# Nasal NSAIDs for Alzheimer's Disease

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# Nasal NSAIDs for Alzheimer's Disease

**Steven Lehrer, MD**[1]

**Abstract**

Alzheimer's disease may result from low-grade inflammation of the brain, and the characteristic amyloid β may be a protective response. Epidemiological observation indicates that long-term oral administration of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen to patients having rheumatoid arthritis results in reduced risk and delayed onset of Alzheimer's disease. However, oral ibuprofen, flurbiprofen, and other NSAIDs are not an effective treatment. The NSAIDs may work as an Alzheimer's preventive but not a treatment because the oral dose to the brain is too small, 1% to 2% of the total plasma concentration. The NSAID brain dose could be significantly increased by delivering the drug intranasally. Flurbiprofen would be preferable to ibuprofen because flurbiprofen has 12½ times the potency of ibuprofen. The smaller nasal dose of flurbiprofen than ibuprofen could significantly increase patient compliance. Alzheimer's disease starts in the entorhinal cortex, which is closely connected to the olfactory nerves, and spreads anatomically in a defined pattern. Therefore, a nasal NSAID would readily reach the region of the brain where it is most likely to be therapeutic.

**Keywords**

nasal, flurbiprofen, NSAID, rhinencephalon

Although several initially promising agents have been developed to reverse or at least slow the decline of cognitive function in patients with Alzheimer's disease, successive clinical trials have failed. The most advanced agents are monoclonal antibodies directed to certain forms of amyloid β (Aβ) and τ protein.

## The Amyloid Hypothesis and Its Failings

Amyloid β is toxic to neurons in vitro. Trials aimed at Aβ are now being conducted in mild Alzheimer's disease, in prodromal Alzheimer's disease, and in patients with Aβ plaques and minor memory complaints but no deficits on standard cognitive tests. Other amyloid-based approaches include antiaggregation compounds, inhibitors of β-secretase enzyme, and either modulators or inhibitors of γ-secretase. The τ-protein-lowering approaches include antiaggregation and immunotherapy.[1]

Amyloid-β plaques and τ protein tangles, hallmarks of the pathology, may be a result of the disease process rather than a cause. The pathology of Alzheimer's disease is common in older persons without cognitive impairment,[2] and Aβ in vivo could represent a protective response to neuronal insult.[3]

## Brain Inflammation and Alzheimer's Disease

Some Alzheimer's researchers, skeptical of the amyloid hypothesis, believe that the malady results from low-grade inflammation of the brain.[4] Implication of inflammation in Alzheimer's disease is not surprising, since inflammation underlies many diseases of aging: neurodegenerative,[5] osteoarthritis and rheumatoid arthritis,[5] cardiovascular disease,[6] and cancer.[7] In addition, the apolipoprotein (apo) E4 allele, which increases the risk of Alzheimer's disease, is associated with significantly greater systemic and brain elevations of the proinflammatory cytokines Tumor necrosis factor α and interleukin 6, as compared with their apoE3 counterparts. These elevations suggest an isoform-specific effect of the immunomodulatory properties of apoE.[8]

Epidemiological observation indicates that long-term oral administration of nonsteroidal anti-inflammatory drug (NSAID) to patients having rheumatoid arthritis of the ibuprofen results in reduced risk and delayed onset of Alzheimer's disease. However, oral ibuprofen, flurbiprofen, and other NSAIDs are not an effective treatment.[9-12] Nonsteroidal anti-inflammatory drugs could work as an Alzheimer's preventive but not a treatment because the oral dose to the brain is not high enough. An analogous situation may be diabetic retinopathy, which has an inflammatory component. High doses of aspirin are associated with decreased severity of diabetic retinopathy in patients with concurrent rheumatoid arthritis. However, clinical trials of low and intermediate doses of aspirin failed to show a beneficial effect.[13]

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## Nonsteroidal Anti-inflammatory Drug Administration, Oral Versus Nasal and Brain Dose

Ibuprofen, which is highly lipophilic, readily crosses the blood–brain barrier after an oral dose but is poorly distributed.[14] Also, the amount of ibuprofen that reaches the brain after an oral dose is small. Most NSAIDs that exhibit good activity against Alzheimer's disease models, such as ibuprofen, flurbiprofen, and indomethacin, distribute poorly to the brain. For example, in 1 study, after multiple oral doses of ibuprofen the concentration in fat was 58.4 μg/g tissue, while brain concentration was 0.4 μg/g.[15] Plasma protein binding limits brain NSAID uptake by reducing the free fraction of NSAID in the circulation. For ibuprofen, the vascular-corrected brain concentration at steady state is only 1% to 2% of that of the total plasma concentration. Similar low values have been reported for flurbiprofen, ketoprofen, and naproxen. Cerebrospinal fluid distribution is also minimal, less than 1% to 5% of plasma for many NSAIDs. Together, these results suggest that some barrier exists that limits brain uptake of oral NSAIDs.[14]

The NSAID brain dose could be significantly increased by delivering the drug intranasally. Nasal drug delivery that exploits the olfactory and trigeminal neuronal pathways to convey drugs to the brain is being widely explored by pharmaceutical companies. Low-molecular-weight lipophilic drugs, such as ibuprofen, are readily absorbed into the brain by the intranasal route.[16] Intranasal insulin is already being tested as a treatment for Alzheimer's disease.[17] In addition, Alzheimer's disease starts in the entorhinal cortex, which is connected to the olfactory nerves, and spreads outward in an anatomically defined pattern.[18] Therefore, nasal NSAIDs would readily reach the region of the brain where they are most likely to be therapeutic.

Because ibuprofen and other NSAIDs might prevent Alzheimer's disease, it would certainly be worthwhile to test intranasal ibuprofen, flurbiprofen, naproxen, or other intranasal NSAIDs as a form of therapy. Flurbiprofen would be preferable to ibuprofen because flurbiprofen is more potent and has 12½ times the power of ibuprofen to inhibit the formation of prostaglandin E2 from arachidonic acid.[19] The smaller nasal dose of flurbiprofen could significantly increase patient compliance. In addition, flurbiprofen inhibits both cyclooxygenase 1 (cox-1) and cox-2 and could be more effective than a selective cox-2 inhibitor, such as celecoxib. The activity of Cox-1 precedes cox-2 induction in Aβ-induced neuroinflammation,[20] and cox-1 inhibition reduces amyloid pathology and improves memory deficits in a mouse model of Alzheimer's disease.[21]

R-flurbiprofen, an enantiomer of flurbiprofen, failed a phase III clinical trial for the treatment of Alzheimer's disease. However, R-flurbiprofen is devoid of any direct cyclooxygenase inhibition, which is associated with the S-enantiomer of flurbiprofen that was not tested.[22]

The difference between preventing and treating brain inflammation with NSAIDs might be covered by the proverb, the ounce of prevention and the pound of cure. Once Alzheimer's disease develops, the patient needs the nasal pound of cure not the oral ounce of prevention.

### Declaration of Conflicting Interests

The author declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Lehrer has filed a patent application covering the use of nasal NSAIDs for the treatment of Alzheimer's disease.

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