Scientific Research Publishing

Advances in Alzheimer's Disease, 2023, 12, 17-28
https://www.scirp.org/journal/aad
ISSN Online: 2169-2467
ISSN Print: 2169-2459

Non-Steroidal Anti-Inflammatory Drugs as Protective Factor in Alzheimer's Diseases: A Systematic Review and Meta-Analysis Protocol

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How to cite this paper: Asthana, A., Agarwal, R. and Tripathi, S. (2023) Non-Steroidal Anti-Inflammatory Drugs as Protective Factor in Alzheimer's Diseases: A Systematic Review and Meta-Analysis Protocol. *Advances in Alzheimer's Disease*, **12**, 17-28.
https://doi.org/10.4236/aad.2023.122002

Received: April 29, 2023
Accepted: June 16, 2023
Published: June 19, 2023

Abstract

Introduction: NSAIDs inhibit COX-2, which is responsible for regulating neurons leading to neurodegeneration in Alzheimer's disease. Alzheimer's disease is a neurodegenerative disease affecting the geriatric population, as it affects more than two third cases of dementia in the sphere. Results obtained from experimental and observational studies were unclear regarding the protective role of NSAIDs in AD, therefore this justifies the need for meta-analysis. **Methods:** Database search was PubMed, Web of Science, and Embase. Experimental studies and Observational studies investigating the effect of NSAIDs on AD. For experimental studies indicators used were MMSE score, ADAS-cog score, CDR-sob score, NPI score, and Hazard ratio. Similarly for Observational studies, Odds Ratio and Relative Risk are used. **Results:** As this is the study protocol, therefore it is not possible to write the results of the study in the study protocol. There is a total of 06 (MMSE, ADAS-cog, CDR-sob, HR, RR, and OR) indicators used in the study, so 06 results will be obtained showing the pooled effect size which will indicate the use of NSAIDs as a protective factor for Alzheimer's disease. **Discussion:** The present systematic review will improve the understanding of the relative efficacies of NSAIDs in AD and possibly guide clinical practices by providing the current best evidence on the efficacy of various regimens of NSAIDs in the management of AD subjects. **Conclusion:** Conclusion can be drawn only after the final meta-analysis using three study design (RCT, Cohort and Case-control study designs) and six indicators.

Keywords

Alzheimer's Disease, NSAIDs, Meta-Analysis, RCT, OR, RR

1. Introduction

Alzheimer's disease is one of the major problems faced by old age citizens in the contemporary globe; therefore it is a neurodegenerative disease affecting the geriatric population, as it affects more than two third cases of dementia in the sphere [1]. Five million subjects in 2014 were facing AD-related dementia and it is projected to be more than 13.9 million by 2060 [2]. The cost of health is increasing at a high pace as AD along with other dementias is a major and increasing global health challenge [3] [4] [5]. Factors responsible for the pathogenesis of AD are multiple factors like age, environmental and genetic factors, along with the accumulation of senile plaques and neurofibrillary tangle [6]. Either all the above factors initiate the pathogenic cascade together or one leads to disease onset or subsequent factors are involved in disease progression [7]. Inflammation of the microglia appears before brain damage is proposed by neuroinflammatory theory for the pathogenesis of AD [8] [9]. Studies have shown that in neurotic plaques and tangles there are chronically activated microglia and increased expression of the cycloxygenase-2 enzymes [10] [11].

Non-steroidal anti-inflammatory drugs, 7.7% of worldwide prescription of which 90% are in subjects over 65 years old, hence it is a widely used anti-inflammatory analgesic [12]. There was a 40% increase in NSAID use between the period 2005 & 2010 in the US, out of which 26% report using more than the recommended dose [13] [14] [15]. COX-2 is inhibited by NSAIDs, which are responsible for up-regulating neurons leading to neurodegeneration in AD [16]. A small number of NSAIDs (like ibuprofen, sulindac acid, and indomethacin have nonamyloidogenic activity *in vivo*, a function independent of COX inhibition [17] [18].

The results obtained from experimental studies were inconclusive with NSAIDs playing a protective role in AD, with few studies showing that NSAIDs are protective in AD [19], on another hand few studies had shown that NSAIDs are not protective [20]. Similarly results obtained from observational studies were also inconclusive with NSAIDs playing a protective role in AD, with few studies showing that NSAIDs are protective in AD [1], on the other hand, other studies had shown that NSAIDs are not protective [8].

1.1. Research Question

Is non-steroidal anti-inflammatory drugs act as protective factor in Alzheimer's disease?

1.2. Objective of Study

1) Role of NSAIDs, as a protective factor for AD in Experimental study design.

2) Role of NSAIDs, as a protective factor for AD in Cohort study design.

3) Role of NSAIDs, as a protective factor for AD in Case-Control study design.

