Long-Term Care Updates

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Low-dose aspirin for the prevention of dementia

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Introduction

Low-dose acetylsalicylic acid (LDASA), more commonly known as low-dose aspirin, is a nonsteroidal anti-inflammatory drug (NSAID) sometimes used for prevention of atherosclerotic cardiovascular disease (ASCVD). Aspirin provides protective effects through antiplatelet and anti-inflammatory properties. During an ASCVD event, such as a heart attack or stroke, platelet aggregation forms on damaged vessels and can prevent proper blood flow to critical tissues. The antiplatelet properties of aspirin irreversibly bind to cyclooxygenase-1, inhibiting synthesis of platelet thromboxane A_2, which reduces thrombus formation. When injury occurs to blood vessels, inflammation is a natural response of the body. The release of prostaglandins increases blood flow to the site of injury to aid the body in healing the damaged tissue. Aspirin reduces inflammation through prevention of prostaglandin formation.[1,2]

Dementia is a progressive neurocognitive disorder of declined mental functioning, memory loss, language difficulties, impaired judgment, or disorientation that may also involve behavioral symptoms.[3] Although the exact cause of dementia is unknown, literature implicates cardiovascular disease as a risk factor, suggesting that inflammation influences brain changes. Inflammatory processes may reduce cerebral blood flow, further deteriorating brain vasculature and contributing to neurological insult seen in vascular dementia. It is believed that neuroinflammation plays a role in the onset and progression of Alzheimer's disease (AD) and its degenerative effects tied to amyloid plaques and neurofibrillary tangles. Thus, medications with anti-inflammatory properties could be beneficial for dementia prevention.[4,5]

This newsletter will review clinical research regarding efficacy of low-dose aspirin in reducing dementia risk in adults.

Clinical Evidence

A meta-analysis published by Nguyen et al evaluated two prospective cohort studies that assessed the link between LDASA and dementia: ESTHER and UK Biobank. A total of 310,652 subjects >50 years of age with underlying cardiovascular risks were assessed for incidence of all-cause dementia, AD, and vascular dementia (VD). Use of LDASA was identified by clinical documentation, physician confirmed prescriptions, or participant questionnaires. In the ESTHER trial, adults received aspirin dosed less than 300mg daily, but there were no recorded doses in the UK Biobank trial. Subjects were categorized into four groups: non-aspirin use, use < 5 years, use from 5 to 10 years, and use ≥10 years. Baseline characteristics differed among the trials, with UK Biobank participants predominantly 64 years or younger, while a large proportion of ESTHER subjects were above 70 years. Further variances were found in physical activity, years of education, cholesterol levels, and comorbid conditions (i.e.: hypertension, depression, diabetes, and coronary heart disease). A mean 13 year follow-up revealed that when comparing ESTHER to UK Biobank participants, 9% and 1.8% were diagnosed with all-cause dementia, 3% and 0.66% with AD, and 3.4% and 0.47% with VD, respectively. There were no adverse events evaluated in this meta-analysis. LDASA did not demonstrate a statistically significant reduction in the occurrence of all-cause, Alzheimer's, or vascular dementia in the general population. Further stratification found a significant association between reduced dementia risk and LDASA use for 10 or more years in subjects with coronary heart disease: all-cause dementia (HR 0.69; 95% CI: 0.59-0.80), AD (HR 0.58; 95% CI: 0.51-0.68), and vascular dementia (HR 0.48; 95% CI: 0.42-0.56). Limitations of this meta-analysis included lack of peer review as a pre-print article, an observational study design which did not allow for causal conclusions, and discrepancies in baseline characteristics and doses of aspirin received. Nonetheless, the researchers concluded that long-term use of LDASA was effective in decreasing risk of dementia in those with cardio- or cerebrovascular disease, but not in the general population.[6]

