# CATIE-AD Data Presented: Conclusions to Come

## *Investigators are comparing drug treatments for psychosis and agitation in Alzheimer's patients.*

BY DOUG BRUNK
*San Diego Bureau*

SAN DIEGO — Phase I results from the Clinical Antipsychotic Trial of International Effectiveness–Alzheimer's Disease (CATIE-AD) unveiled for the first time at the annual meeting of the American Association for Geriatric Psychiatry are so new that the presenting investigators emphasized that they're still trying to make sense of it all.

"The data we're presenting today are preliminary. We've barely gotten to understand them ourselves," said Lon Schneider, M.D., professor of psychiatry, neurology, and gerontology at the University of Southern California, Los Angeles, who is one of the study's lead investigators. "We first saw them Feb. 4. The data should be considered preliminary until the full report is evaluated by peer review for scientific validity and clinical importance. I hope you'll keep that in mind."

The main goal of the trial is to compare the efficacy and effectiveness of risperidone, olanzapine, and quetiapine, and examine treatment algorithms over the course of 36 weeks in treating psychosis and severe agitation in community-dwelling patients with Alzheimer's disease. The trial design has been previously described in medical literature (Am. J. Geriatr. Psychiatry 2001;9:346-60).

"This is not your pharmaceutical company's clinical trial," Dr. Schneider remarked. "This is not a simple randomization of drug or placebo and 10 weeks later declare victory for one or another. It's also not FDA's idea of an efficacy trial. The FDA needs trials from which they can generate labeling about a drug's use. We're trying to generate information to inform clinicians on the subtleties of using medication."

Investigators enrolled 421 Alzheimer's disease patients with a median age of 78 years in the trial from 10 private clinic sites, 25 university sites, and 2 Veterans Affairs sites nationwide, reported Pierre Tariot, M.D., the study's other lead investigator. More than half (56%) were female, 79% were white, and 18% were African American. About one-quarter did not complete high school and 34% had a high school education or GED.

Nearly 60% were married or had been married at some point, 73% lived in their own homes, 16% lived in the home of a family member, and about 10% lived in an assisted living facility.

The patients' average Mini-Mental State Exam score was 15 and the Brief Psychiatric Rating Scale (BPRS) for conceptual disorganization, suspiciousness, or hallucinatory behavior showed moderately severe psychopathology with a fairly wide range.

In terms of functional independence, about three-quarters were receiving care equivalent to nursing home care.

The trial consisted of three phases. In phase I, all 421 patients were randomized to receive one of the three atypical antipsychotics or placebo.

"At any time if a patient was not responding, they could continue the medication, increase the dose, or order a switch to a new medication," Dr. Schneider explained. "That was done in double-blind fashion to a medication not used previously."

Of the 421 patients, only 77 remained in phase I.

Of the remaining 344 patients, 253 moved to phase II, which started when the patient was randomized in a double-blind fashion to a second medication. If the second medication was continued, the patients remained in this phase.

"At any time if a physician, patient, or caregiver thought it was in the best interest of the patient, the patient could be pulled out into a open choice phase of the trial where the physician would treat as he might in the community," Dr. Schneider said.

By week 4 of the trial, about one-quarter of patients discontinued their medication in phase I for "all-cause" reasons such as inadequate treatment response, study drug not sufficiently optimal, symptoms worse, unacceptable side effects, study drug no longer needed, patient or caregiver decision, or death.

By week 8, almost half of study participants had discontinued their phase I medication, and by week 12, almost three-quarters had discontinued phase I. "People were leaving the initial phase very rapidly, [but] we have not done analysis of these data adjusted for dose or length of drug exposure," said Dr. Tariot, professor of psychiatry, medicine, neurology, and aging and developmental biology at the University of Rochester (N.Y.).

"That's critical in understanding the full meaning of these data. It's probably premature to say this, but what I'm thinking about in my own practice is whether I should treat longer with the first agent I start on," Dr. Tariot said at the meeting. "How long do we need to treat somebody to see an effect?"

Dr. Schneider noted that there are "multiple reasons" why a study investigator could have discontinued treatment in phase I. "One main reason is that they were not being required to keep the patient in the study for 10 weeks," he said.

"Other reasons have to do with patients or caregivers discontinuing the trial, period. Lastly, switching medication at 2 and 4 weeks is congruent with what experts say when they're asked, 'How long do you keep a dementia patient with psychosis on an antipsychotic?' On average, it's 2-4 weeks."

