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## REPORT

**Over-The-Counter Drug is Treatment for Alzheimer's**

by Terri Mitchell and Amber Needham

People in pain, take heart. There may be an upside to having arthritis and other pain disorders. If you're one of the millions who takes non-steroidal anti-inflammatory drugs (NSAIDs) on a regular basis, you may have reduced your risk of getting Alzheimer's disease. Those of you who consistently take other kinds of anti-inflammatories such as indomethacin, or antioxidants such as curcumin or fish oil, may have reason to rejoice as well.

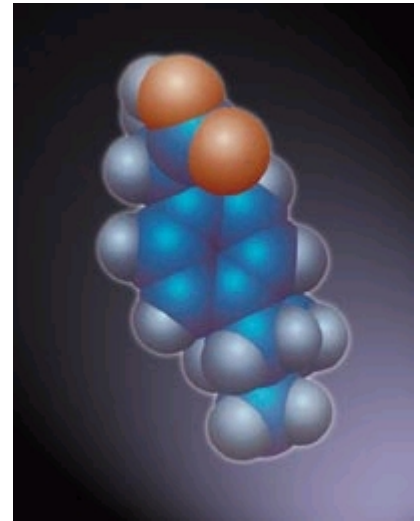
New research shows that the over-the-counter NSAIDs such as ibuprofen enhance cognitive performance, delay onset of the disease and suppress inflammation in the Alzheimer's-afflicted brain. Millions of potential Alzheimer's disease victims may prevent or significantly delay this horrible disease with non-prescription NSAIDs they can buy right now in any pharmacy in America. Those who already have Alzheimer's may prolong their ability to function, thus delaying the necessity of full-time care.

**Why ibuprofen?**

A new study from the University of California at Los Angeles is the latest proof that the NSAID, ibuprofen, helps stop Alzheimer's. The study was done in the mouse model of Alzheimer's. Ibuprofen was chosen as a potential therapy because almost two dozen studies show that people who take non-steroidal anti-inflammatory drugs (NSAIDs) are less likely to get Alzheimer's disease, and ibuprofen was the drug people with low risk took most often. One study in particular is very persuasive. In female twins, anti-inflammatory drugs slashed the incidence of Alzheimer's disease by about 75%. Although these drugs didn't work as well in men, it's still good news since women have two-to-three times the risk of getting Alzheimer's disease than men.

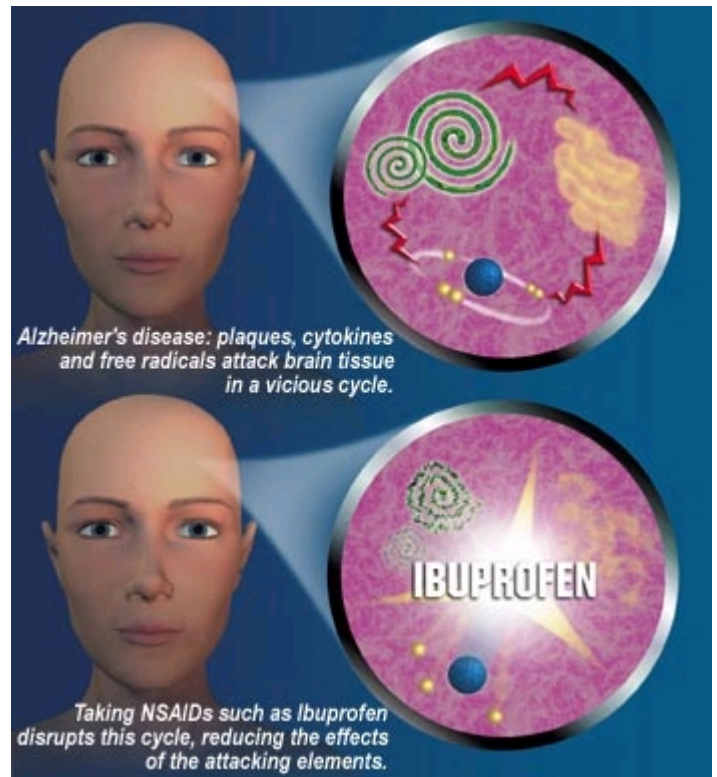
It's ironic that with all the millions being spent on finding a treatment for Alzheimer's disease, that something as simple as an over-the-counter inflammation blocker would show the most promise. But

How ibuprofen minimizes the severity of Alzheimer's disease



according to Dr. Gregory M. Cole, lead author of the study, there may be many ibuprofens out there that are good treatments for Alzheimer's. He believes that too much emphasis is being put on finding out the hows and whys of Alzheimer's so drug companies can design an Alzheimer's drug, rather than using what we already know about the disease, and devising treatments around that. He thinks it would be irresponsible not to test possibilities like curcumin and omega-3 fatty acids.

