Published in final edited form as:

Am J Geriatr Psychiatry. 2008 December ; 16(12): 999–1009. doi:10.1097/JGP.0b013e31818cd3a4.

Cognitive and Cerebral Metabolic Effects of Celecoxib Versus Placebo in People With Age-Related Memory Loss: Randomized Controlled Study

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Abstract

Objective—Because anti-inflammatory drugs may delay cognitive decline and influence brain metabolism in normal aging, the authors determined the effects of the cyclooxygenase-2 inhibitor, celecoxib, on cognitive performance and regional cerebral glucose metabolism in nondemented volunteers with mild age-related memory decline.

Design—Randomized, double-blind, placebo-controlled, parallel group trial with 18-months of exposure to study medication.

Setting—University research institute.

Participants—Eighty-eight subjects, aged 40–81 years (mean: 58.7, SD: 8.9 years) with mild self-reported memory complaints but normal memory performance scores were recruited from community physician referrals, media coverage, and advertising. Forty subjects completed the study.

Interventions—Daily celecoxib dose of 200 or 400 mg, or placebo.

Main Outcome Measures—Standardized neuropsychological test battery and statistical parametric mapping (SPM) of FDG-PET scans performed during mental rest.

Results—Measures of cognition showed significant between-group differences in executive functioning ($F [1, 30] = 5.06, p = 0.03$) and language/semantic memory ($F [1, 31] = 6.19, p = 0.02$), favoring the celecoxib group compared with the placebo group. Concomitantly, FDG-PET scans

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The University of California, Los Angeles, owns a U.S. patent (6,274,119) entitled “Methods for Labeling β -Amyloid Plaques and Neurofibrillary Tangles,” that has been licensed to Siemens. Drs. Small, Huang, and Barrio are among the inventors, have received royalties, and will receive royalties on future sales. Dr. Small reports having served as a consultant and/or having received lecture fees from Abbott, Brainstorming Co., Dakim, Eisai, Forest, Myriad Genetics, Novartis, Ortho-McNeil, Pfizer, Radica, Siemens, and VerusMed. Dr. Small also reports having received stock options from Dakim. Dr. Lavretsky reports having received lecture fees from Eisai, Janssen, and Pfizer and having received a grant from Forest. Dr. Huang reports having received lecture fees from GlaxoSmithKline. Dr. Barrio reports having served as a consultant and having received lecture fees from Nihon Medi-Physics Co, Bristol-Meyer Squibb, PETNet Pharmaceuticals, and Siemens. Drs. Ercoli, Siddarth, Miller, Phelps, and Bookheimer have no financial conflicts of interest.

Presented at the Alzheimer's Association International Conference on Prevention of Dementia, June, 2007.

demonstrated bilateral metabolic increases in prefrontal cortex in the celecoxib group in the vicinity of Brodmann's areas 9 and 10, but not in the placebo group. SPM analyses of the PET data pooled by treatment arm corresponded to a 6% increase in activity over pretreatment levels ($p = 0.01$, after adjustment for multiple comparisons).

Conclusions—These results suggest that daily celecoxib use may improve cognitive performance and increase regional brain metabolism in people with age-associated memory decline.

Keywords

Cyclooxygenase-2 inhibitor; celecoxib; positron emission tomography; age-related memory complaints

Epidemiological studies have demonstrated an association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and a lower risk for developing Alzheimer disease (AD).^{1–4} Preclinical studies have implicated several mechanisms for this potential neuroprotective drug effect, including reduction of brain inflammation, amyloid plaque antiaggregation, and inhibition of cyclooxygenases, the rate-limiting enzymes in the formation of prostaglandins.^{5–9}

Although the positive epidemiological and laboratory studies support plausible mechanisms for NSAID effects on cognition, most study results from randomized, placebo-controlled clinical trials of both selective cyclooxygenase (COX)-2 inhibitors and nonselective NSAIDs have been negative in patients with AD.^{10–13} One explanation for the negative results in a dementia population is that the neuroprotective effects of such drugs occur before dementia symptoms are clinically obvious.¹⁴

