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Nonsteroidal Anti-Inflammatory Drugs and Cognitive Function

Do They Have a Beneficial or Deleterious Effect?

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Abstract

Studies suggest that high dose NSAID use may be associated with a reversible impairment of cognition in the elderly. Prolonged NSAID use, on the other hand, may prevent the decline in cognition associated with aging. However, it has yet to be to be definitively determined whether this protection arises from an anti-inflammatory effect that modifies pathways involved in Alzheimer's dementia, or is mediated by a platelet effect that decreases the risk of cerebrovascular disease.

Further large-scale, randomised, controlled trials using NSAIDs are needed before patients can be advised that the known risks of NSAIDs are outweighed by their potential long term benefits on cognition. While clinicians await the results of such studies, they should continue to be alert to the possibility of acute CNS adverse effects in their elderly patients who are receiving NSAIDs and to prescribe the minimum dose that is necessary to control pain and inflammation.

For the older person, intact mental function is a highly valued component of quality of life. Medications that either advantageously or deleteriously alter cognitive function in the elderly have come under increasing scrutiny. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a class of medications frequently used by the elderly that have been evaluated both for their therapeutic potential for preserving cognitive function, and as a source of avoidable cognitive dysfunction.

Up to 40% of NSAID prescriptions are written for people over the age of 60 years[1] and at least 10 to 15% of people over the age of 65 years take these medications.[2] Older individuals are at higher risk for NSAID-associated adverse effects, partly because of age-related alterations in drug metabolism. As hepatic and renal function decline with age, drug clearance is slowed and the half-lives of NSAIDs are extended. Decreases in serum albumin levels in the elderly may also lower the fraction of protein-bound drug and increase the unbound, active fraction. Each of these metabolic changes leads to an increased likelihood of drug toxicity. Studies of the effects of NSAIDs on cognition in the elderly indicate that in the short term the older patient may be at risk for CNS adverse effects. However, in the longer term increasing evidence suggests that NSAIDs may provide protection against the cognitive decline associated with aging.

1. Assessing the Impact of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) on Cognitive Dysfunction

NSAIDs have been recognised as a possible cause of CNS perturbations for almost 30 years. Between 1964 and 1973, the UK Committee on Safety of Medicines received 397 reports of indo-

Table I. Effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on cognition

Reference	Study design (duration)	No. of patients	Setting	Drugs evaluated	Cognitive outcomes measured	Results
Goodwin et al.[5]	Case reports	8	Rheumatology practice	Naproxen, ibuprofen	NA	Reversible subjective symptoms
Wysenbeek et al.[6]	Non-controlled clinical trial	12	NA (elderly OA patients)	Naproxen	Wechsler adult intelligence scale (digit span, digit symbol, block design), Bender Gestalt test	Decline in 1 or more tests in 4 of 12 patients (p = 0.1)
Rozzini et al.[7]	Prospective cohort (3 years)	6068	Community	NSAIDs	SPMSQ score	Decreased decline, RR = 0.82 (95% CI = 0.69-0.98)
Sturmer et al.[8]	Prospective cohort (6 years)	2023	Community	Aspirin (acetylsalicylic acid)	SPMSQ score	No change, RR = 0.97 (95% CI = 0.82-1.15)
Hanlon et al.[9]	Prospective cohort (3 years)	2765	Community	NSAIDs	SPMSQ score	Decreased decline, indeterminate NSAID use (p < 0.05)
					OMC test	Improved concentration, continuous NSAID use (p < 0.05) Poorer memory with high dose NSAID use (compared with low dose use)
Saag et al.[10]	Prospective cohort (3 years)	2087	Community	Non-aspirin NSAIDs	Word recall	Increased decline, high dose NSAID use OR = 2.06 (95% CI = 1.1-3.9)

CI = confidence interval; **NA** = data not available; **OA** = osteoarthritis; **OMC** = Orientation-Memory-Concentration; **OR** = odds ratio; **RR** = relative risk; **SPMSQ** = Short Portable Mental Status Questionnaire.

methacin-related nonfatal CNS adverse effects, which included headache, giddiness, vertigo, confusion and visual changes.[3] In 1991, Hoppmann et al.[4] identified 23 case reports, in the world literature, of NSAID-associated aseptic meningitis, although 14 of these patients had an underlying diagnosis of systemic lupus erythematosus or mixed connective tissue disease.