When Dr. Cole designed the Alzheimer's experiment, one of his goals was to try something already tested in humans. This avoids, he says, the disappointment of discovering a treatment that may work great for rodents, but fails in humans. His second criteria was to try something with known side effects such as generic drugs with a long history of use behind them. That way, time is not wasted on things which might be a good treatment for Alzheimer's but have such adverse side effects, nobody could take them. His third criteria was to get at an underlying mechanism rather than treat something unique to Alzheimer's. In this case, there is overwhelming evidence that inflammation not only plays a major role in Alzheimer's, but other age-related diseases such as colon cancer and aortic valve stenosis as well. Why take 400 different pills for 400 different maladies, he asks. Why not get at an underlying mechanism and stop multiple problems?



What is Alzheimer's?

Alzheimer's is named after the scientist, Alois Alzheimer, who first identified it in 1907. While scientists don't know for sure what causes Alzheimer's disease, they do know what it is. The main feature is highly abnormal structures known as plaques and tangles. They provoke an immune reaction that creates oxidative stress. This stress causes tissue destruction and loss of blood supply.

The brain's immune reaction is created by cells surrounding the neurons. In Alzheimer's, these cells are "activated," and one of the goals of Alzheimer's treatment is to deactivate these cells because their immune response is creating oxidative stress that damages the brain. Both the mouse study, and a new study from Finland, confirm that NSAIDs significantly reduce activation of these cells (microglia, astroglia and glia). This results in lower amounts of free radicals and pro-inflammatory substances known as cytokines.

Cytokines are produced by immune cells. Extremely powerful, these proteins cause immune cells to multiply and create oxidative chemicals such as hydrogen peroxide that generate free radicals. The free radicals, in turn, drive the production of more cytokines and more activation. Ibuprofen (and other anti-inflammatories) work to stop this vicious cycle in two important ways.

How it works

First, ibuprofen blocks a protein known as nuclear factor kappa B (NFkB). NFkB promotes the production of three cytokines elevated in Alzheimer's disease: tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6). All three increase naturally with age, but in Alzheimer's, levels are highly elevated. These three provoke a host of destructive immune responses, such as complement—a protein that pokes holes in cells. By blocking NFkB, ibuprofen reduces cytokine levels, stops the production of free radicals, and deactivates immune cells.

The second way ibuprofen works is by interfering with an enzyme that provokes pro-inflammatory substances known as prostaglandins. Prostaglandins are created from arachidonic acid, an omega-6 fatty acid found in cell membranes. There are several types of prostaglandins. One type maintains the lining of the stomach and promotes kidney function. Another is a type that generates free radicals. The first is provoked by the enzyme known as cyclooxygenase-1 (COX-1). The second by cyclooxygenase-2 (COX-2). It's not clear whether it's important to block COX-1, COX-2, or both in Alzheimer's. Ibuprofen inhibits both.

By blocking prostaglandins, COX inhibitors, including ibuprofen, lessen the free radical attack on brain tissue. Free radicals not only damage tissue directly, they provoke glutamate and nitric oxide, which can also be damaging. Plus, free radicals can also activate NF B, setting off a new round of cytokines and free radical production.

Questions about plaques and tangles

Whether or not NSAIDs can reduce the number of senile plaques and neurofibrillary tangles is still under investigation. These

abnormal clumps are made up of pieces of protein known as amyloid peptides. A study published in 1996 shows that in cell culture, the NSAID drug, dexamethasone, slashes the amount of amyloid by 66% in rat microglia. Indomethacin reduces it by 54%. The recent UCLA study confirms that ibuprofen cuts the number of plaques in the mouse model of Alzheimer's in half.

But two smaller studies in human postmortem tissue show that even though patients who took NSAIDs did much better, with shorter duration of illness, they did not have fewer plaques. In one of them, a study from Finland, the amount of amyloid beta was actually increased even though deactivation and reduced numbers of damaging cells was reported, along with improvement of the patients. According to the lead author, Dr. Irina Alafuzoff, this tends to confirm what some researchers have been saying for a long time: reducing the number of plaques and tangles may not be as important as stopping the activation of cells creating tissue damage. In this study, patients were taking ibuprofen (600 mg/day), ketoprofen (100 mg/day) or naproxen (500 mg/day).