Despite the putative cognitive benefits of NSAIDs, safety concerns could limit their use as a prevention treatment. In a study of more than 58,000 patients with first-time myocardial infarctions,¹⁵ an analysis of the risk of rehospitalization for acute myocardial infarction and death related to the use of NSAIDs found that selective COX-2 inhibitors in all dosages and nonselective NSAIDs in high dosages increase mortality in patients with previous myocardial infarction. The authors concluded that NSAIDs should be used with particular caution in such patients. In a population-based, retrospective cohort study of 2,256 patients aged 66 or older,¹⁶ NSAIDs increased the risks of death and recurrent congestive heart failure, although celecoxib seemed safer than rofecoxib and other NSAIDs in elderly patients with congestive heart failure.

Positron emission tomography (PET) scanning after intravenous injection of [fluorine-18] fluorodeoxy-glucose (FDG) provides a measure of regional cerebral glucose metabolic activity, which reflects both cerebral blood flow and synaptic activity.¹⁷ Previous studies indicate that FDG-PET improves dementia diagnostic accuracy and is a sensitive early measure of neuronal dysfunction before dementia onset.^{18–24} FDG-PET also has been used as a biomarker to track treatment effects on brain function in clinical trials of anticholinesterase inhibitors in patients with AD.^{25–27}

The risk for mild cognitive symptoms increases with age.²⁸ An estimated 40% of people, 65 years and older, have age-associated memory impairment, characterized by self-perception of memory loss and a standardized memory test score demonstrating lower objective memory performance compared with young adults.^{29,30} Such mild age-related memory changes are usually relatively stable, but as these symptoms progress with age, dementia risk may increase. Patients with mild cognitive impairment, characterized by greater cognitive decline without impairment of activities of daily living, are at risk for progressing to AD at a rate approaching 15% each year.³¹ The apolipoprotein E-4 (APOE-4) allele is associated with an increased risk

for developing dementia³² and such nongenetic factors, as level of physical activity and diet, have also been found to influence dementia risk.^{33–35}

To determine potential cognitive benefits and cerebral metabolic effects of an anti-inflammatory treatment, we randomized middle-aged and older adults to the selective COX-2 inhibitor celecoxib or placebo. Because prior controlled trials of patients with dementia have been negative, we studied nondemented individuals with only mild age-related cognitive complaints who may be at risk for dementia in the future. To our knowledge, this is the first study to determine both FDG-PET and objective cognitive effects of an anti-inflammatory drug in such individuals. We hypothesized that celecoxib treatment would maintain or improve cognitive performance scores and regional glucose metabolic rates compared with placebo.

METHODS

Study Design

The study used a randomized, double-blind, two-group parallel design comparing active drug to placebo. All subjects had a 1-week placebo lead-in followed by the treatment period of 18 months. All studies were performed at a single site (Semel Institute for Neuroscience and Human Behavior, University of California, Los Angeles).

We selected a COX-2 inhibitor rather than a non-selective NSAID because of concerns about tolerability of the latter in an older population.³⁶ Subjects were randomized to either celecoxib (200–400 mg) or placebo in a twice-daily regimen (i.e., 100–200 mg of celecoxib in the morning and the evening). Dosages were reduced for subjects experiencing side effects at higher doses of either celecoxib or placebo. We chose a treatment period of 18 months because of an earlier pilot study showing efficacy with short-term anti-inflammatory treatment³⁷ and the estimated duration of follow-up needed to observe cerebral metabolic decline in nondemented people with age-associated memory complaints.^{21,24}

The medical center pharmacy used a randomization table to assign subjects to treatment arms. After the 1-week lead-in period, participants received a 2-month supply of placebo or active drug. Thereafter, they returned every 3 months for placebo or drug supplies. Vital signs, electrocardiograms, serum electrolytes, thyroid function, and complete blood counts were performed at baseline, at 9 months, and at posttreatment to monitor safety.

Subject Selection and Assessment

We performed baseline cognitive assessments and PET scanning on 88 subjects selected from a pool of 196 middle-aged and older potential volunteers (age, 40–81 years) who were willing to participate in the study. These volunteers were recruited through study advertisements on mild memory complaints, media coverage, and referrals from physicians and families. Our study protocol detailed the methods and procedures and prespecified inclusion and exclusion criteria.

