

## Meeting Highlights

# 58th Annual Meeting of the American Academy of Neurology

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More than 10,000 neurologists, psychiatrists, surgeons, neuroscientists, and other health care professionals gathered in San Diego, California, from April 1 to 8, 2006, to hear the latest developments in the prevention, treatment, and control of neurological disorders. Areas of interest included approaches for emerging multiple sclerosis, a patch as adjunctive therapy in Parkinson's disease, a new first-line treat-



ment for epileptic seizures, two options for migraine, an established drug for severe Alzheimer's disease, an agent for Parkinson's disease that is also recommended for restless legs syndrome, a nonstimulant drug for attention-deficit/hyperactivity disorder and comorbid Tourette syndrome, and a well-known anticonvulsant for relieving neuropathies and neuralgias.

### Interferon Beta-1b for Multiple Sclerosis

**Speaker:** Ludwig Kappos, MD, Professor of Neurology and Clinical Neuroimmunology, Department of Neurology and Research, University of Basel and University Hospital Basel, Basel, Switzerland

In a large-scale European clinical trial, interferon beta-1b (IFN  $\beta$ -1b) (Betaseron, Schering AG, Germany) was effective, safe, well tolerated, and well accepted for patients with a first clinical event suggestive of multiple sclerosis (MS).

The Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment (BENEFIT) trial enrolled 468 patients with a first clinical demyelinating event and at least two clinically silent brain lesions, as shown by magnetic resonance imaging (MRI). The patients were randomly selected to receive, in a 5:3 ratio, 250 mcg of IFN  $\beta$ -1b subcutaneously ( $n = 292$ ) or placebo ( $n = 176$ ) every other day until a diagnosis of clinically definite MS (cd MS) was confirmed or until they had been observed for 24 months.

To achieve maximum tolerability, the researchers escalated the dose during the first three weeks and encouraged administration with an auto-injector. Concomitant ibuprofen or acetaminophen was also used to reduce flu-like symptoms. Patients who completed the study could participate in a follow-up study with open-label IFN  $\beta$ -1b for up to five years.

Primary efficacy endpoints were the time to cd MS and the time to diagnosis of MS, according to the McDonald criteria. Other endpoints included safety and tolerability.

IFN  $\beta$ -1b significantly delayed the risk of progression from the first clinical event to cd MS by 50% ( $P < .0001$ ) and for "McDonald criteria" MS by 46% ( $P < .00001$ ). In terms of safety and tolerability, only 7.2% of patients receiving IFN  $\beta$ -1b discontinued the study prematurely, compared with 5.7% of the placebo group. Regarding adherence to therapy, only 15.1% of the IFN  $\beta$ -1b patients and 10.2% of the placebo group discontinued therapy. Nearly all patients received at least 80% of the scheduled treatment until the end of the study (97.6% who took the study drug and 97.2% who took placebo).

Of all patients who reached the end of the study as scheduled, 418 (96%) entered the follow-up study. Of these, 261 patients (96%) had received IFN  $\beta$ -1b in the double-blind phase of the BENEFIT study and 157 (95%) had received placebo. Of these, 96% of the two groups (combined) chose to receive IFN  $\beta$ -1b 250 mcg every other day.

Patient-reported outcomes, including quality-of-life measures, did not indicate a negative impact of typical adverse effects from IFN  $\beta$ -1b.

### Rotigotine Patch in Parkinson's Disease

**Speaker:** Peter LeWitt, MD, Professor of Neurology and Psychiatry, Wayne State University School of Medicine, Detroit, Michigan, and Clinical Neuroscience Center, Southfield, Michigan

The rotigotine transdermal system (Neupro, Schwarz Pharma), a non-ergolinic dopamine receptor agonist, when administered once daily, has been shown to be safe, well tolerated, and effective in patients with late-stage Parkinson's disease who have not responded to levodopa. The patch provided statistically significant reductions in "off" time as an adjunct to levodopa without an increase in "on" time in patients with troublesome dyskinesias. (After a number of years of treatment with levodopa, about 80% of patients begin to experience fluctuations in their response—the "on-off" effect.)