Another recent study of five Alzheimer's disease patients who took naproxen found that patients did much better mentally than patients who did not take the drug. Again, the benefits were not attributed to decreased numbers of plaques.

How much ibuprofen?

One of the often-repeated criticisms of ibuprofen is that it causes severe side effects. Because it inhibits COX-1, ibuprofen has the potential to cause gastrointestinal bleeding and loss of kidney function. There is, however, not much support for these side effects at 800 mg/day—the average dose that seems to reduce the risk for Alzheimer's disease. In this amount, the risk of serious side effects is less than a comparable amount of aspirin, and significantly less than other anti-inflammatories such as indomethacin or naproxen. Eight hundred milligrams is considered a relatively low dose of ibuprofen—far less than the 2400 mg+ frequently prescribed for osteoarthritis and other pain disorders. According to Cole, 90% of the population should have no serious side effects at 800 mg/day. Frail elderly people, or those with kidney disease are more likely to have serious side effects, and should carefully weigh the risks and benefits. People with heart disease should be aware that these drugs block nitric oxide, which is beneficial for blood vessels (this effect can be reversed with fish oil—see below).

Natural alternatives

A drug is still a drug, and some people may ask if there is something natural that will do the same thing. Cole believes there may be. A number of natural compounds possess many of the same actions as ibuprofen. Combinations of these natural substances may work even better than single agents.

Among the most promising is curcumin. This polyphenol from the root of a plant similar to ginger is a powerful anti-inflammatory that inhibits all aspects of arachidonic acid metabolism, including COX-1, COX-2 (which catalyzes inflammatory prostaglandins), thromboxane and LOX (which catalyzes leukotriene B4, an inflammatory factor that may play a major role in aging of the brain). And most importantly, curcumin interferes with NF B to stop immune activation and lessen tissue destruction.

Omega-3 fatty acids such as fish oil are anti-inflammatories that possesses some of the same properties as ibuprofen. In studies done mostly in tissue other than brain tissue, fish oil or its major components, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), inhibits COX-2 and LOX. Importantly, fish oil blocks the formation of leukotriene B4 from LOX. This inflammatory substance is accused of being one of the major players in aging of the brain, as well as Alzheimer's disease.

Another feature of omega-3 oil that makes it important for Alzheimer's disease is that it increases nitric oxide in blood vessels. Nitric oxide is very important in maintaining the integrity and function of blood vessels. One of the features of Alzheimer's disease is the destruction of the blood supply. Part of this destruction may be due to amyloid interference with nitric oxide in blood vessels, which causes them to shrink. Omega-3 enhances nitric oxide in blood vessels, possibly reversing this adverse effect of amyloid.

While nitric oxide is generally considered a destructive factor in Alzheimer's disease, with regard to Alzheimer's, it might actually be beneficial. In blood vessels, nitric oxide blocks NF B and stops the production of IL-6, one of the cytokines elevated in Alzheimer's disease. Estrogen, which has been shown to reduce the risk of Alzheimer's disease, promotes the synthesis of nitric oxide, and also blocks IL-6. It has been proposed that fish oil helps prevent Alzheimer's disease by augmenting (not reducing) nitric oxide and blocking cytokines.

Omega-3 fatty acids such as fish oil work in an interesting way. Rather than blocking the production of inflammatory factors, it replaces their parent substance, arachidonic acid. Inflammatory prostaglandins and leukotrienes are synthesized from arachidonic acid, which is an omega-6 fatty acid. When omega-3 fats such as fish oil are eaten, they substitute for arachidonic acid in cell membranes. Because omega-3 is not as easily converted to inflammatory factors, less inflammation is produced.