To be included in the study, volunteers needed to be at least 40 years of age and have objective cognitive performance scores that were normal for their age group. All subjects had mild age-related memory complaints, which is present in nearly half of individuals age, 50 years and older.³⁰

From the original subject pool, individuals were excluded if they had conditions that increased the risk of adverse events associated with anti-inflammatory drug treatment or had illnesses that might respond to NSAIDs (e.g., arthritis) or might worsen by an anti-inflammatory drug (e.g., cardiovascular disease, hypertension). Volunteers also were excluded if they were taking drugs that could influence cognition (e.g., cholinesterase inhibitors, sedative-hypnotics) or

modify COX-2 drug safety (e.g., aspirin) or supplements that could have such effects (e.g., phosphatidyl serine, ginkgo biloba). Volunteers with a history of excessive alcohol or tobacco use were also excluded from participation. The most frequent reasons for exclusion were preexisting gastrointestinal (N = 26), neuropsychiatric (N = 25), or cardiovascular (N = 14) conditions.

At baseline, all subjects had neurological and psychiatric evaluations, routine screening laboratory tests, and magnetic resonance imaging (MRI) scans to rule out reversible causes of cognitive impairment.³⁸ In addition, subjects were given the Mini-Mental State Examination,³⁹ Hamilton Rating Scale for Depression,⁴⁰ and the Hamilton Rating Scale for Anxiety.⁴¹ Subjects showing evidence of depression or scoring less than 26 on the Mini-Mental State Examination were excluded. Potential participants meeting diagnostic criteria for dementia, mild cognitive impairment, or other major psychiatric disorders also were excluded.^{42–45}

A comprehensive neuropsychological test battery^{46,47} was performed at baseline and after treatment. The battery assessed six cognitive domains: psychomotor speed (Trail Making test A, WAIS-III Digit Symbol Substitution); visuospatial functioning (WAIS-III Block Design Test, Rey-Osterreich Complex Figure Test [copy]); executive functioning (Trail Making test B, Stroop Interference [Kaplan version], F.A.S. Letter Fluency Test); learning (Bushke-Fuld for Selective Reminding Test [total recall], Wechsler Memory Scale-3rd Edition [WMS-III] Verbal Paired Associations I, Benton Visual Retention Test); delayed recall (Bushke-Fuld for Selective Reminding Test [Delayed Recall], Rey-Osterreich Complex Figure Test [recall], WMS-III Verbal Paired Associations II); and language or semantic memory (Boston Naming Test, Animal Naming Test). Raw scores for cognitive tests in each domain were converted to Z scores and then averaged to form an average Z score for each domain. These domain Z scores were then used as the dependent variables for comparing the two groups. Because repeated neuropsychological testing has been found to cause practice effects in people with mild, age-related cognitive complaints,⁴⁸ the neuropsychological test battery was repeated only once after the treatment period at 18 months postbaseline.

Written informed consent was obtained from all subjects in accordance with the University of California, Los Angeles Human Subjects Protection Committee procedures. The trial began on April 14, 2000 and was terminated early on December 23, 2004 because of cardiovascular safety concerns regarding the use of NSAIDs, such as celecoxib. Cumulative radiation dosimetry for all scans was below the mandated maximum annual dose and in compliance with state and federal regulations. One potential volunteer experienced anxiety during the MRI scan and discontinued enrollment. Three minor adverse events occurred during PET scanning: 1 subject had an episode of hyperventilation, another subject experienced temporary lethargy after the scan, and a third had an infiltration at the venipuncture site.

Genetic Analysis

DNA was obtained from blood samples. APOE genotypes were determined using standard techniques as previously described.³² Genetic data were available for 38 of the subjects completing the study.