A total of 351 patients with late-stage Parkinson's disease were enrolled in a double-blind, placebo-controlled, multicenter trial. The patients were randomly assigned to wear the patch (delivering 18 or 27 mg/day) or to take placebo. The trial included a four-week pre-treatment phase, a five-week titration phase, a 24-week maintenance phase, a de-escalation period, and an unspecified open-label extension.

The primary efficacy outcome was reduction in "off" time in all-day hourly home assessment and responder rates.

Of the 351 randomly selected patients—111 receiving rotigotine doses of 18 mg/day, 120 receiving doses of 27 mg/day, and 120 taking placebo—260 individuals (74%) completed the

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maintenance phase. A data analysis of these patients was performed. Ninety-nine percent of those who completed the study then entered the open-label extension.

Compared with their baseline measures, those who wore the patch at a dose of 27 mg had an adjusted mean daily decrease of 2.1 hours in “off” time. Patients who received the 18-mg dose had a mean reduction of 2.7 hours in “off” time. For the placebo group, the adjusted mean daily reduction was 0.9 hours. The differences between both rotigotine doses and placebo were significant in favor of rotigotine (18 mg/day,  $P < .001$ ; 27 mg/day,  $P < .003$ ). Responder rates were 57% with 18 mg/day, 55% with 27 mg/day, and 34% with placebo, respectively.

There were no increases in “on time” for patients in either active-dose group who had troublesome dyskinesias. Common adverse events with the patch were application-site reactions, somnolence, nausea, and dizziness.

### Levetiracetam Beneficial against Partial-Onset or Generalized Tonic–Clonic Seizures

**Speaker:** Elinor Ben Menachem, MD, PhD, Professor, Department of Clinical Neuroscience, Sahlgrenska Academy at Gothenburg University, and Sahlgren University Hospital, Gothenburg, Sweden

Results from a phase 3, randomized, non-inferiority comparison trial indicated that levetiracetam (Keppra, UCB) was effective as monotherapy in the first-line treatment of newly diagnosed epilepsy in patients with partial-onset or generalized tonic–clonic seizures. Its efficacy was similar to that of controlled-release (CR) carbamazepine (Tegretol, Novartis) and was much more tolerable when optimal doses of both drugs were used.

Adults with newly or recently diagnosed epilepsy (but excluding idiopathic generalized epilepsy) were selected to receive levetiracetam 1,000 mg/day or carbamazepine CR 400 mg/day after a three-week period of upward dose titration. This dose was maintained for a six-month evaluation period or until the next seizure. When a seizure occurred, doses were increased to levetiracetam 200 mg/day plus carbamazepine CR 800 mg/day or to levetiracetam 3,000 mg/day plus carbamazepine CR 1,200 mg/day. After patients remained free of seizures for six months, they entered a six-month maintenance phase.

Of the 472 patients who adhered to the treatment protocol, 73% of those using levetiracetam and 72.8% of those using carbamazepine CR were seizure-free for 12 months. Among patients completing the maintenance phase, 56.6% of the levetiracetam patients and 58.5% of the carbamazepine CR group were seizure-free for 12 months.

It is significant that fewer patients taking levetiracetam (16.1%) needed to stop treatment or change their dose because of an adverse event, compared with 23% of those taking carbamazepine CR ( $P = .046$ ).

### New Sumatriptan Formulation for Acute Migraine

**Speaker:** Roger Cady, MD, Director, Headache Care Center and Primary Care Network, Springfield, Missouri

A new formulation consisting of a fixed-dose, single tablet containing sumatriptan succinate 85 mg with RT Technology (Suma RT) with naproxen sodium 500 mg (NAP) (Suma

RT/NAP) (Trexima, GlaxoSmithKline/Pozen) showed superior results in treating acute migraine pain compared with either the separate components or placebo. (Trexima is the proposed brand name for the combination of sumatriptan [Imitrex], formulated with RT Technology, and naproxen.) Significantly more patients were “satisfied” or “very satisfied” with the combination compared with Suma RT, NAP, or placebo.