Studies suggesting a specific causative link between NSAIDs and cognitive dysfunction are more limited (see table I). In a retrospective study from 1982, Goodwin and Regan[5] identified 8 patients over 65 years old from their rheumatology practice who had developed subjective symptoms such as forgetfulness, inability to concentrate, or personality change, after the initiation of an NSAID. Symptoms in 6 of 8 patients began within 2 months of starting to take the drug and in all patients the symptoms cleared within 2 weeks of discontinuing it.

In a small prospective study, Wysenbeek et al.[6] evaluated cognitive function at baseline and following a 3-week course of naproxen 750 mg/day in 12 elderly patients with osteoarthritis who had not previously taken NSAIDs. A battery of 4 cognitive tests assessed attention, memory span, psychomotor speed, visual organisation and coordination. Four of the 12 patients showed a decline in 1 out of 4 tests, although these findings did not reach statistical significance. While these 2 studies are often cited in support of the deleterious effect of NSAIDs on cognition in the elderly, both are limited by their small sample size. The observations of Goodwin and Regan[5] are also limited by lack of objective criteria for cognitive dysfunction.

2. Protection Against Alzheimer's Disease?

Parallel with this research on the short term cognitive effects of NSAIDs, other investigators have explored the possibility that NSAIDs protect against Alzheimer's disease; one of the most important causes of cognitive decline among the el-

derly (see table II). A case-control study by Jenkinson et al.[11] was the first to provide indirect evidence in support of this theory. 192 consecutive inpatients in a geriatric unit, all over 65 years old, were serially screened for Alzheimer's disease. Patients without dementia or with Hachinski ischaemic index[18] scores greater than 5 of 18 (indicating ischaemic dementia) were used as a control group. All patients were then evaluated for rheumatoid arthritis using at least a medical record review and physical examination. Of the 96 patients with Alzheimer's disease, only 2 were found to have rheumatoid arthritis, compared with 12 of 92 patients in the control group ($p < 0.005$). The authors speculated that this negative association might be due to genetic factors. Other investigators have hypothesised that the long term use of NSAIDs that occurs in most patients with rheumatoid arthritis may offer an alternative explanation for this association.

In a meta-analysis of case-control studies on Alzheimer's disease, Breteler et al.[19] found that both osteoarthritis [relative risk (RR) = 0.7, 95% confidence interval (CI) = 0.5 to 1] and severe headaches/migraine (RR = 0.7, 95% CI = 0.5 to 1) seemed to be linked with a decreased risk of Alzheimer's disease, suggesting that long term use of NSAIDs in these conditions might be the common basis for these apparent protective effects. However, their meta-analysis did not confirm the protective effect of rheumatoid arthritis on risk of Alzheimer's disease (RR = 1, 95% CI = 0.4 to 2.9) found by Jenkinson et al.[11]

Several other case-control studies have more directly addressed the association between NSAIDs and Alzheimer's disease and produced conflicting results. A large population-based study in Canada matched 258 patients with probable Alzheimer's disease (cases) with 535 control individuals in order to determine risk factors for Alzheimer's disease.[12] They found a significant inverse relationship between Alzheimer's disease and both arthritis [odds ratio (OR) = 0.54, 95% CI = 0.36 to 0.81] and NSAID use (OR = 0.55, 95% CI = 0.37 to 0.82).

A smaller study from Australia comparing 170 patients with Alzheimer's disease with 170 age- and gender-matched control individuals confirmed a significant protective effect for arthritis on Alzheimer's disease (OR = 0.56, 95% CI = 0.36 to 0.87), but not analgesics (OR = 0.71, 95% CI = 0.46 to 1.17).[12] In this study, non–NSAID analge-

Table II. Nonsteroidal anti-inflammatory drugs (NSAIDS) and the risk of developing Alzheimers disease (AD)