2. Methods and Materials

2.1. Design

Present systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis [19], and Meta-Analysis of Observational Studies in epidemiology statements and followed a prior defined but unpublished protocol [21].

2.2. Protocol Registration

Our protocol has been registered on PROSPERO, with registration number [CRD42022301179].

2.3. Inclusion Criteria

1) Studies conducted on a population of age 55 years and above.

2) Experimental Clinical Trials, to evaluate the use of NSAIDs as a treatment for AD in subjects with Alzheimer's.

3) Studies using diagnostic criteria NINDS-ARDEN for the outcome of AD describe exposure to NSAIDs.

4) Hazard Ratio is reported in studies or enough data reported in a study to calculate Hazard Ratio or having enough information to calculate estimates required.

5) Cohort Study was designed, to evaluate the use of NSAIDs as a treatment for AD in subjects with Alzheimer's.

6) Relative Risk is reported in studies or enough data reported in a study to calculate Relative Risk or having enough information to calculate estimates required.

7) A case-control study was designed, to evaluate the use of NSAIDs as a treatment for AD in subjects with Alzheimer's.

8) Odds Ratio is reported in studies or enough data reported in a study to calculate Odds Ratio or having enough information to calculate estimates required.

9) Paper published in English Language only.

10) Studies published from 2000 to 2021.

2.4. Time

Experimental and Observational studies were identified by searching PubMed, Web of Science, and Medline from 1st January 2000 to 31st December 2021. All those studies (experimental & observational) satisfying the above-mentioned criteria will be included. Relevant studies even published in other language will also be included if their English translation is available. The corresponding author of studies in another language will be contacted for the possible English translation of their article.

2.5. Information Sources and Searches

2.5.1. Bibliographic Database

PubMed, Web of Science, and Medline are databases that will be used to identify

Experimental studies and Observational studies. A reference list of relevant articles and abstracts from major conferences on AD will also be searched. All the studies (Experimental and Observational studies) in previous systematic review/meta-analyses, if any, will also be included.

2.5.2. Search Limits

At stage of searching of online databases, it will not be restricted on the basis of language but will be restricted on basis of time.

2.5.3. Search Terms

The search strategy is developed as per the Cochrane checklist for developing a search strategy [22]. Text words are defined for the population (Alzheimer's disease or if Alzheimer's disease is not given then dementia will be used), Intervention (NSAIDs), Experimental, Cohort, and Case-control study design. Different kinds of NSAIDs and synonyms of these text words considering brand names of drugs are also identified.

2.6. Study Selection

All the extracted records retrieved by three databases will be merged and duplicates will be removed based on title and year of publication, using MS Excel 2007. In the first phase, two reviewers with experience in health research methodology will screen the title and available abstracts independently and in duplicate and provide a reason for the non-screening of articles. Articles screened by any reviewers which are potentially eligible, the full text will be acquired and assessed against predefined inclusion criteria. Disagreement between reviewers will be resolved by consensus or if any discrepancies persist, through discussion by RA.

2.7. Data Collection Process

The abstraction form has been designed as per the Cochrane guideline of systematic reviews of interventions [22]. Two reviewers ST and AA will abstract the data independently and duplicate it for each eligible study. The following information will be extracted from eligible studies:

- Publication details: Year, language, country, authors, journal, phase
- Baseline Factors: Age, AD stage
- Size of study population: Overall as well as in treatment and placebo group
- Follow-up time: Drug, dose, and duration
- Indicators: ADAS-cog score, MMSE score, CDR-sob score, Hazard ratio, Odds Ratio, and Risk Ratio

2.8. Quality of Study

1) Cochrane collaboration tool

ST will assess the risk of bias within each experimental study by Cochrane collaboration tool for assessing the risk bias [23] [24]. The risk of Bias tool cov-

ers six domains of Bias.

a) Selection bias: Random sequencing and concealment of the subject are checked in this method.

b) Performance bias: This method assesses whether subjects and study personnel are blinded.

c) Detection bias: The outcome assessment process is blinded and is assessed by this method.

d) Attrition bias: Appropriate statistical technique is used to evaluate the magnitude and impact of incomplete data.

e) Reporting bias: It checks whether reporting of study outcome is based on the pre-specified method in Clinical Trial Registration.

f) Other bias: Any sources of bias influencing the data in the study will be assessed.

For each domain, reviewers will respond as "Definitely Yes", "Definitely No" and "Unclear" Symbols used for "Definitely Yes" is "+", "Definitely No" is "–" and "Unclear" is "?".

2) Jadad Score assesses the methodological quality of experimental studies [25]. It is also called the Oxford scoring system. This System allocates trials score between zero (very poor) and 05 (rigors). Scoring is done according to the presence of three domain features in methodological features first Randomization, second Blinding, and third accountability of all subjects [26].