Initially, two identical, randomized, double-blind, placebo-controlled, parallel-group, single-attack (moderate or severe) multicenter studies of adult migraineurs were performed. Study I enrolled 1,470 patients, and study II enrolled 1,441 patients.

Patients were randomly assigned to receive Suma RT/NAP, Suma RT 85 mg, NAP 500 mg, or placebo. Primary endpoints were assessments of pain and associated symptoms.

The patients completed the eight-item Patient Perception of Migraine Questionnaire (PPMQ)—a previously validated treatment satisfaction testing instrument—at the baseline evaluation and at 24 hours after receiving the dose. The PPMQ used a 7-point scale (ranging from very unsatisfied to very satisfied) to measure:

- relief of migraine pain
- relief of other migraine symptoms
- speed of relief of pain or other migraine symptoms
- drowsiness from the medication
- duration of effect
- doses needed for symptom relief
- speed of return to usual activities
- overall medication effectiveness

The percentage of patients who were satisfied or very satisfied with Suma RT/NAP was consistently higher than the percentage of those taking placebo for all PPMQ items in both studies ( $P < .001$ ). The percentage was also consistently higher for the active comparators (Suma RT and NAP) for all PPMQ items ( $P < .05$ ) except for drowsiness in study I. In both trials, Suma RT/NAP provided better two-hour and four-hour pain relief compared with Suma RT, NAP, and placebo. More migraineurs in the Suma RT/NAP group reported satisfaction with this agent compared with their previous treatment.

### Botulinum Toxin Type A for Migraine Prophylaxis

**Speaker:** Andrew Blumenfeld, MD, Director, The Headache Center of Southern California, Scripps Memorial Hospital, Encinitas, California

In a comparison of botulinum toxin type A (BoNT-A) (Botox, Allergan) and divalproex sodium (Depakote, Abbott) to prevent episodic migraine, the two active treatments were similar in efficacy as migraine prophylaxis, but BoNT-A was more effective in reducing headache pain and demonstrated a superior safety and tolerability profile than divalproex.

Sixty patients were enrolled in a randomized, evaluator-masked, single-center study. To be enrolled in the study, they had to be experiencing at least two but less than eight migraine headaches per month. The patients were assigned to take 105 to 260 units of BoNT-A or 500 mg of divalproex twice daily. Efficacy was assessed by mean differences from baseline in Migraine Disability Assessment (MIDAS) scores. Patients

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received treatment at day zero (0) and were evaluated at 30, 60, and 90 days. At day 90, the mean difference from baseline in MIDAS total scores was significantly greater with BoNT-A than with divalproex ( $-8.05$  vs.  $-0.27$ ;  $P = .0375$ ). At day 0, the mean number of headache days was 11.60 with BoNT-A and 16.10 with divalproex ( $P = .074$ ), from a baseline of 14.27 and 13.83, respectively.

At all times, the reduction in average headache pain was greater with BoNT-A than with divalproex. Fewer adverse events appeared to be related to BoNT-A (nine) than to divalproex (21). None of the BoNT-A patients discontinued treatment as a result of adverse events, although six patients in the divalproex group stopped therapy.

### Donepezil and Severe Alzheimer's Disease

**Speaker:** Bengt Winblad, MD, PhD, Professor and Director, Neurotec Department, Division of Geriatrics, Alzheimer's Disease Research Center, Karolinska Institute and Karolinska University Hospital, Huddinge, Sweden

Donepezil (Aricept, Eisai/Pfizer), well known for its value in the treatment of patients with mild-to-moderate Alzheimer's disease (AD), has shown substantial benefits in cognition and clinical global improvement in patients with severe AD.

