Pharmacologic management of Alzheimer disease: Part III: nonsteroidal antiinflammatory drugs - emerging protective evidence?

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Authors' objectives
To provide information out research evaluating the role of nonsteroidal antiinflammatory drugs (NSAIDs) in the prevention, or delay in the onset of, Alzheimer disease (AD).

Searching
A computerised search of MEDLINE (Jan 1990-Dec 1996) was carried out. In addition the bibliographies of retrieved articles were searched. Additional articles from 1996 to June 1999 (found in the time from submission to publication of the review) were listed in the addendum.

Study selection

Study designs of evaluations included in the review
All studies, review articles and editorials addressing NSAID pharmacotherapy research.

Specific interventions included in the review
Unspecified NSAIDs (prescription and non-prescription) were included, with the exception of one study using indomethacin. In many cases the NSAIDs were prescribed for arthritis. Comparison groups included patients receiving aspirin, paracetamol and no NSAIDs.

Participants included in the review
A priori details of participant inclusion criteria were not reported. Participants included in the review were either diagnosed, or probably/possibly suffering from AD. Patients undergoing treatment with NSAIDs for other conditions such as arthritis were also included. Approximate age range of participants was 52-96yrs.

Outcomes assessed in the review
Cognitive function tests including standardised measures (e.g. the Mini-Mental State Examination (MMSE), Wechsler Memory Scale, Wechsler Adult Intelligence Scale (WAIS) etc.), and telephone/face-to-face interviews with patients or proxies. Adverse effects were also recorded.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
Pertinent information was selected and presented in tables including: bibliographic details, study design, study population, cognitive function tests and results.

Methods of synthesis
How were the studies combined?
A narrative summary was used to group the studies together.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

**Results of the review**

Thirteen studies (1 double-blind placebo-controlled study; 2 cross-sectional studies; 1 cohort study; 1 retrospective audit; 7 case-control studies; 1 meta-analysis including 17 studies) including a total of 10,227 participants.

Three studies (all case-control studies using patients diagnosed with AD) showed no significant protective association between taking NSAIDs for arthritis and AD. In contrast the 10 remaining studies (1 double-blind placebo-controlled study; 2 cross-sectional studies; 1 cohort study; 1 retrospective audit; 4 case-control studies; 1 meta-analysis including 17 studies) suggested that NSAIDs may have some protective effect against AD.

Three studies showed a significant negative association between arthritis patients taking NSAIDs and AD (ORs ranging from 0.16 (95% CI: 0.05, 0.51) to 0.56 (95% CI: 0.36, 0.87)). Four studies showed significantly lower risks of AD in NSAIDs users vs non-users (ORs ranging from 0.38 (95% CI: 0.15, 0.95) to 0.55 (95% CI: 0.37, 0.82)). One of the four studies reported a significant (log rank chi-squared=11.97, df=1, p=0.0005) age-specific AD risk with the daily use of non-aspirin NSAIDs for longer than 1mth (vs not stated). Another of the four studies showed a relative risk (RR) of 0.40 for patients receiving NSAIDs for longer than 2yrs (vs not stated). One additional study showed a significant inverse relationship between AD and receiving steroids or NSAIDs, however the data for patients only receiving NSAIDs was inconclusive. Of the three remaining studies one showed a significant average improvements in cognitive tests among those taking NSAIDs compared to placebo, and another showed significantly less decline in spatial recognition, verbal fluency and orientation amongst patients taking NSAIDs compared to non-NSAID patients.

The final study was a review featuring meta-analyses. This showed significantly lower numbers of patients with AD (compared to the general population) amongst patients with arthritis (OR=0.556, p<0.0001, 7 case-control studies) and those using NSAIDs (OR=0.496, p=0.0002, 3 case-control studies).

Several of the studies noted adverse effects associated with NSAIDs including diarrhoea, ulcers, ulcer bleeding or perforation, renal or hepatic toxicity, hypertension and decreased platelet activity with a higher risk of bleeding.

**Authors' conclusions**

Preliminary evidence suggests that NSAIDs may have a protective effect against the development of AD. Not all elderly patients are candidates for NSAIDs. Determining the definitive mechanism of action of NSAIDs in AD may suggest alternative agents that have similar pharmacologic activity, but are associated with fewer adverse side effects.

**CRD commentary**

This review lacks methodological detail and fails to establish clear inclusion/exclusion criteria prior to study selection. The literature is based on only one database and excludes non-English language papers, therefore relevant studies may have been missed, and the risk of publication bias is high. In the majority of cases the specific NSAID used is not stated, although this may be a reflection of the original studies. Consequently, it is not possible to identify whether the affects are associated with one particular NSAID.

The review includes a wide range of study designs, the majority of which are designs, which fall into the lower categories of the design hierarchy. The evidence from such studies is therefore less convincing. In addition the validity of each individual study was not formerly assessed. The authors do however discuss a number of issues that may limit their review. Taking into consideration these comments, the author's findings should be treated with great caution, although their recommendations for future research would appear to be valid.

**Implications of the review for practice and research**

Practice: The authors state that 'the risk of NSAID-associated adverse effects is not insignificant, particularly in frail elderly patients' and that 'a critical risk/benefit ratio must be conducted to determine the clinical utility of NSAIDs'.

Research: The authors state that 'further prospective, double-blind, placebo-controlled studies are needed to determine
the role of NSAIDs in AD’. In addition ‘the dose-finding studies should focus on specific agents and identify the dosage and duration of therapy necessary for a protective or therapeutic effect’; furthermore ‘these studies will need to address the issues of diagnosis of AD’.

Bibliographic details

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.