Are the benefits of NSAIDs to decrease the risk of Alzheimer's disease a MIRAGE?

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The Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, commissioned by the National Institute on Aging in 1991, has recently released data gathered by a questionnaire process from May 1996 to May 2002 [1]. The MIRAGE data reveal an inverse association between nonsteroidal anti-inflammatory drugs (NSAIDs) and Alzheimer's disease (AD). The inverse association was more robust among subjects who carried the apolipoprotein E ε4 allele. An inverse association between NSAIDs and AD has long been suspected. Numerous studies [2–10] have demonstrated an inverse association, others [11–13] have not. Table 1 puts these studies into perspective.

Methods of the MIRAGE study
The MIRAGE study is a multicenter study of genetic and environmental risk factors for AD. Subjects consisted of 691 AD patients and 973 family members enrolled at 15 US research centers between 1996 and 2002. The age-, gender-, education- and race-matched first-degree family members serving as a control elegantly provided additional, although informal, matching regarding socioeconomic status and health-seeking behavior. The primary independent variable was NSAID use of at least 6 months and occurring at least 1 year prior to the retrospective identification of AD. The dependent variable was AD case status, verified by review of medical records in the AD group and by modified Telephone Interview of Cognitive Status (mTICS) in the control group. AD information was supplemented by informants and medical records in both groups. The dataset was stratified to evaluate whether the association between NSAID use and AD was similar in ApoE-ε4 carriers and noncarriers, and in Caucasians, African-Americans, and other ethnicities as an effect modifier.

Results
NSAID use was inversely associated with AD by virtue of being more frequent in controls compared with AD cases in the overall sample (adjusted-odds ratio [OR]: 0.64; 95% confidence interval [CI]: 0.38–1.05). The benefit of NSAID use appeared more pronounced among subjects who carried the apolipoprotein (Apo) E variant form, ε4 allele. The data presented by Yip and colleagues [1] is currently the largest sample comparing NSAID use in a well-characterized AD group and in a well-matched control group. The study was also sufficiently powered to examine effect modification by the ApoE genotype. ApoE has three common variant forms: ε2, ε3 and ε4. The lifetime risk for AD is heightened with ε4 and diminished with ε2 [18]. The presence...
of one ApoE-ε4 allele is associated with a two- to threefold increased incidence of AD, whereas two ApoE-ε4 alleles carry an eight- to tenfold increase in risk. The MIRAGE study did not differentiate subjects who carried one ApoE-ε4 allele from those who carried two.

The MIRAGE study, by not separating NSAID users from less efficacious aspirin and by not selecting the longer- and earlier-use patterns that other studies have found to be more effective, could be expected to have less robust data than a study designed to include consideration of these features. Not being a prospective, randomized controlled trial, MIRAGE is not definitive nor of greater relative importance than the studies that have preceded it. Nevertheless, the findings are positive, and in spite of the generalities of the questionnaire, are promising, consistent with other major NSAID/AD studies, and are a valuable addition to the cumulative evidence to date. The MIRAGE authors suggest that prospective studies and clinical trials of sufficient power to detect effect modification by ApoE-ε4 carrier status are needed.

**Perspective**

The contemporary papers highlighted in Table 1, because they are designed heterogeneously, variously support or contradict the findings of the MIRAGE study group. Typical of epidemiologic data supporting the MIRAGE data is a report (not in Table 1) of a long-term observational study that revealed approximately 50% less AD in those who were using NSAIDs [19]. Epidemiologic studies examining the protective effect of NSAIDs against the development of AD have generally been positive, even at low doses, but mixed, owing to the differences in timing, duration and tracking methods of NSAID use [2-10,19]. These variables were considered and addressed in a large (n = 6989) prospective, population-based cohort study performed in The Netherlands [8]. Computerized pharmacy records of individuals aged 55 and older were examined for an average of 6.8 years. Of the subjects who took NSAIDs for a month or less, the relative risk (RR) for developing AD was 0.95 (95% CI: 0.7-1.29). For those taking NSAIDs for more than 1 but less than 24 months, the RR for developing AD was 0.83 (95% CI: 0.62-1.11); and for subjects using NSAIDs for 24 months or more of cumulative use, the RR for developing AD was 0.20 (95% CI, 0.05-0.83). The clear benefit from NSAID use was in long-term users (2 or more years before the onset of dementia), thus suggesting that there may be a critical time period or duration of use required in order for NSAID therapy to be neuroprotective.

The MIRAGE study required only 6 months of NSAID use for inclusion criteria in the NSAID cohort. If the questionnaire had been structured to identify individuals with more substantial use patterns, that is, greater than 2 years, neuroprotection with NSAIDs might have been more prevalent in actuality and the data might have been more robust consequently.