Because cholinesterase inhibitors were thought to be helpful for patients with severe AD, 248 patients at 50 centers in Sweden were enrolled into a six-month, double-blind, placebo-controlled, multicenter trial. They were randomly assigned to take placebo or donepezil 5 mg daily for 30 days, followed by donepezil 10 mg daily for the remainder of the study period.

Criteria for enrollment in the study for severe AD included (1) Mini-Mental State Examination (MMSE) scores of 1 to 10 and (2) Functional Assessment and Staging Scale (FASS) scores at stage 5 (patient needs help in selecting proper clothing) to stage 7C (patient unable to walk without assistance).

The overall objectives were to examine the efficacy variables of the MMSE, the Clinical Global Impression of Improvement (CGI-I), and the Neuropsychiatric Inventory (NPI) in order to evaluate cognition, global function, and behavior.

At the six-month follow-up evaluation, for the intent-to-treat (ITT) populations, the donepezil patients showed greater improvement in MMSE scores (1.5) than the placebo patients (0.1). (The ITT population was defined as all randomly selected and treated patients with a baseline efficacy value and at least one corresponding post-baseline efficacy value). CGI-I scores were "much improved," "improved," and "minimally improved" with donepezil, compared with placebo.

In general, no differences were observed between the active-treatment patients and the placebo group; both patient groups showed improved NPI scores from the baseline measure to the sixth month. However, a greater (although not statistically superior) improvement was observed with donepezil.

### Pramipexole Helps Restless Legs Syndrome

**Speaker:** John W. Winkelman, MD, PhD, Assistant Professor of Psychiatry, Harvard Medical School, Boston, Massachusetts; Associate Director for Sleep Disorders, Brigham and Women's Hospital, Boston; and Clinical Director, Sleep Health Center, Newton Centre, Massachusetts

Pramipexole (Mirapex, Boehringer Ingelheim), a dopamine agonist indicated for the signs and symptoms of idiopathic Parkinson's disease, was found to be safe and effective for patients with restless legs syndrome (RLS).

Because controlled trials had demonstrated that six weeks of pramipexole treatment improved RLS symptoms, a study was conducted to explore the value of three fixed doses of pramipexole over 12 weeks in patients with RLS. In a double-blind, placebo-controlled, parallel-group study, 344 patients with RLS received 12 weeks of treatment with pramipexole 0.25 mg, 0.50 mg, or 0.75 mg or with placebo. The patients were entered into a four-week titration phase, starting at 0.125 mg and ending at each patient's randomized dose. The patients then entered an eight-week maintenance phase and received their randomized doses.

Primary efficacy endpoints were (1) changes in total scores of symptom severity on the International Restless Legs Scale (IRLS), compared with baseline examinations through week 12, and (2) CGI-I scores at week 12.

A total of 339 patients were evaluable. The mean baseline IRLS score was 23.4, and 88.5% of patients were rated as at least moderately ill on the CGI-Severity of Illness Scale (CGI-S). At 12 weeks, all three doses of pramipexole produced significant improvements in IRLS total scores, compared with placebo.

The adjusted mean reductions from baseline IRLS scores, for each dose of pramipexole versus placebo, were  $-12.8$  with 0.25 mg ( $P = .0086$ ),  $-13.8$  with 0.50 mg ( $P = .0011$ ),  $-14$  with 0.75 mg ( $P = .0005$ ), and  $-9.3$  with placebo.

Treatment with pramipexole also resulted in a statistically significant improvement in CGI-I scores, compared with placebo, as measured by the percentage of patients meeting the criteria for a CGI-I responder. The responder rates, for each dose of pramipexole versus placebo, were 74.7% with 0.25 mg ( $P = .0005$ ), 67.9% with 0.50 mg ( $P = .0484$ ), 72.9% with 0.75 mg ( $P = .0038$ ), and 51.2% with placebo.