3) Newcastle-Ottawa Scale (NOS) is a tool for Quality assessments of non-randomized studies with its design, content, and ease of use directed to the task of incorporating the quality assessments in the interpretation of meta-analytic results [27]. Three areas in which studies are judged by this scale are a) Selection of study groups b) Comparability of the group's c) Ascertainment of either exposure or outcome of interest done by this star system. The goal of this instrument is to provide an easy and convenient tool for quality assessment of non-randomized studies, in the systematic review [27]. Visual assessment is done and stars are awarded for each quality item. High-quality studies are awarded up to nine awards.

Interpretation of the NOS scale on basis of good, fair and poor is as follows:

a) Good quality

The selection domain gets 03 or 04 stars' the comparability domain gets 1 or 2 stars and the outcome domain gets 02 or 03 stars.

b) Fair quality

Selection Domain gets 02 stars, comparability gets 01 or 02 stars and outcome gets 02 or 03 stars.

c) Poor quality

The selection domain gets 00 or 01 stars, the comparability domain gets 00 stars, and the outcome domain gets 00 or 01 stars.

2.9. Data Analysis

For Experimental studies, the effect size under consideration will be measures of

different scores used for Alzheimer's disease. (ADAS-cog score, MMSE score, CDR-sob score, and NPI score). Also effect size under this study design will be Hazard Ratio for studies providing data for time to event of the outcome of interest (Here the event of interest will be Development of AD). For Cohort studies, the effect size under consideration will be Relative risk, but for studies not providing Relative Risk the frequency to calculate Relative risk will be extracted. For Case-control studies, the effect size under consideration will be Odds Ratio, but for studies that do not provide Odds Ratio the frequency to calculate Odd Ratio will be extracted.

Statistical Heterogeneity will be assessed by Cochrane Q-statistics and I^2 statistics. If heterogeneity is low (I^2 < 30%) fixed effect model is used and if heterogeneity is high (I^2 > 30%) then a Random effect model is used for analysis.

Also, sensitivity analysis will be performed by removing each study one after another and then checking the change in I^2. Minimum I^2 obtained by removal of a particular study will be reported and a separate forest plot will be drawn.

Publication bias will also be observed by the graphical method (the funnel) and computation of publication bias by the Mathematical Method (Linear regression test and Rank Correlation Test).

2.9.1. Q-Statistics and I²-Statistics

Q-statistics is statistics that are sensitive to the ratio of observed variation to within-study error rather than their absolute values [28]. Q-statistics is a standardized measure that is not affected by the metric of effect size Index. Computations of Q-statistics are done by estimating the deviation of each effect size from the mean and then squaring this deviation. Then it is weighted by inverse variance for that study and adds these values over all studies to yield a weighted sum of the square. I^2-Statistics is said to be the proportion of observed dispersion (real). This statistic is not dependent on scale. It is said to be the ratio of excess dispersion to total dispersion [28]. Model for I^2 (when heterogeneity is independent of scale)

$$I^2 = \frac{Q - df}{Q} * 100\% \tag{1}$$

$$I^2 = \frac{\text{Variance between}}{\text{Variance total}} * 100\% \tag{2}$$

2.9.2. Fixed Effect Model

In this model, the assumption is made that all studies in analysis share a similar true effect size. The average effect size in this model is an estimate of this common effect size. Each effect size is given weight, which is directly proportional to its precision and inversely proportional to variance. If I^2 < 30%, a fixed effect model is used.

Model

Let μ be a single fixed effect size and variation in effect size (if any) is due to chance alone. It assumes y_i is effect size distribution follows normally distributed

mean (μ) and variance (v_i) *i.e.* $y_i \sim N(\mu, v_i)$, where $v_i = \sigma_i^2$. Let $y_i = \mu + \varepsilon$, is individual effect size where ε_i is sampling error and $\varepsilon_i \sim N(0, \sigma_i^2)$ for $i = 1, 2, \cdots, k$ (k is several studies in meta-analysis). $W_i = 1/\sigma_i^2$ where W_i is the weight associated with the ith study and σ_i^2 is the variance of effect size. Pooled effect size ($\hat{\mu}_F$) is obtained as:

$$\hat{\mu}_F = \frac{\sum y_i w_i}{\sum w_i} \tag{3}$$

The variance of this pooled effect size is

$$V(\hat{\mu}_F) = \frac{1}{\sum w_i} \tag{4}$$

2.9.3. Random Effect Model

In this model, it is assumed that the true effect size varies from study to study which is selected for meta-analysis. This model is applicable when effect sizes vary at random and effect sizes are normally distributed. There can be two sources of variation; one is between study variations and the second, is within-study variation. If I^2 > 30% Random effect Model is used. To address variation across studies, it is recommended to perform a Random effect model.