Scanning Procedures

At baseline and after the 18-month treatment period, subjects underwent PET scanning. Intravenous lines were placed 10–15 minutes before tracer injection. FDG was used to assess regional cerebral metabolism during mental rest, essentially as previously described.^{47,49} In brief, subjects were scanned in the supine position, 40 minutes after the injection of 370 MBq FDG in a dimly lit room having low ambient noise, with eyes and ears unoccluded. PET was performed with 3-dimensional acquisitions, collecting 63 contiguous data planes parallel to

the canthomeatal line in a 128×128 image matrix using a CTI HR and a scanner (CTI, Knoxville, TN). Transmission scans obtained with a positron-emitting source were used for attenuation correction. Six 5-minute frames were acquired and summed-frame images were produced, after excluding frames for patient motion, if necessary.

Anatomical brain MRI scans were obtained using either a 1.5 Tesla or a 3 Tesla magnet (General Electric-Signa, Milwaukee) scanner. Fifty-four transverse planes were collected throughout the brain, superior to the cerebellum, using a double-echo, fast-spin echo series with a 24-cm field of view and 256 × 256 matrix with 3 mm and 0 gap (TR = 6000 [3T] and 2000 [1.5T]; TE = 17/85 [3T] and 30/90 [1.5T]). An intermodality image coregistration program⁴⁹ that preprocesses image segmentation and simulation was used to coregister PET and MRI scans of each subject.

Image Analysis

For comparisons between the active drug and the control groups at baseline and follow-up, PET data were subjected to statistical parametric mapping (SPM) analysis. Briefly, images were coregistered and reoriented into a standardized coordinate system⁵⁰ using the nonlinear spatial transformation package in SPM2,⁵¹ spatially smoothed with a three-dimensional Gaussian smoothing filter having a full-width half-maximum of 16 mm and normalized to mean global activity before carrying out analyses. The pooled data were then assessed on a voxel-by-voxel basis to identify the profile of voxels that differed within each treatment condition between those scans obtained at baseline and the scans acquired after the drug or placebo treatment, to directly assess the profile of voxels where that change significantly differed according to therapy arm.

To examine results of the PET scan data, we used independent methods of analyses (SPM, dedicated region of interest [ROI] analysis on original scan data, and standardized ROI analysis on scans transformed to template space). Following the SPM as the primary exploratory analysis, we performed a dedicated ROI method to provide corroborative support based on original (i.e., spatially untransformed) scan data. As these ROI analyses were explicitly used for the purpose of corroborating the SPM results (which reparameterize the PET data based on one-tailed probabilities of significant change derived from the voxel-based z-values), by quantifying regional metabolism on the original PET scans (i.e., before their spatial transformation to the template space employed in SPM), the one-tailed paired Student's t test, $df = 21$, was employed. Significance of change was examined in four regions selected a priori to best correspond to the voxels of significant increase in the vicinity of Brodmann's areas 9 and 10 located by SPM analysis, assessing the left and right superior frontal and middle frontal gyri. Rules for ROI drawing were based on the identification of gyral and sulcal landmarks on MRI scans with respect to the atlas of Talairach and Tournoux,⁵⁰ as previously described⁴⁷ on regions sensitive to early neurodegeneration. Uptake quantification for FDG-PET was performed on summed images (30–60 minute after injection).

General Statistical Analysis

Before statistical analyses, all data were inspected for outliers, skewness, kurtosis, and homogeneity of variance to ensure their appropriateness for parametric statistical tests. The active drug and placebo groups were compared on baseline demographic and clinical characteristics with chi-square statistics for categorical measures and t tests for continuous measures. The two groups were compared on their postintervention cognitive domain scores using analyses of covariance, controlling for baseline score. In addition, age, gender, and APOE-4 status were used as covariates. Given the relationship between cognition and age, gender, and APOE-4 status,¹⁴ we controlled for these demographic measures in the between-group comparisons. All tests were two-tailed and a significance level of 0.05 was used for all

inferences. To reduce the likelihood of spurious findings, we delimited the number of identified primary outcome measures at the study outset (i.e., from 15 test scores to 6 domain scores) and report results of all proposed analyses.

RESULTS

Participant Flow and Follow-up

A total of 88 subjects, who met the study inclusion criteria completed baseline clinical assessments, neuropsychological testing, and scanning, were randomized and 16 of them withdrew from participation after randomization but before initiation of treatment (Fig. 1). Of the remaining 72 subjects, 36 were randomized to the celecoxib group and 36 to the placebo group.