### Atomoxetine Benefits Attention-Deficit/Hyperactivity Disorder and Comorbid Tourette Syndrome

**Speaker:** Thomas J. Spencer, MD, Associate Professor, Department of Psychiatry, Harvard Medical School, and Assistant Director, Pediatric Psychopharmacology Clinic, Department of Pediatric Psychopharmacology, Massachusetts General Hospital, Boston, Massachusetts

Atomoxetine (Strattera, Lilly), a nonstimulant indicated for attention-deficit/hyperactivity disorder (ADHD), has been shown to be safe, well tolerated, and effective for children with ADHD and comorbid Tourette syndrome by treating ADHD symptoms without exacerbating tic symptoms. Because the psychostimulants traditionally used to treat ADHD sometimes trigger or worsen motor or vocal tics in patients with ADHD and Tourette syndrome, a study was performed to examine the change in severity of tics and symptoms of ADHD during atomoxetine treatment.

Initially, 148 ADHD patients were assigned to treatment; 117 of these patients also had Tourette syndrome. All of these children, 7 to 17 years of age, were entered into a two-week screening and washout period, followed by an 18-week, double-blind, placebo-controlled, acute-treatment phase. They

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were randomly assigned to receive atomoxetine 0.5 to 1.5 mg/kg per day or placebo twice daily for up to 18 weeks.

Results were based on an *a priori*-defined secondary analysis of the subgroup of 117 ADHD patients meeting the full criteria of Tourette syndrome. Atomoxetine significantly decreased symptoms of ADHD in patients with Tourette syndrome. These patients showed significant improvement in the ADHD Rating Scale total scores and in CGI overall severity scores.

No worsening of tics was observed with atomoxetine; in fact, this agent appeared to have a beneficial effect on tic severity and was associated with a greater reduction in tic severity at the endpoint compared with placebo. Such reductions were measured by total scores on the Yale Global Tic Severity Scale and by CGI Severity of Tic/Neurological Symptoms Scale scores, but not by total scores on the Tic Symptom Self-Report.

Atomoxetine was generally well tolerated, although patients taking this drug experienced greater increases in pulse rate, decreased body weight, and treatment-related decreased appetite and nausea. No other clinically relevant treatment-related adverse events were seen for any other vital signs, laboratory parameters, or electrocardiographic measures.

### Pregabalin Relieves Neuropathy and Neuralgia

**Speaker:** Russell Portenoy, MD, Chairman, Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, New York

A number of short-term, randomized clinical trials have shown that pregabalin (Lyrica, Pfizer), an anticonvulsant used to relieve seizures and nerve pain, has a rapid onset of effect in painful diabetic peripheral neuropathy (DPN) and post-herpetic neuralgia (PHN), often by the second day of treatment.

To describe the time to onset and the duration of analgesia during studies of pregabalin for peripheral neuropathic pain, investigators evaluated data from seven placebo-controlled, short-term, randomized, controlled trials (five to 13 weeks in length) and four open-label extension trials (two years in duration). A total of 1,543 patients (940 taking pregabalin and 603 taking placebo) were enrolled. Patients with DPN received pregabalin 300 or 600 mg daily or placebo. Patients with PHN received pregabalin 150 mg/day, 300 mg/day, or 600 mg/day or placebo.

In the open-label extension studies, 444 patients received flexible dosing, and pain data were reported for 251 patients. The time of onset was defined by the first day on which numeric daily pain scores (ranging from 0 to 10) were significantly lower than placebo on two consecutive days.

In nine of 11 study arms in the trials that demonstrated significant efficacy at the endpoint, the onset of analgesia occurred on the first or second day of treatment. In these nine treatment arms, the therapeutic effect, as measured by daily pain scores on the first confirmed day of response, ranged from  $-0.70$  ( $P = .004$ ) to  $-1.40$  ( $P < .001$ ) in the patients with DPN and from  $-0.45$  ( $P = .036$ ) to  $-0.66$  ( $P = .004$ ) in those with PHN.

For patients in the open-label extension studies, pain remained consistent from the first quarter to the two-year follow-up, and there were no clinically meaningful variations in mean dosage of pregabalin during this period. ■