



Observational study

Impact of analgesics on executive function and memory in the Alzheimer's Disease Neuroimaging Initiative Database



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HIGHLIGHTS

- Data from Alzheimer's Disease Neuroimaging Initiative was used to study NSAIDs.
- NSAID users had higher executive function scores than controls.
- NSAID use was associated with higher memory scores in cognitively normal females.
- In specific cortical regions, NSAID users had larger cortical dimensions.
- Executive function scores correlated with cortical dimensions.

ARTICLE INFO

Article history:

Received 19 January 2017

Received in revised form

30 September 2017

Accepted 2 October 2017

Available online 2 November 2017

Keywords:

Cognitive impairment

Executive function

Memory

Non-steroidal anti-inflammatory drugs

Pain

ABSTRACT

Background and aims: Pain is common in older adults but may be undertreated in part due to concerns about medication toxicity. Analgesics may affect cognition. In this retrospective cohort study, we used the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the interaction of cognitive status and medications, especially non-steroidal anti-inflammatory drugs (NSAIDs). We hypothesized NSAID use would be associated with cognition and that this could be mediated through changes in brain structure.

Methods: In this post hoc analysis of the ADNI database, subjects were selected by searching the "concurrent medications log" for analgesic medications. Subjects were included if the analgesic was listed on the medication log prior to enrollment in ADNI and throughout the study. Subjects taking analgesics, particularly NSAIDs, at each study visit were compared to control subjects taking no analgesics. Using descriptive statistics as well as univariate, multivariate and repeated measure ANOVA, we explored the relationship between NSAID use and scores for executive function and memory related cognitive activities. We further took advantage of the extensive magnetic resonance imaging (MRI) data available in ADNI to test whether cognitive change was associated with brain structure. The multitude of imaging variables was compressed into a small number of features (five eigenvectors (EV)) using principal component analysis.

Results: There were 87 NSAID users, 373 controls, and 71 taking other analgesics. NSAID use was associated with higher executive function scores for cognitively normal (NL) subjects as well as subjects with mild cognitive impairment (MCI). NSAID use was also associated with higher memory scores, but for NL females only. We analysed MRI data using principal component analysis to generate a set of five EVs. Examining NL and MCI subjects, one EV had significantly larger values in subjects taking NSAIDs versus control. This EV was one of two EVs which significantly correlated with composite executive function and memory scores as well as cognitive diagnosis.

Abbreviations: ADNI, Alzheimer's Neuroimaging Initiative Database; NL, cognitively normal; MCI, mild cognitive impairment; ADNI-EF, composite score for executive function; ADNI-MEM, composite score for memory; EV, eigenvector; CDR, clinical dementia rating; CFI, confirmatory fit index; TLI, Tucker Lewis Index; RMSEA, root mean squared error of approximation; PCA, principal component analysis.

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<https://doi.org/10.1016/j.sjpain.2017.10.003>

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Conclusions: NSAID use was associated with higher executive function, and memory scores in certain subjects and larger cortical volumes in particular regions. Limitations of the study include secondary analysis of existing data and the possibility of confounding.

Implications: These results suggest it is important to consider the secondary effects of medications when choosing a treatment regimen. Further prospective studies are needed to examine the role of analgesics on cognition and whether NSAIDs act through cortical dimension changes and how they are related to gender and cognitive diagnosis.

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1. Introduction

Pain is common in older adults. In studies of community-dwelling older adults aged 65 or greater in the United States, the prevalence of reported pain ranged from 52.9 to 78.3% [1,2]. In studies of community-dwelling older adults with dementia the prevalence of pain was 52.9–57.3% by self-report, greater with caregiver report [3,4].

Pain may be pharmacologically undertreated in older adults. In a study of community-dwelling adults aged 65 and greater, of those subjects who reported pain, 28% were not using pain medications [2]. In a study of older adults aged 70 or greater, only 29% of those reporting chronic pain were using analgesics daily [1]. Pain may be undertreated in older adults in part due to concerns about medication toxicity. In choosing therapy it is important to consider side effects and to weigh the risks and benefits of each class of drug. Age related changes occur that may affect the pharmacokinetic and pharmacodynamic responses to medications. Comorbid conditions are common and can further affect the response to drugs [5]. Acetaminophen may be associated with hepatotoxicity. Older patients using non-steroidal anti-inflammatory drugs (NSAIDs) may be at greater risk of gastrointestinal side effects [6]. NSAIDs also have renal and cardiovascular risks [7]. Opioids may be associated with increased risk of injuries such as falls and fractures in older adults [8]. Opioids also carry risks such as respiratory depression, constipation, and nausea.

