Donepezil Therapy in Alzheimer’s Disease

Speaker: Jeffrey Cummings, MD, Professor of Neurology, Department of Neurology, University of California, Los Angeles, School of Medicine, Los Angeles, California.

Therapy with donepezil (Aricept®, Pfizer) has been found to significantly improve behavioral symptoms in patients with mild-to-moderate Alzheimer’s disease (AD). A 20-week study was designed primarily to compare the efficacy and safety of the antidepressant sertraline (Zoloft®, Pfizer) with placebo in patients already receiving donepezil therapy. The patients were not depressed but were exhibiting substantial behavioral symptoms, with Neuropsychiatric Inventory (NPI) total scores above 5 at screening and NPI severity scores in at least two domains.

The patients received open-label donepezil 5 mg daily for four weeks, followed by four weeks of donepezil 10 mg daily in an open-label fashion. At the eighth week, patients receiving donepezil were randomly assigned to receive placebo or sertraline 25 to 200 mg/day, in addition to the open-label donepezil 10 mg/day.

The primary efficacy variables were:

- 10-item and 12-item NPI scores.
- Clinician’s Global Impression Scale for Improvement (CGI–I) and Severity (CGI–S) subscales.

The secondary efficacy measures included:

- behavioral symptoms, as assessed by the Behavioral Pathology in Alzheimer’s Disease Rating Scale (BEHAVE–AD) and the Cohen–Mansfield Agitation Inventory–Community (CMAI–C).
- cognition, as assessed by the Alzheimer’s Disease Assessment Scale–Cognition subscale (ADAS–Cog) and the Mini-Mental State Examination (MMSE).

The randomized placebo cohort included 121 patients who received donepezil monotherapy only during the 20-week study period. After 20 weeks of monotherapy, statistically significant improvements from baseline were observed in the NPI-12 scores, (of –8.2 and a relative change of 27.6%) and in NPI-10 scores (of –7.2 and a relative change of 28.7%). Statistically significant differences in both the CGI–S and CGI–I measures were observed from baseline to the end of the 20 weeks.

The BEHAVE–AD scores, as well as two items on the CMAI–C, also improved significantly. Cognition, as measured by the MMSE and ADAS–Cog, was maintained at or above baseline values at the end of the study.

Overall, donepezil was well tolerated. Adverse drug events (ADEs) led to discontinuation in 10.8% of patients receiving donepezil monotherapy. The most common side effects involved the digestive and nervous systems.

Memantine Monotherapy in Mild-to-Moderate Alzheimer’s Disease

Speaker: Steven G. Potkin, MD, Professor of Psychiatry and Human Behavior, and Director of the Brain Imaging Center, University of California at Irvine, Irvine, California.

Memantine (Namenda™, Forest) monotherapy has been shown to be effective and safe for the treatment of mild-to-moderate AD and superior in efficacy to placebo on measures of cognition, global status, and behavior.

A total of 403 patients were enrolled into a randomized, double-blind, parallel-arm, placebo-controlled phase III clinical trial at 42 U.S. centers. These patients, all of whom had mild-to-moderate AD, were randomly assigned to receive memantine 10 mg twice daily or placebo for six months. The two primary outcome measures were the ADAS–Cog and the Clinician’s Interview-Based Impression of Change–Plus version (CIBIC–Plus). Secondary outcomes included:

- daily functioning, as assessed by the Alzheimer’s Disease Cooperative Study–Activities of Daily Living Inventory (ADCS–ADL), with 23 items.
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- behavior, as assessed by the 12-item NPI.
- safety, as measured by the incidence of ADEs and changes in laboratory parameters, electrocardiograms, and vital signs.

Overall, 394 patients were included in the intent-to-treat (ITT) population. As assessed by the ADAS–Cog, patients receiving memantine monotherapy maintained their cognitive abilities above baseline values for the entire 24 weeks of the study. In contrast, patients receiving placebo exhibited a progressive decline during the study, and the difference between the two treatment groups was statistically significant.

Patients who took memantine had significantly better global status than did those taking placebo, as measured by the CIBIC–Plus.

A pilot study of positron emission tomography (PET) to evaluate memantine’s action on brain metabolism in a subset of 10 patients from the phase III trial demonstrated a statistically significant increase in glucose metabolism in several regions of the brain associated with language and attention in these patients. In contrast, the placebo patients showed metabolic declines in these same regions.

