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NSAIDs in the prevention of dementia
A Cache-22?

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Multiple epidemiologic studies have reported an association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and a reduced risk of Alzheimer disease (AD). In a recent meta-analysis, use of non-aspirin NSAIDs was associated with a 26% risk reduction of AD, with an even greater reduction (RR = 0.42; 95% CI 0.26 to 0.66) if NSAID use was sustained for at least 2 years. In vitro and in vivo animal studies also suggest that certain NSAIDs lower amyloid-beta-42 (Aβ-42) peptide levels independent of anti-inflammatory, cyclooxygenase-mediated effects. Despite these encouraging epidemiologic and laboratory data, randomized controlled trials of various NSAIDs have failed to demonstrate a significant effect on the rate of cognitive decline in patients with AD or on the rate of conversion to AD in patients with mild cognitive impairment. Furthermore, the eagerly awaited AD Anti-inflammatory Prevention Trial (ADAPT) using naproxen or celecoxib was terminated in December 2004 over concerns about cardiovascular risks.

In this issue of Neurology, Hayden et al. provide further epidemiologic evidence in support of a role for NSAIDs in reducing the risk of AD. They report the latest results from the Cache County Study on Memory Health and Aging, a large, population-based, longitudinal study of cognition in elderly individuals. The authors investigate the effect of NSAID use on the rate of cognitive decline, as measured by the Modified Mini-Mental State Examination (3MS), in 3,383 previously healthy subjects for an average of 6.5 years) and propose that this subgroup may represent individuals who initiated NSAIDs prior to the onset of cognitive decline. In other words, the observed beneficial impact of NSAIDs appears to be limited to a particular subgroup of users (ApoE4+ individuals who started NSAIDs before age 65), indicating that NSAIDs may only be effective if started early enough, taken for long enough, or both.

What about the observation that ApoE4 genotype appears to modulate the effects of NSAIDs on cognitive decline? The decreased rate of decline in ApoE4+ individuals taking NSAIDs prior to age 65 is intriguing and, if replicated in future studies, raises important questions for further research. If NSAIDs are truly neuroprotective against AD, does this occur through an ApoE-mediated process? Alternatively, is the observed differential effect mainly due to reduced statistical power in the ApoE4− subgroup, since fewer of these individuals would be ex-
pected to decline during the course of the study? As for the increased rate of decline in ApoE4—patients taking NSAIDs after age 65, one should take caution in assigning too much weight to this finding, given the small difference in 3MS scores over time (−0.16 points/year) and borderline significance of the effect (p = 0.054 after correction for survival bias).

Should these data encourage clinicians to prescribe NSAIDs to patients at risk for dementia? The authors appropriately indicate that no clinical recommendations can be made from observational studies, since such studies cannot control for confounding variables that might be present in individuals who choose to take NSAIDs vs those who do not, such as comorbid disease or health/lifestyle differences. These confounders can only be excluded in a randomized controlled primary prevention trial of NSAIDs in AD. Unfortunately, the trial that was designed to answer this question was halted due to concerns over cardiovascular risks, including a significant increase in the composite outcome of cardiovascular death, stroke, TIA, myocardial infarction, or congestive heart failure. Therefore, clinicians trying to weigh the risks and benefits of NSAIDs in AD prevention face a Catch-22 (or, in this case, a “Cache-22”). In order to quantify the risks of NSAID use, one needs data from a primary prevention trial. However, such a trial is unlikely to occur, because it is currently thought to be too risky.

In the absence of definitive evidence from a randomized trial, what should clinicians do? In counseling a patient about an intervention, we try to weigh the specific risks and benefits for a particular individual. To decide whether to prescribe NSAIDs for the prevention of AD, we need our colleagues pursuing research in this area to continue asking questions from observational studies to define these risks and benefits as accurately as possible. When should NSAIDs be started? How long should they be taken? Which ones should be used? What are the different cardiovascular outcomes based on timing and duration of use? Is there a subset of patients that might benefit the most from treatment? Is there a subset at highest risk for adverse events? Once we are closer to answering these questions, a select group of individuals might emerge whose risk/benefit profile appears favorable, prompting a focused, randomized controlled trial in this patient population. However, until these questions can be clarified sufficiently, it is prudent for clinicians to refrain from recommending NSAIDs for use in AD prevention.

NOTE ADDED IN PROOF
The cognitive outcome data from the ADAPT trial were published while this editorial was in press. These data demonstrate no benefit of either naproxen or celecoxib in preventing AD when started a median of 2 years prior to the onset of dementia. Surprisingly, both NSAID treatment groups showed a trend toward an increased rate of dementia compared to placebo. These results reinforce concerns about the extent to which timing of NSAID use may impact the course of AD.

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