Vitamin E

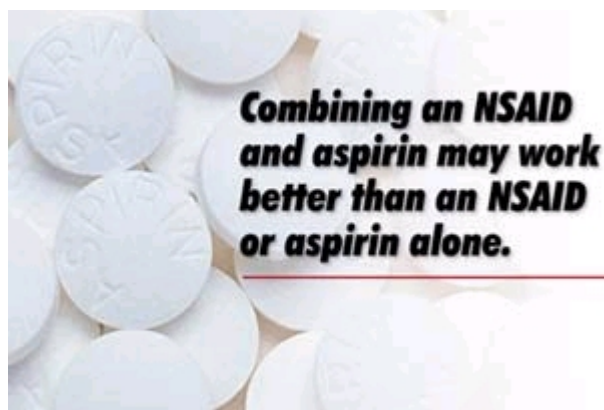
This antioxidant vitamin is not generally considered to be an anti-inflammatory in the classic sense. Its mode of action in Alzheimer's disease is probably its free radical scavenging action, which has an indirect effect on inflammation. There are several indications that vitamin E may help the brain stand up to the effects of beta-amyloid. Neurons are extremely sensitive to the damaging effects of the amyloid peptides. Vitamin E clearly blocks this toxicity in cell culture. A study from the National Institute

on Aging also shows that vitamin E helps reverse amyloid's suppression of the muscarinic receptor—essential for memory. These test tube findings have been confirmed in studies on people.

The Honolulu-Asia Aging Study shows that a combination of vitamins C and E significantly reduces vascular and other types of dementias. It also improves cognitive effect in people without dementia. The study did not show a protective effect against Alzheimer's type dementia, unfortunately. But the Alzheimer's Disease Cooperative Study did. In that study, 2000 IUs of vitamin E per day slowed the progression of the disease. According to the findings, vitamin E may preserve that ability of a person with Alzheimer's disease to take care of themselves longer. Neither study looked at what might happen if a person started taking vitamin E early on—in their 40s or 50s, for example.

## Aspirin

Although aspirin is technically a NSAID, its mode of action is different than drugs like ibuprofen. However, it too, may reduce the risk of Alzheimer's disease, although the data is not as compelling as for other NSAIDs. In an analysis of data from the Baltimore Longitudinal Study of Aging, the relative risk of getting Alzheimer's disease was reduced 26% by aspirin. By comparison, taking a non-aspirin NSAID two years or longer reduced it 60%. However, aspirin might have an advantage. Unlike other NSAIDs, aspirin didn't show a duration effect. So aspirin's protective effect might kick in quicker than other NSAIDs. Better yet, a combination might work even better. Data from the Cache County Study shows that combining an NSAID and aspirin works better than an NSAID or aspirin alone. As with ibuprofen, a low dose appears to be all that's needed. Most of the people in the study were taking a low dose for cardiovascular protection. (Low-dose aspirin is considered to be 81 mg a day, or 1/4 of a regular aspirin tablet).



### A cautionary note on COX-2 inhibitors

The discovery that COX-2 is a factor that generates inflammation, as opposed to COX-1, has set off a frenzy by drug companies to invent drugs that selectively inhibit COX-2. Potentially, these drugs will be free of the side effects caused by blocking both forms of cyclooxygenase. So-called "COX-2 inhibitors" are expected to become a \$10 billion dollar product within the next decade, and have already spawned a major lawsuit over the patent.

However, data is beginning to appear that suggests that COX-2 inhibitors may not be as great as everyone originally thought. Nature Medicine published research by scientists at the Veterans Affairs Medical Center in Long Beach, California that challenges the notion that COX-2 inhibitors won't harm the gastrointestinal tract. That research shows that the line

dividing COX-1 and COX-2 is not so neat, and that COX-2 also has potential to affect the gut.

Other research goes even further. It suggests that when cyclooxygenase is inhibited, a different inflammatory product, lipoxygenase (LOX) is increased. LOX-induced leukotrienes are as dangerous to brain cells as COX-induced prostaglandins.

While confirmation of these findings is pending, it's important to remember that only the older NSAIDs like ibuprofen have the most data behind them as far as Alzheimer's. Curcumin and omega-3 fatty acids such as fish oil are the most well-studied natural anti-inflammatories, although most of the studies have been done in organs other than the brain. Nonetheless, it's a good bet that these safe, inexpensive, readily available compounds are worth the price of admission. People who are concerned about the disease, especially those with a family history, should start now. Don't wait until symptoms appear to start thinking about Alzheimer's prevention.

## Study in the works

As exciting as it is, the new research on NSAIDs has raised questions. How do they work? How do they interact with amyloid? What is the lowest dose a person can take and still see an effect? To answer these questions, a new study is being set up in conjunction with the National Institutes of Health (NIH). It will follow people with a family history of Alzheimer's disease for several years.

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