Model

Let Q_i be the deviation between individual-level study effect size (y_i) and true effect (μ) in the population exceeds that due to sampling variation (ε_i) alone.

The model of Individual effect size is

$$y_i = \mu + \theta_i + \varepsilon_i \tag{5}$$

θ_i depends on between study variance (T^2) and ε_i depends on within study variance (σ_i^2) alone.

Where $Q_i \sim N(0, T^2)$ and $\varepsilon_i \sim N(0, \sigma_i^2)$

Here random effect model considers two sources of variation, one between study variance and the second within study variance, the weights (w_i') associated with individual studies are inverse of this total variation

$$w_i' = 1/(\sigma_i^2 + T^2) \tag{6}$$

The pooled effect of y_i is $\hat{\mu}_R = \sum y_i w_i' / \sum w_i'$, where $y_i \sim N(\mu, \sigma_i^2 + T^2)$

The variance of this estimated effect size is

$$V(\hat{\mu}_R) = 1/\sum w_i' \tag{7}$$

2.10. Dissemination of Work

The result obtained from the study will assist end users including Neurologists, Policy Makers, and Researchers working on a similar area through the presentation at national and international conferences, symposiums, and meetings regarding the role of NSAIDs as a protective factor for AD.

2.11. Patient and Public Involvement

No patients involved.

3. Discussion

The present systematic review will evaluate the Protective role of different NSAIDs in Alzheimer's disease. The latest Meta-Analysis performed on NSAIDs' protective role in Alzheimer's disease using an RCT study design was published in 2015 [6]. In our analysis publication bias is also analysed in both graphical and mathematical ways including in recent studies. Similarly, an observational study was also conducted in 2004 [14] on the same topic. But our Meta-analysis will provide recent evidence by including more recent studies in all three possible study designs (RCTs, Cohort, and Case-Control study design) providing a robust result, and accordingly, it will facilitate evidence-based management of AD subjects. Therefore, this systematic review will benefit a wide audience including AD subjects, Neurological professionals, insurers, policymakers, and researchers working in the field of AD.

During the recent literature search few conjectures are made to understand the protective role of NSAIDs in AD, first, literature shows that AD develops over the course of decades with pathological changes occurring more than 20 years before cognitive decline [29] Hence NSAIDs exposure in preclinical/early phases may be protective but not effective in later stages of AD. Szekely *et al.*, 2008 [30] observed a reduced risk of AD in NSAID users which was significant in the younger age group. Hayden *et al.*, 2007 [31] also reported use of NSAIDs before the 65 years age group had less cognitive decline as compared to individuals more than 65 years of age. Second, the dosage of NSAIDs is a major contributing factor that may affect their therapeutic relevance of them in AD. These dosages may have been too low for a therapeutically relevant γ-secretase modulatory effect in AD patients [32]. Third, factors like associated co morbidities may have played role in modifying the protective effect of NSAIDs on the progression of AD [12]. Fourth, the role of the APOE gene may alter the association between NSAID use and the risk of developing AD. One study found a lower risk of AD only in NSAID users with an APOE ε4 allele [30]. Finally, poor adherence to NSAIDs like aspirin and ibuprofen due to their severe gastrointestinal effects may lead to loss of subjects in follow-up during these studies [12].

4. The Uniqueness of the Study

As per the author's literature search this is the only study involving all three study designs in a single meta-analysis study. Our study is trying to answer the research question mentioned above by involving the studies from three different study designs (randomized control trials, cohort study design, and case-control study design). As there are inconclusive results in all different RCTs [1] [16] [32] [33], cohort study designs [34] [35] [36] [37], and case-control study designs [38] [39] [40] [41]. Marina *et al.* 2015 [6] conducted a meta-analysis only on RCTs, whereas Etminan *et al.* 2003 [14] conducted a meta-analysis only in studies having cohort study design and case-control study design. Any variation in answering the above-mentioned research question due to choosing different

study designs can be answered by involving all the study designs in a single study of meta-analysis. Additionally, the highest dose of the NSAIDs is taken in the present meta-analysis, which can be treated as the opposite of the worst-case scenario.

List of Abbreviations

AD: Alzheimer's disease, NSAIDS: Non-steroidal Anti-Inflammatory Drugs, MMSE: Mini-Mental State Exam, ADAS-cog: Alzheimer's disease Assessment Scale, CDR-sob: Clinical Dementia Rating-the sum of boxes, HR: Hazard Ratio, RR: Relative Risk, OR: Odds ratio, NPI: Neuropsychiatric Inventory.

Declaration

Ethics approval and consent to participate are not applicable because this paper is a Systematic Review and Meta-Analysis based on already published studies.

Availability of Data and Materials

Data from this study is extracted from already published studies.

Author's Contribution

AK, ST, and RA contributed to designing the study protocol equally.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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