

# Valproate Does Not Delay Psychosis in AD

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VIENNA — Valproate treatment over 2 years does nothing to delay the onset of agitation or psychosis in patients with Alzheimer's disease, and patients taking the anticonvulsant showed significantly more brain volume loss on MRI at year 1 than did those taking placebo.

But because the changes in brain volume did not correlate with any clinical differences between the groups, it's difficult to know just what to make of the observed volume loss, Dr. Pierre Tariot said at the International Conference on Alzheimer's Disease.

"Interpretation of these results really isn't possible at this juncture," said Dr. Tariot of the Banner Alzheimer's Institute, Phoenix, in an interview. "It could theoretically represent damage to the brain, but that seems unlikely due to the absence of correlation with clinical decline that is seen in natural history studies. There are case reports of 'pseudotrophy' associated with valproate use, which may be relevant here."



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We have an ongoing analysis, and the full details will be presented at a later time."

The trial randomized 313 patients with mild-moderate Alzheimer's disease who lacked agitation or psychosis at baseline to either placebo or an extended-release form of divalproex sodium (Depakote ER) at a dose of 10-12 mg/kg per day. The primary outcome was time until the emergence of agitation and/or psychosis. The symptoms had to last at least 2 weeks, and had to be clinically significant in the opinion of the site physician.

Secondary end points included changes in the Neuropsychiatric Inventory (NPI) score the Cohen-Mansfield Agitation Inventory (CMAI), Mini-Mental State Exam (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) domain, and the Alzheimer's Disease Cooperative Study activities of daily living (ADCS-ADL) domain. MRI of the brain was performed on a subset of 90 patients at baseline and 1 year.

The patients' mean age was 75 years; their mean MMSE at baseline was 17 and the mean NPI score was

3. Most of the patients (70%) were positive for the high-risk apolipoprotein E e4 (ApoE e4) allele.

There were no between-group differences in time to agitation or psychosis. In fact, although the study assumed an incidence of 50% by the end of the trial, only 17% of the entire cohort developed either of these symptoms, said Dr. Tariot, who received consulting fees and research funding from Abbott Laboratories, which manufactures Depakote ER. Abbott supplied the drugs for the trial and funded the MRI portion of the trial.

There also were no between-group differences in any of the secondary end points, confirming that valproate confers no clinically discernible neuroprotective benefit. Patients taking placebo had a slightly better score on the ADCS-ADL at 24 months, Dr. Tariot said, but that difference did not reach significance after adjustment for multiple comparisons.

Consistent with known effects of the medication, patients taking valproate had significantly more central nervous system and gastrointestinal side effects. Patients in the active treatment group also experienced mild decreases in neutrophils and platelets.

The conference was sponsored by the Alzheimer's Association. ■

## Dementia Continues to Rise Among Even the Oldest Old

VIENNA — Dementia does not appear to spare the oldest old, contrary to findings of prior studies suggesting that the incidence tapers off after age 85.

Studies presented at the International Conference on Alzheimer's Disease suggest that dementia rates continue their linear increase even as people approach 100, with a doubling of incidence every 5 years.

"We believe there is now convincing evidence that, unfortunately, this disorder does not go down with age," Dr. Claudia H. Kawas said at the meeting, which was sponsored by the Alzheimer's Association. The findings are especially important, given that the population of those 90 years and older will increase 10-fold by the middle of this century, said Dr. Kawas, the Al and Trish Nichols Chair in Clinical Neuroscience at the University of California, Irvine. "As more individuals live to these extreme ages, dementia in the oldest old could become an epidemic with enormous public health impact."

Dr. Kawas and her colleagues presented data from The 90+ Study, a population-based study established in the early 1980s in a California retirement community. Out of the original 14,000 enrolled, her sub-study comprised 330 who were aged 90 years or older at the beginning of 2003, available for in-person interviews, and nondemented.

At baseline, the participants ranged in age from 90-108 years; the mean age was 94 years. Most (54%) were still living alone; 29% were living at home with a relative; and 17% were in a group facility or nursing home. Seventy percent were women.

