lifestyle changes that lower BP.[10]

So what are some reasonable take-home messages from this intriguing pair of studies? One is that the consequences of BP lowering and the possible effects of specific drug classes on cognitive decline and risk of dementia are important and potentially rewarding, but that further study is warranted. Inclusion of cognitive test batteries and brain imaging (including amyloid imaging) in clinical trials of antihypertensive medications and further observational studies in other large existing cohorts of various ethnicities are indicated. It is also possible to build a strong case for the inclusion of antihypertensive medications in randomized trials to study modifiers of progression from MCI to clinical dementia. A rational approach to antihypertensive medications may shore up one weak link in our attempts to preserve cognitive function as the brain ages.

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DISCLOSURE

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