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November 16, 2011 (San Diego, California) There is growing evidence pointing to the memory-enhancing effect of a nutritional intervention (*Souvenaid*, NV Nutricia), at least in the early stages of dementia.

The results of a clinical trial called Souvenir II, released here at the 4th International Conference on Clinical Trials in Alzheimer's Disease (CTAD), suggest that daily intake of Souvenaid improves memory in drug-naive patients with mild Alzheimer's disease (AD) up to 24 weeks.

However, the study only included results related to memory function, with no electroencephalogram (EEG) confirmation of brain changes. Further, other research released at the meeting seemed to indicate that the medical food does not work in patients with more severe AD who are already taking medications.

"I would be cautious at this point," said lead researcher Philip Scheltens, MD, PhD, professor of cognitive neurology and director, Alzheimer Center, VU University Medical Center, Amsterdam, the Netherlands. "I think we need some further studies. We need to see the effects in the brain."

Patented Combination

Souvenaid contains a patented combination of vitamins and other nutrients (*Fortasyn Connect*, NV Nutricia) designed to promote the synthesis of new brain synapses. Its 3 phosphatide precursors (omega-3 polyunsaturated fatty acids, nucleotide uridine, and choline) synergistically increase levels of the phosphatide molecules in the brain that make up most synaptic membranes. Animal and in vitro research shows that these nutrients cause dendritic sprouting, which also leads to increased synapse production.

The randomized, controlled, double-blind Souvenir II trial included 259 patients with mild AD (mini-mental state examination scores ≥ 20; mean, 25.0) at 27 centers in 6 European countries who were randomly assigned to drink 125 mL Souvenaid or an iso-caloric control drink once daily.

Researchers evaluated memory performance at baseline, 12 weeks, and 24 weeks. They tested immediate recall, delayed recall, and recognition performance, using composite Neuropsychological Test Battery (NTB) scores. Investigators also assessed executive function and other subcategories of the NTB. They recorded EEG data in 220 patients and magnetoencephalogram data in a small subset of patients.

At 24 weeks, Souvenaid significantly improved memory performance on composite NTB scores compared with the control product "We used *z*-scores to test the difference between control and active group, and the difference was 2.2, and this was statistically significant over the whole trajectory from 0 to 24 weeks," said Dr. Scheltens.

EEG Results to Come

Detailed analyses of EEG data, which may help explain the effect of Souvenaid on functional connectivity, are still ongoing. "We haven't yet shown any marker of biological efficacy," said Dr. Scheltens. He added that these results "will be really important to show," and should be available early next year.

Of the 259 randomized participants, 238 (91.9%) completed the study. The compliance rate was 97%, which "reflects the fact that people actually liked it," said Dr. Scheltens. "With the amount of fish that's in it, you would suspect it would smell like fish, but it doesn't," he said.

The "milky" drink comes in strawberry and vanilla flavors, but Dr. Scheltens does not like to refer to it as a yogurt drink, milkshake, or other product readily available in supermarkets, as because it is a "medical food," it would only be available on prescription.

Most patients in the study gained some weight during the 6-month trial, and they all said they

felt better, commented Dr. Scheltens.

The study was funded by Nutricia Advanced Medical Nutrition, a subsidiary of Danone.

Results of a follow up, open-label study of this patient population will be presented early next year, said Dr. Scheltens.

S-Connect Trial

Although the Souvenir II trial was positive, another randomized controlled trial presented at the CTAD meeting was not.

The S-Connect trial investigated the 24-week effect of daily Souvenaid or a control product on cognitive performance in 527 patients with AD that was more severe than seen in Souvenir II (mean mini-mental state examination score, 19.4). The ppatients at numerous US centers were receiving stable doses of AD medications, including cholinesterase inhibitors and/or memantine.

This study found no difference between the groups, using the Alzheimer's Disease Assessment Scale cognitive subsccale.

These results suggest that that the synaptic improvements resulting from the nutrient-rich drink "can only occur in the earliest stages," according to Dr. Scheltens.

An abstract detailing a different study LipiDiDiet, a 24-month, randomized, contrrolled double-blind study in 300 elderly patients with prodromal AD in Finland, the Netherlands, and Germany was also released at the meeting. However, results from this "completely independent" European Union funded study are not expected until 2014, said Dr. Scheltens.

Dr. Scheltens and colleagues are now looking at possibly testing the product in elderly patients who have subjective memory complains, or at an even earlier stage of AD.

These trials are the most recent research on Souvenaid. Preclinical studies had shown that the nutrients included in this medical food might stimulate the formation of synapses.

This was followed by a proof of concept study called Souvenir I, involving 225 patients and showing that the product, taken once a day for 12 weeks, improved scores on standardized memory tests: 40% of patients randomly assigned to receive Souvenaid experienced improvements in verbal memory vs 25% of participants taking a control drink.

Still Not Convinced

Approached for comment, William Thies, PhD, chief medical and scientific officer, Alzheimer's Association, said the most recent study results are still not convincing. He is waiting for larger and longer-term studies that rely on "rich measurements" of biomarkers and clinical measures, rather than just memory tests.

"The real question is, if you give this product to someone for 18 months, is he or she functionally different than the person not exposed to it who has the same kind of disease state? Until you see that kind of head-to-head comparison, it's impossible to make a judgment on this kind of product."

That said, Dr. Thies believes the product does make some biological sense. "There's a reasonable body of solid basic science evidence that says that the nutrients that are in this drink are critical to normal synaptic function."

However, he added, there is a lot of solid basic science that does not transfer into effective outcomes in a clinical trial. "So does it make sense? Yes. Is that compelling? No."

There are still regulatory concerns to consider, as the US Food and Drug Administration regulates medical foods differently than drugs, he said. He added that it might be "logical" to move the product into the mild cognitive impairment category because early indications are that it has very low toxicity. "That would make it attractive on a sort of prevention basis."

The good news is that the manufacturer seems to be committed to developing appropriate support for the product in terms of rigorous research, "as opposed to simply trying to grab market share," said Dr. Thies. "If they stay on that track, we'll actually be able to make a final decision on it."

Jeffrey Cummings, MD, director, Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, Nevada, agreed that the trials are thorough.

"The Souvenaid program is a model for the rigorous testing of a medical food," he told *Medscape Medical News* in an email. "The type of assessments being pursued will provide insights into the impact of treatment on patient function, as well as the mechanisms of dementia and cognitive aging."

The study was supported by Nutricia Advanced Medical Nutrition, a subsidiary of Danone. Dr. Scheltens has disclosed no relevant financial relationships.

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