Assessments occurred every 6 months through Jan. 1, 2008, and included a neurologic exam, neuropsychiatric testing, in-

formative questionnaires, and medical records. The mean follow-up time was a little longer than 2 years; almost 400 person-years of follow-up data were collected overall, with 50 person-years of data on those who were 100 years or older. "As far as I know, this is the largest study of dementia in centenarians ever done," Dr. Kawas said.

By the end of the study, 140 cases of dementia had developed: 49 in those aged 90-94; 71 in those aged 95-99; and 20 in those aged 100 and older. The rate was 18% for both men and women.

The investigators found that the risk of dementia doubled every 5 years, from 10% for the 90- to 94-year-olds to 20% for the 95- to 99-year-olds, and 41% for those 100 and older.

An Italian study that examined dementia rates in people 80 years and older came to similar conclusions. "Although not increasing exponentially, the overall prevalence and incidence rates of dementia continue to rise in very old age," Dr. Ugo Lucca of Istituto di Ricerche Farmacologiche "Mario Negri," Milan, wrote in his poster.

Dr. Lucca and his colleagues examined the rate of new-onset dementia in subjects older than 80 years, who were followed for a mean of 3 years. The Monzino 80-plus Study gathered baseline information on 2,138 residents of eight municipalities in Varese province, Italy. Most of the assessment information was gathered at a first visit that occurred at the subjects' residence.

The assessment included neuropsychiatric testing, functional status, and mood and behavioral assessments. Those who screened positive for dementia received additional testing to make a more specific determination of their cognitive status. ■

## Pesticide Exposure Linked to Increased Dementia Risk

VIENNA — Pesticide exposure might increase the risk of later dementia by as much as 70%.

"Exposure to pesticides may have long-term damaging effects on the nervous system that contribute to the development of Alzheimer's or other dementias," Kathleen M. Hayden, Ph.D., said at the International Conference on Alzheimer's Disease. "We need more research to fully characterize the increased risks associated with different types of pesticides, and the duration of their use."

Dr. Hayden of Duke University Medical Center, Durham, N.C., based her study on data from the Cache County Study of Memory, Health, and Aging. The ongoing study began in 1995, and includes 5,092 subjects, who are assessed every 3 years. The study participants were given a questionnaire that focused on pesticide exposure.

The study population was a good one for examining the impact of pesticides because, Dr. Hayden said, the subjects live in a rural area, the economy of which relies heavily on growing wheat, soybeans, apples, corn, and hay.

Dr. Hayden and her colleagues assessed the risk of new-onset dementia and Alzheimer's disease in 4,012 subjects who were free of dementia at baseline. Her logistic regression analysis was based on 6 years of follow-up, and controlled for age, sex, education, and apolipoprotein-E status.

At baseline, the subjects were a mean of 75 years old. Pesticide exposure had occurred in 19% (743). The exposed group was primarily male (89%). After 6 years of follow-up, there were 412 new cases of dementia; 85 of these subjects (21%) re-



More than 18,000 pesticides are licensed for use in the U.S.

ported some degree of pesticide exposure on their baseline assessment.

The analysis found consistent significant relationships between new-onset dementia and exposure to both organophosphates and organochlorines. Any pesticide exposure increased the risk of dementia and Alzheimer's disease by 56%. Exposure to organophosphate compounds increased the risk of dementia by 36% and Alzheimer's by 59%. Exposure to organochlorines increased the risk of dementia by 60% and Alzheimer's by 70%.

The study did not take into account duration or extent of exposure, and does not prove a causal link between pesticides and dementia, Dr. Hayden cautioned. But it does suggest that more study is necessary. "Some pesticides do alter the level of neurotransmitters, and their use has increased drastically in the past 50 years," she said. "According to the Environmental Protection Agency, there are more than 18,000 pesticides licensed for use in the U.S., and each year, more than 2 million pounds are applied to our crops, parks, homes, and forests." ■