The investigators did not report any phase I clinical outcomes. Although they did not draw firm conclusions given the freshness of the data, Dr. Tariot did report that, collectively, active treatment with one of the three antipsychotics was "different" than placebo. Specifically, 39% of phase I patients who took olanzapine discontinued the drug for lack of efficacy, compared with 53% of patients who took quetiapine, 44% of patients who took risperidone, and 70% who took placebo.

In addition, 24% of phase I patients who took olanzapine discontinued the drug for reasons of intolerance, adverse events, or death, compared with 16% of patients who took quetiapine, 18% of patients who took risperidone, and 5% who took placebo.

More data from the trial are expected to be released this spring. The NIMH funded the trial and the pharmaceutical companies that manufacture the antipsychotics supplied drugs for the study. ■

# Onset of Hallucinations Varies Between Dementia Types

BY DAMIAN McNAMARA
*Miami Bureau*

MIAMI BEACH — Onset time of visual hallucinations can help clinicians distinguish between dementia with Lewy bodies and Alzheimer's disease, according to a study presented at the annual meeting of the American Academy of Neurology.

Patients with dementia with Lewy bodies (DLB) or Alzheimer's disease (AD) can experience visual hallucinations, visual misperceptions, elementary auditory hallucinations, and delusions. However, little is known about how these features differ between groups in incidence or character, said Tanis J. Ferman, Ph.D.

"Is there a way to distinguish between psychoses in these two groups clinically?" asked Dr. Ferman, a psychologist at the Mayo Clinic Jacksonville (Fla.).

To answer that question, Dr. Ferman and her associates compared 108 people with DLB with 154 Alzheimer's patients. They administered the Mayo Fluctuations Questionnaire and the Neuropsychiatric Inventory to informants for each participant. A consensus diagnosis came from a clinical interview, neurologic exam, activities of daily living based on Record of Independent Living results, and a neuropsychiatric evaluation.

"For the most part, patients had mild to mild-to-moderate dementia," Dr. Ferman said. Mean scores on the Dementia Rating Scale were 114 for the DLB group and 111 for the AD group.

About one-third of each group had ocular disease such as cataracts or macular degeneration: 35.6% in the DLB group and 31.5% in the Alzheimer's group. The groups' mean ages were similar (73 and 74 years), but the DLB group had more males (69% vs. 42%).

**Visual hallucination onset relative to the estimated onset of dementia was 1.7 years in dementia with Lewy bodies and 6 years in Alzheimer's disease.**

Patients with DLB had a higher frequency of psychotic features than patients with AD. "This was not surprising—it's part of the diagnostic criteria," she said. A total of 63% of the DLB group experienced visual hallucinations, compared with 8% of the AD group.

The onset of visual hallucinations relative to the estimated onset of dementia was 1.7 years in the DLB group and 6 years in the AD group, making it "an absolute discriminator," Dr. Ferman said in reply to a question from a meeting attendee. "In another study, we found that 4 years was a good cutoff for when they occur in AD vs. DLB, and that was the case in this study."

Visual hallucination type, patient insight, and degree of distress did not differ significantly between groups. There were no differences in beliefs between groups regarding danger to self, stealing, abandonment, TV figures being real, spouses or others being someone other than who they claimed to be, or the idea that their house was not their home, she noted.

People and animals were the most common hallucination in both groups (91%). Other common hallucinations involved insects (22%) and objects (14%).

Patients with DLB, however, were more likely to see specific recurrent images (70%) than were patients with AD (45%). "One DLB patient, for example, repeatedly saw children sitting on her countertops," Dr. Ferman said.

In addition, 32% of DLB participants were likely to experience visual hallucinations when drowsy, versus 1% of AD participants. In contrast, 57% of DLB and 90% of AD participants had visual hallucinations when fully awake. "This finding could be secondary to the excessive daytime sleepiness characteristic of DLB patients," she said.

The researchers observed additional differences. DLB participants were more likely to have visual misperceptions, such as mistaking a lamp for a person, and elementary auditory hallucinations like hearing a car drive up.

In DLB, delusions and auditory hallucinations tended to occur only in those with visual hallucinations. With Alzheimer's patients, delusions, visual hallucinations, and auditory hallucinations occurred independent of each other, Dr. Ferman said.

"DLB patients are more likely to report the images, ignore them, or touch them, which is never reported by AD patients," she said. ■