With regard to safety, the incidence of treatment-related ADEs was similar in the memantine and placebo patients. Somnolence was reported in more than 25% of patients taking memantine than in those taking placebo. By the same criteria, more than 25% of patients in the placebo group reported upper respiratory infection and depression.

Botulinum Toxin Injections in Musician’s Dystonia
Speaker: Stephen U. Schuele, MD, Consulting Neurologist, Department of Neurology and Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

Results of an outcome survey of musicians with focal task-specific dystonia (FTSD) treated with injected botulinum toxin A (Botox®, Allergan) suggest that this approach can offer long-term benefit, independent of the musical instrument used.

Because FTSD in musicians often leads to the end of their careers, a study was performed to evaluate the initial and long-term benefits of the toxin. Between 1995 and 2002, musicians with FTSD at the Institute of Music Physiology and Musicians Medicine at the University of Music and Drama in Hanover, Germany, received botulinum toxin A injections. The initial average injected dose was 51.2 units, and the final dose was 40.1 units. A minimum of 2.2 and a maximum of 3.4 injections were administered.

Using telephones and a chart review, investigators surveyed 88 of 225 musicians with FTSD after treatment. Of the 88 musicians, 84 responded to the survey. Assessments included a rating of severity; an estimate of playing ability before and after injection, in percentages; and a rating of treatment response, from worse to none to mild to moderate to marked to remission. Initially, the investigators observed muscle involvement while the musicians were playing and then reported their findings in their charts.

A total of 74 men and 10 women participated in the study group. The group included 25 woodwind players, 25 guitarists, 20 keyboard players, 12 bowed-string musicians, and two brass instrumentalists. Their mean age was 45.9 years, and the mean duration of symptoms was 10.6 years.

As a group, the musicians subjectively rated their playing ability as significantly improved following botulinum toxin A treatment. In a self-rating of treatment response, 69% of the musicians indicated improvement and 45% rated the benefit as sufficient to improve their performance. Twenty-four musicians received ongoing treatment for an average of 36 months; another six patients showed long-lasting benefits without the need for further injections.

Three patients with embouchure dystonia (of the lips and facial muscles) had a poor response. Overall, 30 of the 84 musicians either experienced persisting improvement or continued to benefit from ongoing injections for an average of three years and up to six years.

Topiramate in Newly Diagnosed Epilepsy
Speaker: Elinor Ben-Menachem, MD, PhD, Professor, Department of Neurosciences, Sahlgrenska Academy at Göteborg University, and Director, Clinical Pharmacology and Epilepsy, Department of Clinical Neurosciences, Sahlgrenska University Hospital, Göteborg, Sweden.

Findings from two studies indicate that topiramate (Topamax®, Johnson & Johnson) 100 mg/day is an effective dose in patients with newly diagnosed epilepsy; is at least as effective as the traditional first-line agents carbamazepine (Tegretol®, Novartis) and valproate (Depacon®, Abbott) for previously untreated patients with epilepsy; and is better tolerated.

A dose-controlled study enrolled 470 adults and children with epilepsy that was characterized by partial-onset or primary generalized tonic–clonic seizures. The patients were randomly assigned to take topiramate 50 mg or topiramate 400 mg daily, titrated at 50 mg from the first week to 400 mg at the sixth week. The significant between-group difference in time until the first seizure favoring the higher dose confirmed topiramate’s efficacy as monotherapy. Furthermore, the significant difference between 100 mg/day and 25 mg/day during the dose-escalation phase identified topiramate 100 mg/day as an effective dose and an appropriate target dose for initial therapy in untreated epilepsy.