Analgesics may also affect cognitive function. In some studies, opioid treatment in subjects with chronic pain had adverse effects on cognition [9,10]. In a longitudinal study, the use of opioids alone or in combination with benzodiazepines or other centrally acting medications at baseline predicted cognitive decline at follow-up in an elderly population [11]. In other studies, opioid treatment in subjects with chronic pain has been shown to have either no or positive effects on cognition, suggesting reductions in pain may have beneficial effects on pain-related cognitive impairment [12–14].

Interestingly, the role of NSAIDs in modulating the risk of Alzheimer's disease (AD) has been studied in recent years. Several epidemiological studies have shown the use of NSAIDs may decrease the risk of developing AD [15–17]. Some longitudinal studies have shown NSAID use is associated with less cognitive decline over time compared to no use [18,19]. Other studies have found no differences in the incidence of AD or alteration in cognitive trajectories with the use of NSAIDs compared to placebo [20,21]. One possibility likely involved in the apparent variation in outcome is the fact that AD is an illness that develops over many years. NSAIDs may only protect against cognitive decline with prolonged use at early stages prior to the development of symptoms [15,22,23].

We used the longitudinal Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the interaction of baseline cognitive status and analgesic use, focusing on NSAIDs, on cognitive function and structural brain changes. We hypothesized that NSAID use could be associated with cognition and brain structure. Since Alzheimer's progression is associated with both decreased cognitive performance and altered brain structure, we hypothesized that

NSAID use and brain structure could be associated with an altered risk of transitioning from milder to more severe AD.

2. Methods

2.1. ADNI database

Data used in the preparation of this article were obtained from the ADNI database (<http://adni.loni.usc.edu>). The ADNI database was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. [For up-to-date information, see www.adni-info.org.]

In the ADNI database, part I, there were 1435 research identification numbers for which $n = 819$ were populated by demographics including age, gender, body mass index, apolipoprotein E4 status, blood pressure and heart rate. Subjects, between 55 and 90 years of age, were followed for 2–3 years from enrollment; assessments, including neuropsychological tests and MRIs, were performed at six month intervals. All MRI images were archived by ADNI, and the study volumes were acquired with Freesurfer software and analysed with J-image by the ADNI Center at UCSF. The most recent data was downloaded on January 30, 2014 at which time all the currently active datasets were updated. The ADNI database has previously been used to study the effects of conditions such as sleep-disordered breathing or surgery on cognition and cortical anatomy [24,25].

2.2. Subject selection – drug groups

For all ADNI participants, prescription and over-the-counter medications taken in the previous three months were entered in the “Concurrent Medications Log” at the screening visit. The medication log was updated at each study visit at 6, 12, and 24 months. Subjects for our study were selected by searching the “Concurrent Medications Log” for analgesic medications (e.g., NSAID, acetaminophen, opioids, gabapentinoids, etc.) and indications (e.g., arthritis, joint pain, headaches, neuropathy, back pain, etc.). NSAIDs included the following: celecoxib, diclofenac, etodolac, flurbiprofen, ibuprofen, indomethacin, ketorolac, meloxicam, nabumetone, naproxen, oxaprozin, piroxicam, salsalate, and trisaliclylate. Note that subjects were excluded from ADNI if opioids were used regularly, defined as greater than two doses per week, within four weeks of screening. Subjects were also excluded from ADNI if certain antidepressants, antipsychotics, and benzodiazepines were used within four weeks prior to screening.

To track the effects of analgesics over time, subjects were included if the particular analgesic medication was listed on the medication log prior to enrollment in ADNI and throughout the study at each study visit and the indication was a painful condition. Control subjects were not flagged for any key words. Subjects were excluded if analgesic medication use started or stopped after initial

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