Authors	Study design	No. of participants	Setting	Drugs/disease evaluated	Protection from AD
Jenkinson et al.[11]	Case-control	96 AD, 92 controls (4 excluded)	Extended care facility	Rheumatoid arthritis	$p < 0.005$ (Fishers exact test)
Canadian Health Study[12]	Case-control	258 AD, 535 controls	Institution and community	NSAIDs and corticosteroids	OR = 0.55 (95% CI = 0.37-0.82)
Broe et al.[13]	Case-control	170 AD, 170 controls	Dementia clinics	Analgesics	OR = 0.71 (95% CI = 0.46-1.17)
Kukull et al.[14]	Case-control	268 AD, 258 controls	HMO	NSAIDs (salicylates excluded)	OR = 1.1 (95% CI = 0.7-1.8)
Breitner et al.[15]	Case-control (co-twin)	50 twin pairs[a]	Community	Corticosteroids, corticotrophin (ACTH) or NSAIDs	OR = 0.24 (95% CI = 0.07-0.74)
Andersen et al.[16]	Cross-sectional	6258 (155 AD)	Institution and community	Prescription NSAIDs	RR = 0.38 (95% CI = 0.15-0.95)
Stewart et al.[17]	Prospective cohort	1686 (81 AD)	Community	NSAIDs Aspirin (acetylsalicylic acid)	RR = 0.50 (95% CI = 0.30-0.85) RR = 0.81 (95% CI = 0.52-1.28)

a In 8 twin pairs, both twins had AD; in the remaining twin pairs only one twin had AD.

ACTH = adrenocorticotropic hormone; **CI** = confidence interval; **HMO** = Health maintenance organization; **OR** = odds ratio; **RR** = relative risk.

sics may have minimised the protective effect of NSAIDs.

A third study, by Kukull et al.,[14] compared 268 patients with Alzheimer's disease with 258 control individuals from a single health maintenance organisation. Exposure to NSAIDs was limited to the 6 years preceding the first reported dementia symptoms. In a preliminary report, they did not find that NSAIDs were protective against development of Alzheimer's disease [OR = 0.8 (95% CI = 0.6 to 1.2) for any NSAID use over the 6-year period: OR = 1.1 (95% CI = 0.7 to 1.8) for use of more than 180 standard daily doses of NSAID over this period].

Breitner et al.[15] used a co-twin case-control study design to explore environmental factors that might be associated with development of Alzheimer's disease. They examined 50 elderly twin pairs who were discordant by more than 3 years for onset of Alzheimer's disease. They found a significant protective effect (OR = 0.25, 95% CI = 0.06 to 0.95) for prior treatment with corticosteroids or corticotrophin (adrenocorticotrophic hormone). This trend was stronger when corticosteroids, corticotrophin or NSAIDs were grouped into a single variable of 'anti-inflammatory use' (OR = 0.24, 95% CI = 0.07 to 0.74). Although NSAID use alone did not have a significant protective effect ($p = 0.51$), this was probably due to the small number of twin pairs in this group (n = 6).

In a cross-sectional study from The Netherlands, Andersen et al.[16] analysed data on 6258 individuals, 155 of whom were diagnosed with Alzheimer's disease. They found a lower risk of Alzheimer's disease in users of prescription NSAIDs (RR = 0.38, 95% CI = 0.15 to 0.95) compared with nonusers of NSAIDs.

3. Impact of NSAIDs on Cognitive Decline

While these studies have addressed the association between NSAIDs and risk of Alzheimer's disease, others have examined the impact of NSAIDs on cognitive decline in patients with established Alzheimer's disease. Rich et al.[20] reviewed the records of 210 consecutive patients at the Johns Hopkins Alzheimer's Disease Research Center and compared 32 daily NSAID users (cases) with 177 non- or irregular NSAID users (controls). The NSAID group scored higher at entry on a battery of neuropsychological measures than did the controls. The NSAID users also demonstrated a significantly slower rate of decline in scores on 3 of 10 tests at 1 year than did the controls ($p < 0.04$); whereas, overall, a higher entry score was associated with a larger decline at 1 year ($p < 0.05$).

A clinical trial conducted by Rogers et al.[21] is one of the few interventional studies in Alzheimer's disease to indicate an arrest in decline of mental function attributable to NSAIDs. Alzheimer's patients were randomised to receive either 100 or 150 mg/day (adjusted for bodyweight) of indomethacin (n = 24) or placebo (n = 20) over a 6-month period. These 44 participants were enrolled in the study after diagnosis of probable Alzheimer's disease and provided they scored 16 or higher on an initial Mini-Mental State Examination.