In a comparative monotherapy study, 613 adults and children with epilepsy, with no seizure type excluded, were randomly assigned to receive the following doses:

- topiramate 100 mg/day (median duration, 544 days)
- topiramate 200 mg/day (median duration, 378 days)
- carbamazepine 600 mg/day (median duration, 434 days)
- valproate 1,250 mg/day (median duration, 304 days)

Double-blind treatment continued until six months after the last patient was assigned to a therapy regimen or until a decision was made to change therapy by altering the dose or medication or by discontinuing the study medication entirely. The primary endpoint was the time to exit from the study (when a patient left). The secondary endpoints were (1) freedom from seizures during the last six months of the study and (2) the exit time.
There was no significant difference in efficacy between topiramate 100 mg/day and 200 mg/day, as measured by the time until the first seizure. At most time points, however, the cumulative number of study exits was lower with topiramate than with carbamazepine or valproate. Median retention times were longer with topiramate than with either of the comparator drugs. Topiramate 100 mg/day was better tolerated than topiramate 200 mg/day, carbamazepine 600 mg/day, or valproate 1,250 mg/day. Patient discontinuation rates were 19% with topiramate 100 mg/day, 28% with topiramate 200 mg/day, 25% with carbamazepine 600 mg/day, and 23% with valproate 1,250 mg/day.

Zolmitriptan Nasal Spray for Long-Term Treatment of Migraine
Speaker: Andrew Dowson, MD, Director of the Headache Clinic, Kings College Hospital, London, United Kingdom.

Six-month follow-up results from a large-scale phase III clinical study demonstrate that zolmitriptan nasal spray (Zomig®, AstraZeneca) 5 mg is safe, well tolerated, and reliably effective when used for the long-term acute treatment of multiple migraine attacks. High pain-free rates have been maintained over time.

To assess the spray’s long-term safety and tolerability as well as its efficacy at 5 mg, investigators enrolled 538 patients aged 18 to 65 years of age with a diagnosis of migraine, as defined by the International Headache Society. This open-label, non-comparative study was conducted in 52 centers in Canada, Finland, Germany, South Africa, Sweden, and the United Kingdom. The patients had endured at least three migraine headaches per month in the previous three months.

Patients with headache of any baseline pain intensity—mild, moderate, or severe—were given zolmitriptan nasal spray and a second dose of trial medication; patients with persistent or recurrent headache could take an “escape” medication at more than two hours after the initial dose.

The study population of 538 patients had treated themselves for more than one migraine attack, for a total of 20,717 treated attacks. There was a high rate of treated attacks; 43.9% of patients treated a mean of three or more attacks per month for at least six months. Over the course of the 20,717 attacks treated, ADEs were reported in 85.3% of patients; however, patients reported only 32.8% of the attacks.

The most commonly reported ADEs were unusual taste in 19% of patients and paresthesias in 6.8% of patients. Overall, only 24 patients withdrew from the study because of ADEs.

Patients used a second dose of zolmitriptan nasal spray 5 mg at least two hours after the initial dose to treat 5,101 attacks. The use of two 5-mg doses to treat an individual attack did not change the type, frequency, or maximum intensity of ADEs.

As for efficacy, 53.8% of the 20,717 treated attacks were recorded as pain-free at two hours following treatment. This outcome was maintained throughout the study, and the pain-free rates at two hours were consistent over the four 90-day periods of the study: 51.2% for days 0 to 90; 52.7%, for days 91 to 180; 55.8% for days 181 to 270; and 55.7% for days 271 to 360.

The high efficacy of zolmitriptan nasal spray was not affected by the presence of rhinitis. Two-hour pain-free rates for each 90-day period ranged from 54.4% to 56.6% for attacks treated in the presence of rhinitis.

Levetiracetam for Transformed Migraine
Speaker: Alan M. Rapaport, MD, Co-Director of the New England Center for Headache, Stamford, Connecticut, and Clinical Professor of Neurology, Columbia University College of Physicians and Surgeons, New York.

A prospective, open-label study shows that the antiepileptic agent levetiracetam (Keppra®, UCB Pharma) significantly reduces the frequency and impact of headaches in patients with transformed (chronic, daily) migraine.

Overall, 36 patients (26 women, 10 men; average age, 46.5 years) were enrolled into a prospective, open-label study of levetiracetam for the preventive treatment of refractory transformed migraine. All the participants had previously been unresponsive to one, but not more than three, preventive drugs and had taken no more than one antiepileptic drug. Eleven patients were not using other preventive drugs at the time of enrollment into the study.

After a baseline evaluation, patients received levetiracetam 250 mg/day and increased the dose by 250 mg every fifth day, up to a dose of 1,000 mg daily. After the first month, doses could be further increased to 3,000 mg/day in two divided doses. The treatment phase lasted three months.