Another study design feature conceivably decreasing the strength of the outcomes data is the pooling of aspirin and NSAIDs into one category. A meta-analysis of cohort and case-controlled studies that included The Netherlands study, reported a pooled RR for AD of 0.72 (95% CI: 0.56-0.94) among NSAID users and 0.87 (95% CI: 0.70-1.07) among aspirin users [8,20]. Again, amount and duration of use varied significantly. Short-, intermediate-, and long-term users of NSAIDs demonstrated RRs for developing AD of 0.95 (95% CI: 0.70-1.29), 0.83 (95% CI: 0.65-1.06), and 0.27 (95% CI, 0.13-0.58), respectively.

A 2005 meta-analysis that examined 25 case-control and cohort studies called into question the possibility of various forms of bias, including recall, prescription and publication bias [21]. When the authors divided the reports into studies with prevalent dementia cases, studies with incident dementia cases, and studies where cognitive decline was used as the clinical end point, the pooled RRs of the three groups of studies were 0.51 (95% CI: 0.37, 0.70), 0.79 (95% CI: 0.68, 0.92), and 1.23 (95% CI: 0.70, 2.31), respectively. The benefit of NSAIDs in preventing dementia or cognitive impairment was 50% in studies with prevalent dementia cases and was strikingly heterogeneous (p = 0.001) in this category. However, benefit declined to 20% in studies with incident dementia cases and was absent in studies where cognitive decline was used as the end point, but study designs vary widely.

This meta-analysis calls into doubt our ability to accept the efficacy of NSAIDs to protect against developing AD despite the preponderance of observational data supporting neuroprotection by NSAIDs [21]. Nevertheless, basic science supports the MIRAGE study and other epidemiologic data in two distinct
## Table 1. Key studies of the effect of NSAIDs and aspirin on the risk of Alzheimer's dementia

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Subjects (n)</th>
<th>Intervention</th>
<th>Duration</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen K, Launer LJ, Ott A et al. (1995)</td>
<td>Cross-sectional, general population</td>
<td>NSAID users (n = 365) to nonusers (n = 5893)</td>
<td>Nonaspirin NSAIDs</td>
<td>Current</td>
<td>RR for AD of 0.38 (0.15–0.95) when comparing NSAID users to nonusers</td>
<td>[2]</td>
</tr>
<tr>
<td>Anthony JC, Breitner JC, Zandi PP et al. (2000)</td>
<td>Cross-sectional, general population</td>
<td>201 cases of AD and 4425 controls</td>
<td>Aspirin vs. nonaspirin NSAIDs</td>
<td>Current</td>
<td>Use of NSAIDs and aspirin were specifically associated with a reduced occurrence of AD</td>
<td>[3]</td>
</tr>
<tr>
<td>Broe GA, Grayson DA, Creasey HM et al. (2000)</td>
<td>Case-control, general population</td>
<td>163 in dementia categories and 373 in control</td>
<td>Aspirin vs. nonaspirin NSAIDs</td>
<td>Current</td>
<td>Inverse association between both NSAIDs and aspirin and AD, not observed with vascular dementia</td>
<td>[4]</td>
</tr>
<tr>
<td>The Canadian Study of Health and Aging (1994)</td>
<td>Case-control, general population</td>
<td>258 cases of AD and 535 controls</td>
<td>Aspirin vs. NSAIDs vs. 'any' NSAID</td>
<td>Any history of use of NSAIDs</td>
<td>History of arthritis resulted in a low risk of AD (OR: 0.54; 95% CI: 0.36–0.81), as did a history of the use of NSAIDs</td>
<td>[5]</td>
</tr>
<tr>
<td>in’t Veld BA, Launer LJ, Hoes AW et al. (1998)</td>
<td>Case-control, general population, 6.8 years</td>
<td>6989 subjects</td>
<td>Nonaspirin NSAIDs</td>
<td>Any history of use of NSAIDs</td>
<td>RR of AD was 0.95 (95% CI: 0.70–1.29) with short-term use of NSAIDs, 0.83 (95% CI: 0.62–1.11) with intermediate-term use, and 0.20 (95% CI: 0.05–0.83) with long-term use</td>
<td>[6]</td>
</tr>
<tr>
<td>Stewart WF, Kawas C, Corrada M et al. (1997)</td>
<td>Case-control, general population, 15 years</td>
<td>1686</td>
<td>Aspirin vs. nonaspirin NSAIDs</td>
<td>Any history of use of NSAIDs</td>
<td>With 2 or more years of NSAID use, the RR was 0.40 (95% CI: 0.19–0.84) compared with 0.65 (95% CI: 0.33–1.29) with less than 2 years of use. The RR for AD among aspirin users was 0.74 (95% CI: 0.46–1.18) regardless of duration of use</td>
<td>[7]</td>
</tr>
<tr>
<td>in’t Veld BA, Ruitenberg A, Hofman A et al. (2001)</td>
<td>Prospective, general population cohort study, 6.8 years</td>
<td>6989</td>
<td>Nonaspirin NSAIDs</td>
<td>Any history of use of NSAIDs</td>
<td>&lt;1 month use, RR for developing AD, 0.95 (95% CI: 0.7–1.29); &lt;24 months use, RR for developing AD, 0.83 (95% CI: 0.62–1.11); &gt;24 months use, RR for developing AD, 0.20 (95% CI: 0.05–0.83)</td>
<td>[8]</td>
</tr>
<tr>
<td>Lindsay J, Laurin D, Verreault R et al. (2002).</td>
<td>Prospective, general population, 5 years</td>
<td>194 AD cases and 3894 controls.</td>
<td>Aspirin vs. nonaspirin NSAIDs vs. 'any' NSAID</td>
<td>Any history of use of NSAIDs</td>
<td>Use of NSAIDs, wine, coffee, and/or exercise were specifically associated with reduced occurrence of AD</td>
<td>[9]</td>
</tr>
</tbody>
</table>

