

## Meeting Highlights

# Neuroscience 2004: 34th Annual Meeting of the Society for Neuroscience

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More than 25,000 neurologists, psychiatrists, neurosurgeons, neuroscientists, and other health care professionals gathered from around the world at the 34th annual meeting of the Society for Neuroscience, held in San Diego, California, from October 23 to 27, 2004, to hear the latest developments in the basic research, preclinical animal findings, and human clinical studies concerning every-

thing from normal development; cognition and behavior; sensory, motor, homeostatic, and neuroendocrine systems to neurological and psychiatric disorders. Particular emphasis was placed on the pharmacological treatment of Alzheimer's disease, Parkinson's disease, Down syndrome, autism, schizophrenia, drug addiction, and medication-related adverse drug events.



### Memantine Monotherapy in Alzheimer's Disease

**Speaker:** Steven G. Potkin, MD, Professor, Department of Psychiatry of Human Behavior, University of California, Irvine, Medical Center, Irvine, California.

Memantine (Namenda®, Forest Pharmaceuticals), a low-to-moderate affinity, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist approved for the treatment of moderate-to-severe Alzheimer's disease (AD), has been shown to reverse region-specific metabolic decreases associated with untreated mild-to-moderate AD, resulting in clinical benefits in patients with this disorder.

Investigators enrolled 403 outpatients, 50 years of age or older, with diagnostic evidence and a magnetic resonance imaging (MRI) scan or a computed tomography (CT) scan consistent with probable AD in a double-blind, placebo-controlled, phase III clinical trial, conducted in the U.S. These patients were randomly assigned to receive memantine 20 mg daily or placebo for 24 weeks. Positron emission tomography (PET) scans were performed at the baseline evaluation and at the 24th week in five memantine-treated patients and in five patients taking placebo.

In this study, patients in the memantine group performed significantly better than those in the placebo group, according to a last observation carried forward (LOCF) analysis of both of the two primary outcome measures used—the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) and the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). The PET scans showed significant metabolic increases in glucose metabolism in brain regions of memantine-treated patients, including the orbital, cingulate, retrosplinal, and dorsal lateral prefrontal cortices. In contrast, patients in the placebo group showed significant metabolic declines in these same areas.



*Dr. Prescott is a medical, health, and science writer based in San Diego, California, and a former medical microbiologist and clinical pathologist for the World Health Organization.*

### Glial Cell Line-Derived Neurotrophic Factor in Advanced Parkinson's Disease



**Speaker:** Don M. Gash, PhD, Professor and Chair of Anatomy and Neurobiology, Department of Neurology, University of Kentucky Medical Center, Lexington, Kentucky.

A continuous, unilateral intraputamenal infusion of glial cell line-derived neurotrophic factor (GDNF) results in bilateral neuroprotective and neurorestorative effects in patients with advanced bilateral Parkinson's disease (PD).

Because an earlier study had reported significant improvements in patients with bilateral PD who received bilateral intraputamenal infusions for one year, researchers decided to assess the value of a unilateral intraputamenal infusion of GDNF patients with advanced bilateral PD. Four weeks after implantation of an intraputamenal catheter contralateral to the most affected side, six patients received dose escalations of GDNF at eight-week intervals from 3 mcg/day to 10 mcg/day to 30 mcg/day, for 24 weeks, followed by a four-week drug washout period.

After the 24 weeks, patients' total Unified Parkinson's Disease Rating Scale scores were significantly improved, whether the drug was "off" or "on" (there are well-known fluctuations in response to levodopa), by an average of 0.34% when "off" and 29% when "on." Motor speed, as measured by the Core Assessment Program for Surgical Interventional Therapies in Parkinson's Disease (CAPSIT) test, was faster with the drug both "on" and "off." Bilateral improvements ranged from 40% to 50% in fine-motor control and speed consistent with the bilateral improvements on rating scales of postural stability and gait.

Other parkinsonian features that improved included hypophonia, hypersalivation, and end-of-dose fluctuations. Motor improvements were largely maintained throughout the one-month GDNF washout period.

### Donepezil in Young Adults with Down Syndrome

**Speaker:** Benjamin Seltzer, MD, Professor of Neurology and Psychiatry, Tulane University Neuroscience Program, Tulane University School of Medicine, New Orleans, Louisiana.

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Although results for donepezil (Aricept®, Pfizer) treatment in young adults with Down syndrome are generally superior to those with placebo, surprisingly, the placebo group generally improves as well. Examination of the individual subject data, however, suggests that a subgroup of individuals responds to treatment, mainly persons 25 years of age or older and male.