Of the subjects randomized, a total of 40 completed the study, 22 in the celecoxib treatment arm and 18 in the placebo treatment arm. Subjects who withdrew from the study did not differ significantly from those who completed the study in mean age or baseline cognitive measures. For the celecoxib group, mean (SD) follow-up was 17.6 (5.3) months; for the placebo group it was 18.1 (4.7) months. The treatment groups were similar in baseline demographic and neuropsychological test scores (Tables 1 and 2). Treatment groups did not differ significantly in any of the demographic variables, namely, age, prior educational achievement, sex, APOE-4 status, or family history of dementia (Table 1). Treatment groups also did not differ according to Mini-Mental State Exam scores, estimated full-scale intelligence quotient, Hamilton Rating Scale for Depression, and the Hamilton Rating Scale for Anxiety, or any of the neuropsychological test scores at baseline (Table 2).

Cognitive Outcomes

Of the six cognitive domains assessed, we found significant between-group differences in two of them. After 18 months of treatment, the celecoxib group showed significantly better performance than the placebo group in executive functioning ($F [1,30] = 5.06$, $p = 0.03$) and language or semantic memory ($F [1,31] = 6.19$, $p = 0.02$; Table 2).

Cerebral Glucose Metabolic Outcomes

All three image analysis methods (SPM, dedicated ROI analysis on original scan data, and standardized ROI analysis on scans transformed to template space) identified the most significant before-to-after celecoxib changes as occurring in prefrontal cortex, in the vicinity of Brodmann's areas 9 and 10, although there were some intermethod differences in precise locations, magnitudes, and directions of change. The statistical significance of these changes was greatest using the SPM method, which identified some regional increases in prefrontal cortex bilaterally, which survived the most conservative (Bonferroni-type) multiple comparison corrections. The standardized ROI analyses also indicated that pre-frontal cortical changes were restricted to the celecoxib arm.

The SPM analysis determined the most significant change from before to after celecoxib in a region in the right prefrontal cortex (Fig. 2). The voxel of maximal significance was located at (24, 46, -2) ($z = 4.5$, $p = 0.009$) after Bonferroni-type correction. A region in the left prefrontal cortex (not shown in Fig. 2) was also found to increase significantly after correction (voxel of maximal significance, located at [-20, 16, 34] [$z = 4.8$, $p = 0.003$] after correction). Moreover, the increase in FDG activity associated with celecoxib use in the prefrontal cortex occurred without overlap for any subject, from before to after therapy (Fig. 3).

The dedicated ROI analyses further corroborated significant FDG activity increases in the left and right prefrontal cortex from before-to-after celecoxib treatment. This difference was most

significant in the right superior frontal gyrus, which increased by a mean of 7.5% (one-tailed paired Student's *t* test, *df* = 21, *p* < 0.005), and left superior frontal gyrus, which increased by 7.4% (*p* = 0.007).

Adverse Events

Treatment emergent adverse events were grouped into categories for analysis. Subjects receiving celecoxib were significantly more likely to experience gastrointestinal side effects (primarily transient abdominal pain, gastritis, and nausea) than those receiving placebo (59% versus 22%, $\chi^2 = 5.5$, exact *p* = 0.03). The frequency of other adverse events, such as hypertension, headache, and pain was similar among the two treatment groups (Table 3).

COMMENT

We found that middle-aged and older people with age-related cognitive complaints improved in executive functioning and language or semantic memory after 18 months of daily celecoxib treatment compared with placebo. Moreover, celecoxib treatment resulted in significant increases in cerebral glucose metabolic rates in the prefrontal cortex. These results support our hypothesis that a selective COX-2 inhibitor drug may benefit cognitive performance in people with mild memory complaints, when taken on a daily basis.

Celecoxib significantly improved performances relative to placebo in two of six cognitive domains, suggesting that the effects of celecoxib are modest. Moreover, such effects may have most clinical relevance for cognitive functions involving complex attention, information processing speed, and retrieval of semantic information. By contrast, benefits were not observed in episodic memory performance scores.