ACTH: Adrenocorticotrophic hormone; AD: Alzheimer's disease; CI: Confidence interval; HR: Hazard ratio; NSAID: Nonsteroidal anti-inflammatory drug; OR: Odds ratio; RR: Relative risk.
mechanisms of AD pathology. Inflammation is believed to play an important role in the pathology of AD and cytokine production is a key pathologic event in the progression of inflammatory cascades. Research has shown that the brains of transgenic mice are under an active inflammatory stress, and that the levels of particular cytokines are directly related to the amount of soluble and insoluble Aβ present in the brain suggesting that pathologic accumulation of Aβ is a key driver of the neuroinflammatory response [22]. The role of inflammatory processes in the pathophysiology of AD suggests a valid rationale for the efficacy of NSAIDs.

More dramatic and elegant are experimental observations in cultured cells that ibuprofen, indomethacin and sulindac lowered the production of Aβ by as much as 80%, apparently by direct modulation of γ-secretase activity [23,24]. The effect was not seen with all NSAIDs and was irrespective of cyclooxygenase activity [23]. In contrast to other γ-secretase inhibitors, Aβ-lowering NSAIDs do not impair ancillary mechanisms and therefore underline the striking specificity by which these drugs target Aβ-42 production [24,25].

Expert opinion & outlook
Inhibition of γ-secretase through these three Aβ-lowering NSAIDs is an avenue of research likely to become exciting by demonstrating preventive efficacy in prospective clinical trials and by spurring new pharmaceutical research to develop analogues of these agents that provide greater efficacy and specificity but less toxicity. Randomized trials of NSAIDs or their analogues for primary prevention of AD are unlikely to show effects with treatment until participants have been followed for several years [10]. Rather than yielding new drug targets, a subset of NSAIDs or NSAID analogues will probably contribute to a combination of therapies targeted to different areas and mechanisms of the amyloid cascade.

There is now a glut of observational data concerning NSAIDs and AD, typically showing a reduction in risk of considerable significance.
This author suggests that future research needs to involve definitive prospective, randomized, controlled trials that are designed to reflect the known properties (γ-secretase inhibition) of selected NSAIDs as well as previously demonstrated efficacious patterns of use with regard to length of dosing pattern (>2 years) to affect preventive neurophysiologic influences in order to settle the issue of neuroprotection.

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MIRAGE trial – KEY PAPER EVALUATION

Highlights

- Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study data reveal an inverse association between nonsteroidal anti-inflammatory drugs (NSAIDs) and Alzheimer's disease (AD) that is more robust among subjects carrying the apolipoprotein (apo)E variant form, ε4.
- Most epidemiologic studies of a similar nature that have preceded MIRAGE have also demonstrated an inverse association between NSAID use and AD.
- The MIRAGE study is currently the largest sample comparing NSAID use in a well-characterized AD group and in a well-matched control group.
- The MIRAGE study, by not separating NSAIDs from less efficacious aspirin and by not selecting the longer and earlier use patterns that other studies have found to be more effective, could be expected to have less robust data than an analysis that did account for these distinctions.
- MIRAGE is not definitive, nor of greater relative importance than the observational, epidemiologic studies that have preceded it.
- Prospective randomized controlled trials of sufficient power to detect effect modification by ApoE-ε4 carrier status are needed.
- A 2005 meta-analysis that examined prevalent dementia cases, incident dementia cases, and cognitive decline as the clinical endpoint, observed pooled relative risks of 0.51, 0.79 and 1.23, respectively, casting doubt on the ability of observational data to support claims of neuroprotection by NSAIDs.
- That the levels of particular cytokines are directly related to the amount of soluble and insoluble Aβ present in the brain suggests that Aβ promotes the neuroinflammatory pathophysiology of AD and suggests a valid rationale for the efficacy of NSAIDs.
- Experimental observations in cultured cells reveal that ibuprofen, indomethacin and sulindac (but not other NSAIDs) lower the production of Aβ by as much as 80%, apparently by direct modulation of γ-secretase activity, and suggests an additional rationale for the efficacy of these three NSAIDs.
- Future research should involve definitive prospective, randomized controlled trials that are designed to reflect the known properties (γ-secretase inhibition) of selected NSAIDs as well as previously demonstrated efficacious patterns of use with regard to length of dosing pattern (>2 years) to affect preventive neurophysiologic influences in order to settle the issue of neuroprotection.

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