The primary endpoint was headache frequency. Secondary endpoints included:

- the number of days during which patients experienced moderate or severe headaches.
- Migraine Disability Assessment (MIDAS) scores.
- patients’ scores on the Headache Impact Test (HIT).

These primary and secondary endpoints were assessed at baseline and at monthly intervals.

The median headache frequency at baseline was 24.9 days of headaches per month. Three months of treatment with levetiracetam reduced this number by 35%—to 16.2 days of headaches per month. The average number of moderate or severe days of headache decreased by 42%, from 16.8 days per month to 9.7 days per month, after three months of levetiracetam therapy.

After three months of levetiracetam treatment, MIDAS scores were also significantly reduced by 35% (from 62.8 to 40.8) and HIT scores declined by 6.0% (from 63.4 to 59.4).

Fifteen patients reported drug-related ADEs. Eight patients dropped out of the study because of side effects, although no serious effects were reported.

Interferon Beta-1b and Azathioprine Combination for Multiple Sclerosis
Speaker: Peter A. Calabresi, MD, Associate Professor of Neurology, Department of Neurology, The Johns Hopkins University School of Medicine, and Director of the Johns Hopkins Multiple Sclerosis Center, Johns Hopkins Hospital, Baltimore, Maryland.
Combination therapy with interferon beta-1b (Betaseron®, Berlex/Schering AG) and azathioprine (Imuran®, Prometheus) is safe and effective at reducing inflammatory disease activity in most patients who have multiple sclerosis (MS) with “breakthrough activity” who are receiving interferon beta monotherapy.

Several previous studies have documented the potential benefit of interferon beta plus azathioprine, but because results have been variable, an attempt was made to determine the parameters that might guide optimal dosing.

In an open-label, baseline-versus-treatment study, 15 MS patients with breakthrough activity on relapse received azathioprine, added in a dose-titrated manner to 325 mcg of interferon beta-1b subcutaneously every other day for up to six months. ADEs, blood counts, and serum chemistry profiles were used to assess the safety of therapy.

The primary endpoint was a decrease in inflammatory disease activity, as measured by a reduction in contrast-enhanced lesions. Secondary measures of safety and efficacy included:

- the number of relapses.
- scores on the Kurtzke Expanded Disability Status Scale (EDSS).
- MS Functional Composite (MSFC) scores.
- gadolinium-enhanced lesion counts: three at two months, at one month, and at baseline with monotherapy, and three at four months, at five months, and at six months with combination therapy.

Optimization of dosing was evaluated according to the white blood cell (WBC) count nadir and per 6-mercaptopurine levels, an active metabolite of azathioprine, from red blood cell (RBC) “pellets.”

Three of the 15 patients who received combination therapy discontinued treatment prematurely because of ADEs or noncompliance. Of the 12 patients who completed six months of therapy, gastrointestinal toxicity was the most common clinical ADE. Liver function test abnormalities occurred in five of the 12 patients, but this ADE was resolved in all patients with combination therapy.

There was a statistically significant 63% reduction in contrast-enhancing lesions after combination therapy compared with monotherapy. From the baseline evaluation to the sixth month, EDSS and MSFC scores remained stable in the group as a whole. As predicted, neither active metabolite levels of azathioprine nor WBC levels were correlated with doses of azathioprine. However, WBC and lymphocyte counts were strongly correlated with the reduction in the number of gadolinium-positive lesions, as detected with magnetic resonance imaging.

It should be noted that careful monitoring of liver function tests and WBC counts is necessary to prevent toxicity. Azathioprine should be titrated upward to the highest tolerated dose, and the WBC count should be used to help guide dosing.

Pramipexole for Restless Legs Syndrome

**Speaker:** Markku Partinen, MD, Associate Professor of Neurology, Department of Neurology, University of Helsinki, Helsinki, Finland, and Director of Rinnekoti Research Centre, Espoo, Finland.

Pramipexole (Mirapex®, Pfizer/Boehringer Ingelheim), a dopamine agonist indicated for the treatment of Parkinson’s disease, offers rapid relief of restless legs syndrome (RLS). Typical symptoms include motor restlessness, nocturnal worsening of RLS, and sleep disturbances.

