

By Andrea Gerlin

May 21 (Bloomberg) -- A cheap regimen of vitamins in use for decades is seen by scientists as a way to delay the start of Alzheimer's disease and dementia, a goal that prescription drugs have failed to achieve.

Drugmakers including Bristol-Myers Squibb Co., Pfizer Inc. and Eli Lilly & Co. have spent billions of dollars on ineffective therapies in a so-far fruitless effort to come up with a treatment for dementia and Alzheimer's.

Now, in the latest of a steady drumbeat of research that suggests diet, exercise and socializing remain patients' best hope, a study published today in the Proceedings of the National Academy of Sciences shows that vitamins B6 and B12 combined with folic acid slowed atrophy of gray matter in brain areas affected by Alzheimer's disease.

"You don't have any other options for these patients, so why not try giving them this cocktail of B vitamins?" says Johan Lökk, a professor and head physician in the geriatric department at Karolinska University Hospital Huddinge in Sweden, who wasn't involved in the study.

Alzheimer's disease and dementia mostly affect older people. As people live longer, the number afflicted by the conditions is growing. Delaying dementia with an inexpensive vitamin regimen may help stem the surge in cases, which the World Health Organization predicted would more than triple from

36 million worldwide in 2010 to 115 million in 2050, as well as the cost, estimated at \$604 billion in 2010 by Alzheimer's Disease International.

Vitamin Market

Vitamin makers and retailers such as Pfizer's consumer health-care unit and GNC Holdings Inc. in the U.S. and Reckitt Benckiser Group Plc and Holland & Barrett Holding Ltd. in Europe stand to benefit. The Nutrition Business Journal estimates the global market for vitamins, minerals and supplements was \$30 billion in 2012 and forecasts sales will grow 3.6 percent by 2017.

In the PNAS study, researchers tracked 156 people ages 70 and older who had mild memory loss and high levels of a protein previously linked to dementia. Among people with elevated homocysteine, the study found that the amount of gray matter declined 5.2 percent in those taking a placebo, compared with 0.6 percent in those who took the vitamin cocktail. The supplements cost about 30 cents a day in pharmacies and health- food stores.

First Look

"It's the first and only disease-modifying treatment that's worked," said A. David Smith, professor emeritus of pharmacology at Oxford University in England and senior author of the study. "We have proved the concept that you can modify the disease."

The U.S. Food and Drug Administration hasn't cleared new drugs for memory loss conditions in a decade. Approved medicines such as Eisai Co.'s Aricept ease symptoms without slowing or curing dementia. A joint U.S.-European Union task force in 2011 found that all disease-modifying treatments for Alzheimer's in the previous decade failed late-stage trials "despite enormous financial and scientific efforts."

Since then, at least four more experimental treatments have failed. New York-based Bristol-Myers dropped development of avagacestat in December after data showed the therapy wasn't effective enough to move into the final stage of testing.

Solanezumab, from Indianapolis-based Lilly, failed to meet the main goal of two large studies last year, though the company plans to conduct further research.

Bapineuzumab from Pfizer, Johnson & Johnson and Elan Corp. failed to improve patients' memory or thinking, according to test results released in August. This month, Baxter International Inc. said Gammagard, which is used to help patients with immune disorders, didn't help Alzheimer's patients in a late-stage study.

Meanwhile, scientists are exploring the use of experimental drugs to prevent Alzheimer's. Independent trials will begin this year and run for three to five years.

Shrinking Brains

Older people's brains shrink about 0.5 percent a year from the age of 60, and faster in people with vitamin B12 deficiency, mild cognitive impairment or Alzheimer's disease, Smith said. If that pace can be significantly slowed before full-blown Alzheimer's develops, it may delay the disease's progression so that older people can enjoy better lives until they die from another cause.

"If you delay the onset by five years, you can halve the number of people dying from it," says Jess Smith, a research communications officer at the Alzheimer's Society, a U.K. charity. She isn't related to A. David Smith.

The Oxford group studied people in the Oxford, England, area who had mild cognitive impairment, also known as MCI, or some memory loss. One in six people over 70 have MCI and about half of those develop dementia within five years, A. David Smith said. Alzheimer's accounts for 50 percent to 80 percent of all dementias, according to the Alzheimer's Association.

