

Aspirin and anti-inflammatory drugs for Alzheimer's Disease

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[Intervention Protocol]

Aspirin and anti-inflammatory drugs for Alzheimer's disease

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare aspirin and other anti-inflammatory drugs with placebo in the treatment of Alzheimer's disease.

BACKGROUND

Alzheimer's disease (AD) is the most common form of dementia, and its incidence increases exponentially with age, affecting 1-2% of 65 to 70 year olds and approximately 20% of those over 80 years (Jorm 2003). It results in a progressive deterioration of intellect, memory and personality. Evidence has accumulated to suggest that altered production, aggregation and deposition of amyloid β protein ($A\beta$) plays a critical role in the development of Alzheimer's disease. $A\beta$ is a proteolytic fragment of 40-42 residues derived from Amyloid Precursor Protein (APP). In vitro, the longer $A\beta$ -42 fragment aggregates much more readily, and is felt to be the main culprit in the pathogenesis of AD. Genetic studies of patients with early onset AD who have mutations in APP or presenilins show selective increases in the relative levels of $A\beta$ -42 peptides. This leads to a series of reactions that result in neuronal dysfunction and death. Activation of microglia and astrocytes results in a cascade of inflammatory reactions with elevated levels of cytokines, acute-phase proteins and complement proteins (Aisen 1994). These substances are capable of reciprocally inducing each other and enhancing neurotoxicity.

Attenuation of inflammatory processes can occur through inhibition of the enzyme cyclo-oxygenase which is the mechanism by which non-steroidal anti-inflammatory drugs (NSAIDs) function. This prevents the production of prostaglandins which induce cytokines. Corticosteroids cause alterations in inflammatory responses through other mechanisms.

There is also evidence to suggest that some non-steroidal anti-inflammatory drugs can directly influence the processing of APP via direct modulation of the enzyme γ -secretase (Weggen 2003), leading to alterations in the amount of $A\beta$ -42 produced (Eriksen 2003).

Evidence implicating inflammatory processes in AD also comes from retrospective epidemiological studies. It has been observed that patients who have received treatment with anti-inflammatory drugs; e.g. patients with rheumatoid arthritis; have a lower prevalence of AD (McGeer 1996). Prospective cohort studies have also demonstrated a reduction in the relative risk of developing AD in those taking non-steroidal anti-inflammatories compared with non-users (Rich 1995); as well as a relationship with duration of use (In't Veld 2001).

There has been no meta-analysis of the efficacy of anti-inflammatory drugs as a class in the treatment of Alzheimer's disease, although some of the drugs have previously been reviewed individually by the Cochrane Collaboration (Tabet 2002; Tabet 2003). This analysis will therefore build on previous reviews. The authors also propose to conduct a subgroup analysis looking at drugs that have allosteric modulating properties, as it is hypothesised that subtle differences in their mechanism of action may explain the variability in trial results reported to date.

OBJECTIVES

To compare aspirin and other anti-inflammatory drugs with placebo in the treatment of Alzheimer's disease.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised double-blind placebo-controlled trials assessing the efficacy of aspirin and other anti-inflammatory drugs in the treatment of Alzheimer's disease.

Types of participants

Patients of any age diagnosed with probable Alzheimer's according to internationally recognised criteria such as *NINCDS-ADRDA, DSM and ICD (McKhann 1984; APA 1995; WHO 1992) will be eligible for inclusion. Patients should not have extensive prior use of these medications.

*NINCDS-ADRDA refers to the 'National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association'. DSM refers to the 'Diagnostic and Statistical Manual of Mental Disorders'. ICD-10 refers to World Health Organisation classification of mental and behavioural disorders, the clinical description and diagnostic guidelines.

Types of interventions

Comparisons of aspirin and all other anti-inflammatory drugs at any dose with placebo.