To determine the optimal dose of pramipexole in patients with idiopathic RLS, researchers enrolled 109 patients with RLS in a double-blind, placebo-controlled, single-center, comprehensive polysomnographic study. The patients were randomly assigned to receive pramipexole 0.125 mg/day, 0.25 mg/day, 0.5 mg/day, or 0.75 mg/day or placebo. All of the pramipexole groups were started at 0.125 mg/day, and the doses were increased stepwise for the higher levels of drugs administered.

For patients receiving 0.25 mg, the final dose was reached on the fifth day; for patients receiving 0.5 mg, the final dose was reached on the ninth day; and for patients receiving 0.75 mg, the final dose was reached on the 13th day. The total study period was three weeks at each dose.

The primary endpoint was a reduction in limb movements, as assessed by the Periodic Limb Movement Index (PLMI) during time in bed. Secondary endpoints included changes on (1) the Restless Legs Symptom Rating Scale (RLSRS) and (2) the CGI-I. The mean age of the patients was 57 years, and 74% were women. The mean duration of RLS was 4.74 years.

Pramipexole showed excellent efficacy over the entire dose range of 0.125 to 0.75 mg/day within three weeks of therapy. A statistically significant difference in the reduction of periodic limb movements during time in bed was observed with pramipexole compared with placebo ($P < .0001$).

The responder rate, defined as greater than a 50% reduction on the RLSRS, increased from more than a 60% reduction with pramipexole 0.125 mg to approximately 78% with 0.5 mg, and to 75% with 0.75 mg. At three weeks, CGI-I scores showed “very much” to “much” improvement in 60% of patients taking 0.125 mg, up to approximately 85% with 0.5 mg, and 83% with 0.75 mg.

From the results of the high responder rates and high scores on the CGI-I, it is obvious that the severity of the RLS symptoms was significantly reduced by pramipexole treatment. Clinical efficacy was most prominent in the patients receiving 0.5 and 0.75 mg/day. Furthermore, safety and tolerability were favorable at all dose levels, with no serious ADEs occurring during the study.

Fluphenazine for Tourette Syndrome

**Speaker:** Yavuz S. Silay, MD, Research Coordinator, Parkinson’s Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, Texas.

Fluphenazine (e.g., fluphenazine, Geneva; Proloxin®, Novartis) appears to be safe and effective in the long-term treatment of tics in patients with Tourette syndrome (TS).

To provide data on the long-term safety and efficacy of pramipexole continued on page 460
fluphenazine, investigators enrolled 1,348 patients with a diagnosis of TS, as defined by criteria formulated by the Tourette Syndrome Classification Study Group, between December 14, 1981, and March 24, 2004. A total of 272 patients were randomly selected for further analysis and were grouped into one of three categories:

- patients who had never been treated with fluphenazine
- patients who had tried fluphenazine but discontinued it within the first year
- patients who had taken fluphenazine for at least one year during the past 23 years

Responses to fluphenazine, the main outcome measure, were rated on a clinical rating scale of 1 to 5, with 1 representing a marked reduction in tics and improved function and 5 representing a worsening of tics or a deterioration in function.

The investigators assessed 63 patients; the mean age of those with TS symptoms was 8.3 + 7.2 years (range, 1.2–60 years). The mean age at initiation of fluphenazine therapy was 15.6 + 9.9 years (range, 5.7–60 years). These patients received fluphenazine for a mean of 3.9 + 3.3 years, and their response was rated as 1 or 2 (i.e., marked to moderate improvement) in 84.1% of patients. The mean daily dose of fluphenazine was 3.9 + 2.7 mg/day.

Although tardive dyskinesia did not affect any patients, 23 patients discontinued the study because of (1) the study medication’s lack of efficacy, (2) the occurrence of side effects, (3) the achievement of better results with botulinum toxin, or (4) other reasons.

While acknowledging the limitations of a retrospective analysis, these findings represent the long-term clinical experience in a large number of patients. On the basis of these longitudinal findings of a high degree of efficacy and a relatively low frequency of ADEs, fluphenazine is now considered to be the first-line pharmacotherapy for treating tics at the Movement Disorders Clinic at Baylor College. Although other neuroleptic agents have been reported to cause tardive syndromes in patients with TS, tardive dyskinesia was not encountered in this study. This is a major consideration because tardive dyskinesia is one of the most feared side effects of chronic neuroleptic therapy. It still is prudent for patients to be monitored carefully so that any potentially serious side effects might be detected as early as possible.