Vitamin Cocktail

Study volunteers were given either a placebo or 0.5 milligrams of vitamin B12, 20 milligrams of vitamin B6 and 0.8 milligrams of folic acid. Their brains were scanned using magnetic-resonance imaging and blood levels of the protein homocysteine were measured at the start of the trial and two years later. The MRI scans compared how much gray matter was lost in brain regions most affected by Alzheimer's disease.

"It's a big effect, much bigger than we would have dreamt of," A. David Smith said. "I find the specificity of this staggering. We never dreamt it would be so specific."

Brain Atrophy

The research reinforces previous findings that supplements slowed brain atrophy and cognitive decline in the group.

Smith and his colleagues at Oxford reported in 2010 that the atrophy rate in patients' whole brains was reduced about 30 percent in those taking the vitamins and 53 percent in those on the vitamins who also had elevated homocysteine. They published study results in 2012 of memory tests that found people on the treatment who had high homocysteine were 69 percent likelier to correctly remember a list of 12 words.

The studies, known as Vitacog, were funded by seven charities and government agencies and vitamin maker Meda AB of Solna, Sweden. Smith is an inventor on three patents held by Oxford University for B vitamin formulations to treat Alzheimer's disease or MCI.

Vitamin B12 is found in liver, fish and milk and folic acid in fruit and vegetables. Deficiency of folate and B vitamins is already linked to dementia. Researchers such as Smith are studying whether less-than-optimal levels of B vitamins and folic acid contribute to its development.

Possible Benefit

"If you have somebody who has outright Alzheimer's disease, this isn't really going to help them much," said Joshua Miller, a professor in the department of nutritional sciences at Rutgers University in New Brunswick, New Jersey.

"If you can catch them at an earlier level, they may be able to benefit from it but only if you have elevated homocysteine."

A U.S. study published in 2008 found that people who had moderate or severe Alzheimer's didn't benefit from the supplements. There's no evidence that B vitamins enhance cognitive function in healthy people, A. David Smith said.

Doctors in Sweden began measuring homocysteine in people who report declining memory about two years ago, said Lökk at Karolinska. Swedish patients with high homocysteine are given folic acid and B vitamins, even if they aren't deficient.

Taking Offensive

"We think the increased homocysteine level could be deleterious to the brain," Lökk said. "We wanted to be on the offensive in diagnosing and treating patients. In our opinion, it is harmless and cheap."

Vitamin B12 is probably the key to slowing the brain's shrinkage and cognitive decline, Miller said. The FDA said in

1998 that folic acid had to be added to breads, cereals and other products that use enriched flour, to reduce neural tube defects such as spina bifida in newborns. A study by Miller and his colleagues in people of Mexican and South and Central American ancestry age 60 and older in Sacramento, California, the following year found their homocysteine was still high and that very few had low folate. Europe doesn't require fortification of flour and breads.

Other studies have suggested that folic acid stimulates the growth of existing cancer cells. The data aren't conclusive, so people at risk of cancer should avoid extra folic acid, Lökk said. This could include men older than 70 who may have undetected prostate cancer, A. David Smith said.

"We're not suggesting everyone over 60 take this; we're suggesting it should be targeted to people over 70 with high homocysteine and memory problems," he said.

Too Early

It's too early to put everyone on B vitamins, said Jess Smith of the Alzheimer's Society.

"The evidence for supplementing is just not there yet," she said. "We need bigger studies and more evidence that looks at what homocysteine is doing and what is actually going on in the brain."

A. David Smith agrees. He plans a study of B vitamins in 1,200 people over 70 with MCI and elevated homocysteine. He needs 6 million pounds (\$9.1 million) to pay for it. Miller plans another large study and wants to see if folic acid in flour in the U.S. leads to different results there. Meanwhile, the lack of blockbuster-drug potential presents funding hurdles.

"The pharmaceutical companies aren't going to make any money on this and the supplement companies aren't going to have enough money to do it," Miller said. "This would have to be government-funded. I'm just not sure the climate is right for it now."

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