Because people with Down syndrome who live into middle age (35 years of age or older) develop neurological and neurochemical changes that are virtually the same as those observed in Alzheimer's disease, donepezil might reasonably be expected to produce some improvement in cognition and function in individuals with Down syndrome. With this premise in mind, 193 persons were screened and 123 individuals with Down syndrome, 77 male and 46 female, were enrolled into a randomized, double-blind, placebo-controlled trial. The subjects were assigned to receive either donepezil 5 mg for six weeks, followed by 10 mg for the following six weeks, or placebo for 12 weeks.

The primary efficacy measure was the Severe Impairment Battery (SIB). Secondary efficacy measures included the Vineland Adaptive Behavior Scale (VABS), the Reviewed Behavioral Memory Test for Children (RBMT-C), and the third edition of the Clinical Evaluation of Language Fundamentals (CELF-3). Safety was assessed with physical examinations, electrocardiograms (ECGs), clinical laboratory tests, and the recording of adverse drug events (ADEs).

Overall, donepezil treatment was well tolerated and generally safe. Ninety percent (56) of the 92 patients in the donepezil group and 97% (59) of the 61 patients receiving placebo completed the study. There were no deaths or serious ADEs during the trial. The majority of ADEs in both study groups were rated mild to moderate.

On the SIB test, the primary efficacy outcome, both treatment groups improved significantly from baseline measures, but the difference between the two groups was not statistically significant. While generally favoring donepezil, treatment differences on the RBMT-C and the CELF-3 also were not statistically significant. In addition, a standardized composite score of these three measures, while not statistically significant, strongly favored donepezil.

When these scores were graphed as cumulative percentages of the population, however, it appeared that there was a responding subgroup. When the cumulative response curves were broken down by age, 18 to 24 years old and 25 years of age or older, the treatment differences favoring donepezil approached significance in the older group. When examined even further, this effect reached statistical significance for older males.

### Methylcobalamin for Autistic Children

**Speaker:** Richard C. Deth, PhD, Professor of Pharmacology, Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, Massachusetts.

Studies with methylcobalamin, a form of vitamin B<sub>12</sub> obtained from dietary or vitamin-derived B<sub>12</sub>, may point the way toward new, more effective treatment approaches with autistic children. Because recent investigations have strongly

suggested that neurodevelopmental toxins impair the synthesis of methylcobalamin (methyl B<sub>12</sub>), a key impairment involved in the formation of developmental disorders, it was hypothesized that methyl B<sub>12</sub> might be helpful in the treatment of these conditions.

Autistic children between three and 11 years of age were given subcutaneous injections of methyl B<sub>12</sub> 75 mcg/kg every three days, with no changes made to any of their other treatments. A parental questionnaire was used to evaluate changes in autistic symptoms.

Among the first 85 children treated, parents reported improvements in speech and language in 71% of these youngsters, in attention and awareness in 65%, in cognitive function in 52%, and in socialization and emotional stability in 35%. In 10% of the children, increased hyperactivity was observed during the first several weeks of treatment; however, this phenomenon did not usually require stopping treatment and it decreased with time. Stopping treatment resulted in a worsening of symptoms, which were reversed upon resumption of the methyl B<sub>12</sub> injections. Generally, methyl B<sub>12</sub> significantly improved symptoms for most of the treated autistic children.

### Augmentation of Risperidone with Galantamine in Schizophrenia

**Speaker:** Max H. Schubert, MD, Psychiatry and Behavioral Science, Texas A&M University System, HSC College of Medicine, Temple, Texas.

The addition of galantamine (Reminyl®, Janssen), a well-known cholinesterase inhibitor, to risperidone (Risperdal®, Janssen), a benzisoxazole derivative used to treat schizophrenia, resulted in improved cognition in patients with schizophrenia or schizoaffective disorder.

Sixteen patients were enrolled into an eight-week, double-blind, placebo-controlled trial. They were randomly assigned to receive galantamine 24 mg daily in addition to placebo to risperidone for eight weeks. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was used to assess cognitive changes with drug treatment.

The primary outcome measure was the total RBANS score. Secondary outcome measures included subset scores for the cognitive domains of attention, immediate memory, delayed memory, constructional and visual-spatial memory, and language. A robust improvement in the total RBANS scores, from baseline to the end of the study, was observed between patients treated with risperidone plus galantamine and the risperidone-alone controls ( $P = .02$ ). This dramatic improvement was explained mainly by improvement in two domains: attention ( $P = .02$ ) and delayed memory ( $P = .02$ ). Immediate memory also seemed to improve, but the  $P$  value was not as strong ( $P = .12$ ).