A battery of mental status tests was administered at baseline and after 6 months. The indomethacin recipients exhibited an overall 1.3% improvement in mental function, while the control participants' mental function declined by an average of 8.4% ($p < 0.003$). The decline in the mental function of the control group paralleled findings in untreated participants in other studies.[22] Of note, only 28 patients completed the trial. Five of the 16 patients in the indomethacin group who withdrew from treatment did so because of gastrointestinal adverse effects, compared with only 1 of 12 in the control group. However, 4 of the control patients had to discontinued treatment because of increasingly severe behavioural problems, whereas this occurred in none of the indomethacin recipients.

The results of this small-scale study are encouraging, although the significant incidence of gastrointestinal adverse effects represents a serious concern in the elderly. Larger, controlled trials of NSAIDs in patients with Alzheimer's disease are needed to confirm these findings and to further ad-

dress the safety of indomethacin and other NSAIDs in this age group.

One rationale for the beneficial role of NSAIDs in Alzheimer's disease comes from basic research on the pathophysiology of this form of dementia. Aisen and Davis[23] argue that Alzheimer's disease fits the model of other idiopathic autoimmune diseases, in which the interplay of infectious, environmental, hormonal and genetic factors is believed to trigger deleterious host immune/inflammatory responses.

Evidence for this theory is derived from experiments in Alzheimer's patients indicating elevations of the levels of serum acute phase reactants (such as C-reactive protein, α_1-antichymotrypsin and tumour necrosis factor)[24-26] and from studies of brain tissue revealing complement activation and increased pro-inflammatory cytokines such as interleukin-1 and interleukin-6.[27-29] Although these inflammatory markers may simply represent an epiphenomenon to an underlying genetically determined degenerative process, the authors argue that immune-modulating therapies could influence the progression of Alzheimer's disease. The biological plausibility of a protective effect of NSAIDs on dementia strengthens a possible causal association.

Strong epidemiological evidence for a cause-and-effect relationship between NSAID use and cognitive function is also derived from prospective investigations based on several established cohorts. Stewart et al.[17] analysed data on 1686 participants in the Baltimore Longitudinal Study of Aging (BLSA), to assess whether there was a relationship between risk of Alzheimer's disease and self-reported use of aspirin (acetylsalicylic acid), other NSAIDs or paracetamol (acetaminophen).

In the BLSA, participants undergo 2.5 days of multidisciplinary neuropsychological testing every 2 years, which allows for clinical diagnosis of Alzheimer's disease. Stewart et al.[17] found that non-aspirin NSAIDs appeared to be protective for Alzheimer's disease (RR = 0.50, 95% CI = 0.3 to 0.85). In contrast, neither aspirin, which included low dose cardiac prophylactic use (RR = 0.81, 95% CI = 0.52 to 1.28), nor paracetamol use (RR = 1.0, 95% CI = 0.73 to 2.07), indicated a significant negative association. In addition, Alzheimer's disease risk was found to decrease with increasing duration of NSAID use: for more than 2 years of use the RR dropped to 0.4, whereas for less than 2 years, the RR rose to 0.65.

This study provides further evidence of the anti-inflammatory properties of NSAIDs slowing or preventing the onset of Alzheimer's disease. While this study also suggests a dose-response effect to strengthen support for this hypothesis, the 2-year time lag required to demonstrate this effect slightly weakens this conclusion.

4. NSAID Use and General Cognitive Function

Rather than address the impact of NSAIDs on Alzheimer's disease, several other researchers have used the Established Populations for Epidemiologic Studies of the Elderly (EPESE), to explore the relationship between NSAID use and general cognitive function. The EPESE encompass participants from the US urban populations of East Boston and New Haven, the mixed urban and rural population of the Piedmont region of North Carolina, as well as the primarily rural and small town communities of Iowa. The diversity of these populations enhances the generalisability of results.

Rozzini et al.[7] performed a longitudinal population-based study using the East Boston, New Haven and Iowa cohorts (see table I). Long term NSAID users were defined as those individuals who had taken NSAIDs within the 2 weeks preceding the baseline interview and also in the 2 weeks preceding the 3-year follow-up interview. Cognitive function was then assessed using the Short Portable Mental Status Questionnaire (SPMSQ); scores were compared between interviews at 3 years and 6 years. A further strength of this cohort study is that the exposure, i.e. NSAID use, clearly preceded the assessment of the outcome.