Types of outcome measures

- Cognition (using objective psychometric rating instruments e.g. the Alzheimer's disease assessment scale - cognitive subscale or ADAS-COG)
- Clinical global impression of change
- Mood/depression
- Behavioural disturbance
- Activities of daily living
- Quality of life
- Caregiver burden
- Institutionalization
- Death

Search methods for identification of studies

The trials will be identified from a search of the Specialized Register of the Cochrane Dementia and Cognitive Improvement Group using the following terms: aspirin, aceclofenac, acemetacin, betamethasone, celecoxib, cortisone, deflazacort, dexamethasone, dexibuprofen, dextoprofen, diclofenac sodium, diflusal, etodolac, etoricoxib, fenbufen, fenoprofen, flurbiprofen, hydrocortisone, ibuprofen, indometacin, ketoprofen, lumiracoxib, mefenamic acid, meloxicam, methylprednisolone, nabumetone, naproxen, nimesulide, piroxicam, sulindac, tenoxicam, tiaprofenic acid and triamcinolone.

This Register contains records from all major healthcare databases and many ongoing trial databases and is updated regularly.

Data collection and analysis

Selection of studies

Three reviewers (RQ, MI, NT) will independently examine the titles and abstracts of the trials identified in the search and will consider them for inclusion according to the pre-determined eligibility criteria. Any disparity will be resolved by retrieval of the cited articles and further discussion.

Quality assessment

The quality of the methods used in each study will be examined by the three reviewers using one of the Cochrane approaches:

Grade A: Adequate concealment (randomization; placebo-controlled; concealed allocation).

Grade B: Uncertain.

Grade C: Inadequate concealment; no randomization.

The rating of quality will be described in the table of included studies.

Data extraction

Data will be extracted using a data collection form by two of the authors (RQ, MI), and any disagreements will be resolved by discussion.

'Intention to treat analysis' will be applied to data obtained on every randomized patient.

For continuous variables, or ordinal variables approximated to continuous variables, outcomes of interest will be the assessment score at the time point considered, and the change from baseline.

For some binary outcomes the end point itself will be of clinical relevance. In other cases it may be necessary, due to variation in the way response to treatment is measured, to operationalize outcomes as 'improved' versus 'not improved' regardless of the scales used by the authors.

Data analysis

Missing data and drop out rates will be assessed for each of the included studies. The number of participants who are included in the final analysis will be reported as a proportion of all participants in the study.

For binary outcomes a standard estimation of the odds ratio and risk ratio with a 95% confidence interval will be calculated.

Continuous data with a normal distribution will be analysed by Review Manager software if means and standard deviations are available, to obtain a standardised difference in means (SMD). Appropriate non-parametric tests will be used to analyse data that is not normally distributed.

If there are sufficient data, and it is appropriate to do so (after assessing heterogeneity visually, and utilizing a Chi-squared test), a meta-analysis will be conducted. A subgroup analysis of those drugs with allosteric modulating properties is also planned.

ACKNOWLEDGEMENTS

The authors wish to thank the consumer editor, Lynne Ramsay, for her helpful comments.

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WHAT'S NEW

Date	Event	Description
26 August 2008	Amended	When the full review of "Aspirin and anti-inflammatory drugs for Alzheimer's disease" is published, it will replace the previously published reviews "Ibuprofen for Alzheimer's Disease", "Indomethacin for Alzheimer's Disease", and the previously published protocol "Naproxen for Alzheimer's Disease". At that time, these ibuprofen and indomethacin reviews and this naproxen protocol will be withdrawn from the Cochrane Library.
26 August 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

RQ: Writing & coordinating the review, searching & selecting trials for inclusion, extracting & interpreting data, and entering data on to Revman.

MI and NT will contribute to the searching for trials, obtaining copies of trial reports and to selecting trials for inclusion/exclusion. They will also be involved in data extraction and interpretation, and providing general advice on the review.

Contact editors: Leon Flicker and Gordon Wilcock
 Consumer editor: Lynne Ramsay

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Alzheimer Disease [*drug therapy] [etiology]; Anti-Inflammatory Agents [adverse effects] [*therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [adverse effects] [*therapeutic use]; Aspirin [adverse effects] [*therapeutic use]; Cyclooxygenase 2 Inhibitors [adverse effects] [therapeutic use]; Glucocorticoids [adverse effects] [therapeutic use]; Inflammation [complications] [drug therapy]; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Aged; Aged, 80 and over; Humans