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

John B Standridge

University of Tennessee, Health Science Center College of Medicine, Department of Family Medicine, 1100 East 3rd Street, Chattanooga, Tennessee, 37403, USA
Tel.: +1 423 778 2957
Fax: +1 423 778 2959
John.Standridge@erlanger.org

Evaluation of: Yip AG, Green RC, Huyck M *et al*. Nonsteroidal anti-inflammatory drug use and Alzheimer's disease risk: the MIRAGE Study. *BMC Geriatr*. 5(1), 2 (2005).

The Multi-Institutional Research in Alzheimer's Genetic Epidemiology study data reveal an inverse association between nonsteroidal anti-inflammatory drugs (NSAIDs) and Alzheimer's disease that is more robust among subjects who carried the apolipoprotein E ε4 allele. Randomized trials of NSAIDs for the primary prevention of Alzheimer's disease are unlikely to show effects with treatment until participants have been followed for several years. Inhibition of γ-secretase, as identifiifed in three Aβ-lowering NSAIDs, is an avenue of research likely to demonstrate preventive efficacy in prospective clinical trials. A subset of NSAIDs, or their analogs, will probably contribute to a combination-therapy approach targeted to different mechanisms of the neuropathology associated with the amyloid cascade.

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 (Apo) E variant form, 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.

The issue is of great importance. As burdensome as AD is in the present day [14–16], unless new discoveries facilitate prevention of the disease, the anticipated burden on caregivers and society threatens to overwhelm resources. Interventions that could delay disease onset, even modestly, would have a major public health impact [17].

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 ApoE-ε4 allele carriers (adjusted OR: 0.49; 95% CI: 0.24–0.98) compared with noncarriers, although this association was not statistically significant. The pattern of association was similar in Caucasians and African–Americans.

The data presented by Yip and colleagues [1] is curently 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

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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 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 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 cateory. 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

Source	Design	Subjects (n)	Intervention	Duration	Results	Ref.
Andersen K, Launer LJ, Ott A *et al.* (1995)	Cross-sectional, general population	NSAID users (n = 365) to nonusers (n = 5893)	Nonaspirin NSAIDs	Current	RR for AD of 0.38 (0.15–0.95) when comparing NSAID users to nonusers	[2]
Anthony JC, Breitner JC, Zandi PP *et al.* (2000)	Cross-sectional, general population	201 cases of AD and 4425 controls	Aspirin vs. nonaspirin NSAIDs	Current	Use of NSAIDs and aspirin were specifically associated with a reduced occurrence of AD	[3]
Broe GA, Grayson DA, Creasey HM *et al.* (2000)	Case-control, general population	163 in dementia categories and 373 in control	Aspirin vs. nonaspirin NSAIDs	Current	Inverse association between both NSAIDs and aspirin and AD, not observed with vascular dementia	[4]
The Canadian Study of Health and Aging (1994)	Case-control, general population	258 cases of AD and 535 controls	Aspirin vs. nonaspirin NSAIDs vs. 'any' NSAID	Any history of use of NSAIDs	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	[5]
in't Veld BA, Launer LJ, Hoes AW *et al.* (1998)	Case-control, general population, 6.8 years	6989 subjects	Nonaspirin NSAIDs	Any history of use of NSAIDs	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	[6]
Stewart WF, Kawas C, Corrada M *et al.* (1997)	Case-control, general population, 15 years	1686	Aspirin vs. nonaspirin NSAIDs	Any history of use of NSAIDs	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	[7]
in't Veld BA, Ruitenberg A, Hofman A *et al.* (2001)	Prospective, general population cohort study, 6.8 years	6989	Nonaspirin NSAIDs	Any history of use of NSAIDs	<1 month use, RR for developing AD, 0.95 (95% CI: 0.7–1.29); <24 months use, RR for developing AD, 0.83 (95% CI: 0.62–1.11); >24 months use, RR for developing AD, 0.20 (95% CI: 0.05–0.83)	[8]
Lindsay J, Laurin D, Verreault R *et al.* (2002).	Prospective, general population, 5 years	194 AD cases and 3894 controls.	Aspirin vs. nonaspirin NSAIDs vs. 'any' NSAID	Any history of use of NSAIDs	Use of NSAIDs, wine, coffee, and/or exercise were specifically associated with reduced occurrence of AD	[9]

ACTH: Adrenocorticotrophic hormone; AD: Alzheimer's disease; CI: Confidence interval; HR: Hazard ratio; NSAID: Nonsteroidal anti-inflammatory drug; OR: Odds ratio; RR: Relative risk.

Table 1. Key studies of the effect of NSAIDs and aspirin on the risk of Alzheimer's dementia (Cont.).

Source	Design	Subjects (n)	Intervention	Duration	Results	Ref.
Zandi PP, Anthony JC, Hayden KM *et al.* (2002)	Prospective, general population	104 cases of AD among 3227 participants	Nonaspirin NSAIDs	Current and former use	HR was 0.45 with ≥2 years of exposure former NSAID users showed substantially reduced incidence (est HR = 0.42)	[10]
Breitner JC, Gau BA, Welsh KA *et al.* (1994)	Case-control, family members	50 elderly twin pairs with onsets of AD separated by 3 or more years	Aspirin vs. nonaspirin NSAIDs vs. corticosteroids or ACTH	Prior daily use of NSAIDs	The onset of AD was inversely associated with prior use of corticosteroids or ACTH (OR: 0.25; 95% CI: 0.06–0.95; p = 0.04) and with use of NSAIDs (OR: 0.08; CI: 0.01–0.69; p = 0.02)	[11]
Beard CM, Waring SC, O'Brien PC *et al.* (1998)	Case-control registry-based	302 incident cases AD and 302 age- and sex-matched controls	Nonaspirin NSAIDs	Use for 7 or more days	OR for exposure to a NSAID versus no exposure to any NSAID was 0.79 (95% CI: 0.45–1.38); OR was 1.00 (95% CI: 0.52–1.92) for women and 0.40 (95% CI: 0.13–1.29) for men. Similarly, the overall OR for aspirin was 0.90 (95% CI: 0.54–1.50)	[12]
Henderson AS, Jorm AF, Christensen H *et al.* (1997)	Prospective, general population, 3.6 years	1045 persons aged 70 years	Aspirin vs. nonaspirin NSAIDs	Any history of use of NSAIDs	No difference was found between NSAID or aspirin users and controls, either in cognitive decline or incidence of dementia	[13]

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 analogs 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 inhihition) 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.

Disclosure

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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 inhihition) 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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Affiliation

John B Standridge, MD,
Associate Professor, University of Tennessee, Health Science Center College of Medicine, Department of Family Medicine, 1100 East 3rd Street, Chattanooga, Tennessee, 37403, USA
Tel.: +1 423 778 2957
Fax: +1 423 778 2959
John.Standridge@erlanger.org