The brain region showing the greatest increases in glucose metabolism, the prefrontal cortex, controls executive planning, complex reasoning, and semantic memory, among other mental functions.^{52,53} The neuropsychological tests we used to measure executive functioning also have been used to measure the integrity of the prefrontal cortex.⁵⁴ Evidence from cognitive behavior paradigms, functional brain imaging, and neuropsychological studies of patients with focal insults also points to the prefrontal cortex as a site for semantic memory retrieval.⁵⁵ Thus, our results from cognitive testing and PET imaging of glucose metabolism yielded parallel findings; the cognitive functions showing significant improvement on neuropsychological testing are known to measure functions controlled by brain regions that showed the greatest increases in PET activity.

Several mechanisms have been posited to explain the connection between anti-inflammatory treatments and improved cognitive function. Previous research suggests that inflammatory mechanisms resulting from amyloid β ($A\beta$) deposition play an important role in neurodegeneration.⁵⁶ Brain pathology in amyloid plaques shows evidence of inflammatory activity, including activated microglia and cytokines, suggesting inflammatory mechanisms as contributing to neuronal damage in AD.⁵⁷ The presumed mechanism involves activation of microglia and increased expression of proinflammatory cytokines. The anti-inflammatory effects of NSAIDs are presumed to disrupt this cascade; however, this mechanism may not be relevant to the present study, because celecoxib is not among those NSAIDs that lower production of the 42-residue form of amyloid β ($A\beta_{42}$) in mouse models.⁵⁸

Another proposed mechanism involves disruption of $A\beta$ peptide aggregation into insoluble plaques. Our group has found that some NSAIDs (e.g., ibuprofen, naproxen) exhibit antiaggregation effects on $A\beta$ peptides, suggesting that the binding site on $A\beta$ fibrils and plaques may be a site of antiaggregation drug action.⁶ A recent pooled dataset from six

prospective studies found that NSAID use reduced the risk for AD; however, there was no advantage for NSAIDs shown to selectively lower $A\beta_{42}$.⁵⁹

COX modulation reduces formation of inflammatory prostaglandins and is an alternate pathway for the putative neuroprotective effects of COX-2 inhibitors. COX-2, an enzyme critical to the synthesis of prostaglandins and the inflammatory process, is expressed in neurons and up-regulated in AD.⁶⁰ Expression of cyclooxygenase-2 has been observed in the frontal cortex of patients with AD,⁶¹ and overexpression of COX-2 is associated with elevated production of $A\beta$.⁶²

Another potential mechanism that has received less attention posits that neuroprotection from NSAID use is indirectly modulated through cardiovascular effects on brain function. In other words, people taking NSAIDs might experience less joint discomfort and, thus, spend more time in physical activity. People who are physically active in midlife have been found to have a lower risk for dementia three decades later.⁶³ This mechanism also could explain the observational results of previous epidemiological studies—people reporting a history of prior NSAID use—those with a lower risk for AD might be more likely to have a history of higher physical activity and joint injury leading to greater NSAID use.

In support of this explanation is evidence that aerobic exercise in older adults results in cognitive and cerebral effects consistent with those found in the present study. For example, a 6-month randomized trial comparing aerobic exercise to toning and stretching demonstrated significant increases in pre-frontal temporal gray matter and anterior white matter in the exercise group but not in the control group.⁶⁴ Aerobic conditioning also has been found to alter frontal lobe functional MRI patterns related to significant improvement in selective attention tasks.⁶⁵ Other studies show that physical activity leads to improved executive functioning.⁶⁶ Although subjects with arthritis were excluded from the present study, it is possible that subjects taking celecoxib engaged in more physical activity because the medication relieved minor joint pain and, thus, improved mobility. Future trials that monitor physical activity levels could determine whether this explanation for the findings of the present study holds true.