### Selegiline in Methamphetamine-Addicted Patients

**Speaker:** Richard De La Garza, PhD, Researcher, Department of Psychiatry and Behavioral Science, University of California Los Angeles, Los Angeles, California.

Oral selegiline (Eldepryl®, Somerset), which has been used in the treatment of Parkinson's disease and can attenuate some

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subjective effects produced by cocaine in humans, does not exacerbate the cardiovascular or subjective effects of methamphetamine (Desoxyn®, Abbott) in methamphetamine-dependent patients, indicating that it might be beneficial in the treatment of methamphetamine abuse.

Because selegiline appears to be useful in treating specific aspects of cocaine and nicotine dependence, an intravenous (IV) blind, placebo-controlled study was carried out in 24 methamphetamine-dependent individuals. The purpose of the study was to evaluate the safety of selegiline treatment, compared with placebo, concurrent with IV methamphetamine 15 mg or 30 mg and to assess whether selegiline altered the subjective or cardiovascular response to methamphetamine.

Methamphetamine alone was well tolerated and, as expected, it increased cardiovascular measures such as heart rate and systolic and diastolic blood pressure. In addition, the subjective effects of “high” (getting high), “like” (liking the drug), and “desire” (desiring the drug) were increased in relation to methamphetamine.

In the presence of selegiline, lower mean vital signs were measured in the challenge sessions during the treatment phase and were compared with placebo. There was no indication of any adverse interactions between selegiline and methamphetamine; selegiline treatment tended to diminish rather than exacerbate cardiovascular responses to methamphetamine. Oral selegiline treatment did not increase the subjective effects of methamphetamine for any of the three ratings studied.

### Bupropion in Methamphetamine-Experienced Persons

**Speaker:** Laura Corbit, PhD, Postdoctoral Research Fellow, Department of Psychiatry and Behavioral Sciences, University of California, Los Angeles Neuropsychiatric Institute and Hospital, Los Angeles, California.

Bupropion (Zyban®, GlaxoSmithKline), which has been shown to be effective as an antidepressant and as an aid in smoking cessation, may also be useful in an outpatient setting for the treatment of methamphetamine abuse.

A double-blind inpatient study was carried out to assess the effects of bupropion on cravings for methamphetamine, to evaluate the effects of bupropion on mood and personality assessments and other psychological parameters, and to determine whether bupropion altered subjective or cardiovascular responses to methamphetamine.

Methamphetamine-experienced participants were randomly selected to receive bupropion 150 mg once daily on days 10 to

12, twice daily on days 13 to 25, and once on day 26, or a matched placebo. The participants were also given saline or methamphetamine 15 mg, with the order randomly assigned on days 2 and 3 and on days 18 and 19. Methamphetamine 30 mg was administered on days 5 and 22.

With regard to safety, as expected, methamphetamine administration increased vital signs such as heart rate and systolic and diastolic blood pressure. For the bupropion-treated patients, however, these responses were markedly attenuated. Furthermore, bupropion significantly attenuated the methamphetamine effects for ratings such as “high” (getting high) “stimulated,” “desire” (desiring the drug), and “likely to use.”

Bupropion also decreased cue-induced craving, as indicated by a decrease in the General Craving Scale total score in this group following cue exposure. It also decreased scores on positive outcome, behavior intention, cues effect, and cues situation subscales.

### Isotretinoin and Depression in Patients with Acne

**Speaker:** James Douglas Bremner, MD, Associate Professor of Psychiatry and Radiology, Emory University, Atlanta, Georgia.

In a four-month treatment trial that was conducted to compare isotretinoin (Accutane®, Roche), a well-known retinoid indicated for severe recalcitrant nodular acne, with antibiotics in acne patients, the findings strongly suggested a mechanism by which isotretinoin might act through the brain to result in depression in a subset of vulnerable individuals.

Because case reports have suggested a relationship between treatment with isotretinoin and the development of depression and suicide, a study was carried out to assess the effect of isotretinoin on brain function in acne patients.

Twenty-eight patients were enrolled in the comparative study, 13 in the isotretinoin group and 15 in the antibiotic group. Brain function was measured with fluorine 18-labeled-2'-fluoro-2'-deoxy-D-glucose (FDG) PET scans before and after four months of treatment with isotretinoin or antibiotics.

At the end of the four-month period, PET scans demonstrated that isotretinoin was associated with a 21% decrease in brain function in the orbitofrontal cortex, a brain region that has been implicated in depression. These changes were not observed after a similar course of treatment with antibiotics. The greatest magnitude of decrease was observed in patients who developed symptoms of headache during the course of isotretinoin treatment. Isotretinoin was not associated with any changes in depressive symptom severity, as measured with the Hamilton Depression Scale.