In this large study of 6068 participants, Rozzini et al.[7] found that long term NSAID use was protective (RR = 0.82, 95% CI = 0.69 to 0.98) against

cognitive deterioration over the 3-year follow-up period. Although the SPMSQ has good test-retest reliability as well as sensitivity and specificity for identifying patients with dementia,[30] it is unable to discriminate between forms of dementia. Therefore, it cannot be concluded that the anti-inflammatory properties of NSAIDs blocked the progression to Alzheimer's disease. A plausible alternative hypothesis, proposed by the authors, is that the anti-platelet aggregation effects of these medications prevented the progression of vascular dementia.

It could be expected that the inclusion of salicylates in defining NSAID use to magnify such an effect. A separate EPESE-based study performed by Sturmer et al.[8] using the East Boston cohort specifically explored the role of aspirin in slowing decline in cognitive function. 2023 individuals completed baseline, 3-year and 6-year follow-up evaluations. No significant protection against decline in SPMSQ score was found in the aspirin users (OR = 0.97, 95% CI = 0.82 to 1.15).

Hanlon et al.[9] evaluated the relationship between NSAID use and cognitive function in 2765 participants from the Piedmont EPESE. Their definition of NSAID use excluded salicylates. NSAID usage and SPMSQ scores were determined concomitantly: at baseline and at a 3-year follow-up interview. Their results indicated a protective effect ($p < 0.05$) against decline in SPMSQ scores only for 'indeterminate' NSAID users (over-the-counter or as needed), but not for those using a prescription NSAID regularly ($p > 0.05$).

An additional screening test for cognitive function, the Orientation-Memory-Concentration Test,[31] was applied at the follow-up interview only and demonstrated a better score in concentration for continuous users of NSAIDs compared with non-users of NSAIDs ($p < 0.05$). However, for the memory test current moderate-to-high dose NSAID users (β coefficient = 0.41, 95% CI = 0.08 to 0.74) tended towards worse scores than the low dose group ($\beta = 0.03$, 95% CI = –0.85 to 0.91).

Although the results of this study appear somewhat inconclusive, they do suggest that long term, low dose NSAID use protects against cognitive decline, while higher doses may impair memory. These findings support the earlier conclusions that NSAIDs can cause reversible cognitive dysfunction in the elderly.[5,6] It is worth noting that the Hanlon study[9] was large, had a more powerful methodological design and provided more objective criteria for an alteration in cognitive function than the earlier investigations.

The findings of Hanlon and colleagues[9] partially concur with the data from another EPESE-based study of non-aspirin NSAID use by Saag et al.[10] They tested memory in the Iowa cohort using word recall. Word recall was chosen as a test sensitive to subtle deficits in cognitive function.[32] Current high dose NSAID use was strongly associated with a decline in word recall (OR = 2.06; 95% CI = 1.1 to 3.9), but this association did not hold true for continuous (OR = 1.31, 95% CI = 0.53 to 3.23), or past (OR = 1.38, 95% CI = 0.39 to 4.91), high dose NSAID usage.

As with the Hanlon study,[9] exposure and cognitive function were measured concomitantly and, therefore, it is more difficult to attribute cause and effect. The generalisability of this study is somewhat limited by the homogeneity of the Iowa cohort.

5. Conclusion

Several large longitudinal population-based studies of the elderly support the conclusions of earlier observational and small interventional studies. High dose NSAID use appears to be associated with a reversible impairment of cognition in the elderly. Prolonged NSAID use, on the other hand, may prevent the decline in cognition associated with aging. Whether this protection arises from an anti-inflammatory effect that modifies pathways involved in Alzheimer's dementia, or is mediated by a platelet effect that decreases cerebrovascular disease, has yet to be definitively determined.

Further large-scale, randomised, controlled trials using NSAIDs are needed before patients can be advised that the known risks of NSAIDs are outweighed by their potential long term benefits on cognition. Ideally, the measurement indices ap-

plied to test cognition should be both sensitive to small changes and able to discriminate between subtypes of dementia. While clinicians await the results of such studies, they should continue to be alert to the possibility of acute CNS adverse effects in their elderly patients on NSAIDs and to prescribe the minimum dose that is necessary to control pain and inflammation.

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