Another prospective study found that long-term NSAID use may reduce the incidence of AD when treatment is started years before the age at dementia onset⁶⁷ supporting the notion that a critical intervention period may exist before dementia onset. A recent study⁶⁸ found that the COX-2 inhibitor rofecoxib was no better than placebo in delaying conversion to dementia in patients with mild cognitive impairment, suggesting that if such a critical treatment period exists, it probably occurs before people develop mild cognitive impairment. To further address such issues, the National Institute on Aging initiated the Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) to determine the effects of naproxen or celecoxib in preventing dementia and age-related decline. Recently published results from that study⁶⁹ found that use of naproxen or celecoxib did not improve cognitive function. Moreover, there was weak evidence for a detrimental naproxen effect. Although the ADAPT findings add to the negative evidence for treatment and secondary prevention trials, inflammatory processes are clearly complex and may have both reparative and detrimental effects on neurons.⁷⁰ The ADAPT results may reflect detrimental effects after starting treatment in people with subclinical neuropathology, whereas protective effects may occur when treatment is initiated earlier. To this point, subjects in the ADAPT study were on average more than a decade older than those in the present study. Other studies have shown apparent protective cognitive effects resulting from more distant rather than recent NSAID use.^{2,67} Because of cardiovascular safety concerns, the ADAPT trial was terminated prematurely (December, 2004).⁷¹

The present study also was terminated at that time, which led to a relatively small sample size warranting caution in interpreting our results. With the sample sizes realized in the present study, we would be able to detect a relatively large effect size of 0.89 for the change across testings with 80% power at a significance level of 0.05. The fact that we did find a significant improvement in the celecoxib group suggests that, at least in this small sample, the impact of the treatment was clinically meaningful. Such a small sample, of course, limits the generalizability of any findings. In addition, our study design limited assessments to only two time points and, thus, providing only a “snapshot” of celecoxib effects and further restricting the scope of our conclusions. We also included volunteers who were free of common age-related illnesses that could increase risks of adverse effects from taking a COX-2 inhibitor.

The initial enthusiasm for the COX-2 inhibitors because of their perceived lower side effect profile compared with other NSAIDs has been dampened by greater awareness of treatment-emergent side effects since the initial approval of these drugs. Patients enrolled in the present study who received celecoxib had a significantly higher rate of gastrointestinal side effects, particularly transient abdominal pain, gastritis, and nausea, compared with those taking placebo (Table 3). Although use of COX-2 inhibitors is associated with morbidity and mortality related to cardiovascular effects,^{15,16} our sample size was too small for such adverse effects to emerge. However, it is important to avoid overinterpretation of our results and inappropriate prescription of celecoxib for dementia prevention, to avoid the emergence of untoward and dangerous cardiovascular and gastrointestinal incidents from widespread use.

Despite such concerns, our positive findings that daily use of celecoxib improves cognitive functioning and increases prefrontal regional glucose metabolism are encouraging that NSAID treatment may exert beneficial cognitive effects in people with relatively mild age-related cognitive complaints, perhaps before subclinical neuropathological changes emerge. These results warrant further study in similar populations to confirm the possible cognitive benefits of these drugs and to elucidate the underlying mechanisms that may exert such effects.

Acknowledgments

Supported by NIH grants AG13308, P50 AG 16570, MH/AG58156, MH52453, AG10123, and M01-RR00865; the Department of Energy (DOE contract DE-FC03-87-ER60615); General Clinical Research Centers Program; the Fran and Ray Stark Foundation Fund for Alzheimer's Disease Research; the Lovelace Foundation; the Judith Olenick Elgart Fund for Research on Brain Aging; and the Brewster Foundation. Pharmacia provided celecoxib and matching placebo capsules.

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FIGURE 1.
Flow Diagram Tracking Subjects

FIGURE 2. Sagittal (upper) and Transverse (lower) Images From the SPM Analysis Showing Regions (yellow, arrows) With the Most Significant Increase in Metabolism in the Celecoxib Group
Notes: The yellow color scale represents all voxels where FDG activity is increased with a significance of $p < 0.001$. The voxel of maximal significance is located at (24, 46, -2) ($z = 4.5$, $p = 0.009$ after Bonferroni-type correction). SPM: statistical parametric mapping; FDG: [fluorine-18]fluorodeoxyglucose.

FIGURE 3.