The Aspirin in Reducing Events in the Elderly (ASPREE) trial was a prospective, randomized, placebo-controlled trial conducted by Ryan et al. A total of 19,114 subjects aged 65-95 with a family history of AD were evaluated for dementia triggers through DSM-IV criteria. Alzheimer's disease and mild cognitive impairment (MCI) were diagnosed according to the National Institute on Aging-Alzheimer's Association criteria. Those determined to be free of dementia, cardiovascular disease (CVD), or physical disabilities were randomized to receive either 100mg enteric coated aspirin or a placebo tablet daily. Notably, more subjects enrolled were Caucasian and from Australia. The primary endpoint was efficacy of LDASA in prevention of AD. The secondary endpoints were overall incidence of dementia and MCI. Similarities across treatment groups were reported for subjects who were determined to have clinically probable AD, reached dementia trigger criteria, and cognitive decline. No significant difference was found in those who received aspirin (1.2%) and those who received placebo (1.3%) in risk for AD (HR 0.96; 95% CI: 0.74-1.24). Additionally, no considerable difference was found between groups for the risk of dementia trigger criteria (HR 1.03; 95% CI: 0.91-1.17) or MCI (HR 1.12; 95% CI: 0.92-1.37). Subjects assigned aspirin had higher rates of major bleeding and mortality. Researchers reported after a median follow-up of 4.7 years that negligible clinical or statistical significance was found regarding efficacy of LDASA on incidence of AD, MCI, or cognitive decline in healthy older adults across all baseline characteristics. The main limitation of this study was the population of subjects enrolled, as they were medically healthy with no CVD, whereas other trials found benefit of LDASA in those with CVD for preventing dementia. However, it remains unclear whether the use of LDASA in elderly patients with a history of AD will impact long-term cognition.[7]

A systematic review and meta-analysis of 36,196 subjects across eight studies was conducted by Veronese et al to compare LDASA (< 300 mg/day) to omitted aspirin therapy on cognition in participants deemed dementia-free at baseline. The primary outcome for randomized controlled trials (RCT) was the change from baseline in cognitive tests using the Mini-Mental State Examination (MMSE) and for longitudinal observational studies, the incidence of dementia or cognitive impairment. Baseline demographics found a mean age of 66, more females enrolled (63%), and participants primarily residing in Europe or the United States with a median follow-up time of six years. Three RCTs found no difference in cognitive test scores. Two of the three studies did not find variances in memory; however, did yield slight improvements in executive function and fluency test results in those receiving LDASA, although this was not statistically significant. Additionally, the results of the five observational studies revealed no significant association between aspirin use and dementia or cognitive impairment onset. Of these, three studies found lower dementia risk from baseline to follow-up when compared to two studies looking at cognitive impairment as the outcome. Nonetheless, the association between LDASA and reduction in cognitive outcomes was not significant overall. There was a higher incidence of gastrointestinal side effects in those receiving aspirin (15.2%) and there were fewer participants in the RCTs that completed LDASA therapy compared to the control group (69.9% vs. 75.9%, $p=0.005$). Limitations of this study included undetermined length of aspirin use prior to the study, adherence, and lack of use of a propensity score for observational studies. These limitations lend to the inability to make a conclusion about the long-term effects of LDASA for cognitive test scores, cognitive impairment, and dementia incidence.[8]

Conclusion

Evidence to support the use of LDASA for reducing dementia risk is limited based on the meta-analyses and clinical research. However, one study identified benefit of aspirin use in those with pre-existing cardiovascular disease. It was found that those receiving LDASA had higher rates of gastrointestinal side effects, bleeding, and mortality. Future research could provide guidance and better understanding of dementia risks with long-term LDASA use in those with CVD. It is possible that the pathological changes associated with dementia may occur well before symptom onset and that aspirin may be unable to counter cognitive decline after the diagnosis of dementia is made. LDASA may prolong the progression of dementia in individuals with CVD if initiated at an earlier age and continued for more than ten years. Currently, there is very limited clinical evidence to support recommending LDASA for reducing dementia risk in adults.

References

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