Individual Data Points in a Dot-Plot (Superimposed on a Bar Graph Showing Mean Levels) of the Magnitude of FDG Activity at the Peak Voxel Displayed in the Right Prefrontal Cortex, Before (left dataset) and After (right dataset) Celecoxib Therapy

TABLE 1**Baseline Characteristics of Subjects**

	Celecoxib (n = 22)	Placebo (n = 18)
Age (yrs), mean (SD)	56.6 (10.1)	59.3 (10.5)
Education (yrs), mean (SD)	15.0 (1.7)	15.5 (2.6)
Sex (%), female, number	9 (41)	6 (33)
Mini-mental state examination, mean (SD)	29.2 (1.1)	29.2 (0.9)
Hamilton rating scale for depression, mean (SD)	2.9 (2.9)	1.9 (2.2)
Hamilton rating scale for anxiety, mean (SD) ^a	5.1 (4.6)	3.6 (3.7)
WAIS full scale IQ, mean (SD)	109.2 (9.0)	112.6 (7.0)
Family history of dementia, n (%)	4 (18.2)	8 (44.4)
APOE-4 carriers, n (%) ^b	6 (28.6)	7 (41.2)

^aOne subject in the celecoxib group did not complete this scale.

^bAPOE-4 status missing for one subject each from celecoxib and placebo groups.

TABLE 2
Baseline and Post-Treatment Neuropsychological Test Scores^a Within Each Cognitive Domain

Domain	Test	Celecoxib (n = 22), Mean (SD)		Placebo (n = 18), Mean (SD)	
		Baseline	Post-Treatment	Baseline	Post-Treatment
Psychomotor speed	Trailmaking A	32.4 (12.9)	30.7 (9.7)	29.5 (9.3)	28.3 (9.0)
	WAIS-III digit symbol	70.3 (15.7)	69.0 (17.8)	72.1 (17.1)	74.0 (18.4)
	WAIS-III block design	37.0 (9.8)	40.4 (7.5)	41.1 (11.5)	41.1 (12.7)
Visuospatial functioning	Complex figure, copy	30.4 (4.0)	30.8 (3.3)	31.8 (2.8)	30.6 (2.9)
	Trailmaking B	80.3 (34.1)	78.4 (43.3)	65.6 (22.2)	71.2 (37.5)
Executive functioning ^b	Stroop interference	127.2 (30.1)	121.0 (30.5)	122.9 (36.8)	125.4 (46.6)
	F.A.S. letter fluency	38.4 (13.6)	40.9 (14.3)	41.9 (17.6)	44.2 (18.7)
	Selective reminding, total recall	102.6 (13.5)	103.9 (18.0)	106.9 (20.8)	111.6 (19.0)
Learning	Verbal paired associations I	17.6 (7.6)	20.6 (8.0)	19.5 (9.0)	21.5 (8.6)
	Benton visual retention	3.9 (1.9)	4.3 (2.0)	3.9 (2.5)	4.7 (3.6)
	Selective reminding, delayed recall	7.9 (3.0)	8.3 (2.7)	9.2 (3.6)	9.8 (2.7)
Delayed recall	Complex figure, recall	15.8 (6.9)	17.3 (7.7)	17.3 (7.7)	16.8 (7.5)
	Verbal paired associations II	6.4 (1.7)	6.6 (2.1)	6.2 (2.3)	7.3 (2.6)
	Boston naming	54.9 (3.5)	55.5 (3.6)	55.9 (4.3)	55.7 (5.5)
	Animal naming	21.5 (5.7)	22.5 (4.6)	20.8 (5.0)	19.4 (6.1)
Language/semantic memory ^c					

^a Higher scores indicate better cognitive performance except for Trailmaking A and B, Stroop interference, and Benton Visual Retention, wherein lower scores indicate better performance.

^b $F[1,30] = 5.06, p = 0.03$.

^c $F[1,31] = 6.19, p = 0.02$.

TABLE 3

Treatment Emergent Adverse Events

	Celecoxib, n (%)	Placebo, n (%)
Gastrointestinal symptoms	13 (59)	4 (22)
Hypertension	3 (14)	3 (17)
Headache	2 (9)	2 (11)
Weight gain	2 (9)	1 (6)
Pain	2 (9)	1 (6)
Dizziness	2 (9)	0 (0)
Nasal congestion	1 (5)	1 (6)
Hot flashes	1 (5)	1 (6)
Allergy	1 (5)	1 (6)