Several new studies presented at the AAN Annual Meeting last month explored the potential role of pramipexole ER (Mirapex ER, Boehringer Ingelheim), currently under regulatory review, in patient care. Data support the efficacy and convenience of the formulation.

For patients with early PD, pramipexole IR improves symptoms and can delay the need for levodopa. However, pramipexole IR is administered TID, and a once-a-day ER formulation would increase patient convenience and could improve patient compliance, researchers believe. A double-blind trial pitted pramipexole ER (optimized at 0.375-4.5mg QD) and IR (optimized at 0.125-1.5mg TIS) versus placebo, with all subjects having PD Hoehn-Yahr stage I-III. At 33 weeks, 84 patients remained (35 ER, 31 IR, 18 placebo). In both pramipexole ER and IR groups, “efficacy was maintained at 33 weeks compared with 18 weeks, while placebo patients worsened.”

Maintenance of efficacy was predefined as less than or equal to 15 percent worsening at week 33 compared to week 18. Efficacy was also judged by responder rate of “much” or “very much” improved on the Clinical Global Impression-Improvement and Patient Global Impression-Improvement scales.

Neurologists will need to know how to best transition patients from IR to ER formulations if the latter is approved. Researchers (P06.152) found that 84.5 percent of early PD patients successfully switched from pramipexole IR to ER in overnight switching. The nine-week double-blind, double-dummy, randomized, parallel-group study was conducted on 156 patients with early PD on stable doses of pramipexole IR (2.7 ±0.9mg/day). The primary analysis used one-sided non-inferiority statistical test at five percent significance and non-inferiority margin of 15 percent.

Pramipexole ER was found to be superior to placebo and comparable in efficacy to IR at the same dosage, according to another study (S43.003). Researchers designed an 18-week, randomized, double-blind trial of ER (0.375-4.5mg QD) and IR (0.125-1.5mg tid) versus placebo. All of the patients had PD at Hoehn-Yahr stage I-III (diagnosed in the past five years), no prior levodopa exposure totaling >3 months, no l-dopa within the past eight weeks, and no dopamine agonists within the prior four weeks.

Of the 253 patients who completed the study, 102 were in the ER group, 101 in the IR, and 50 controls. At week 18, mean UPDRSII+III change (adjusted for country, treatment group, and baseline) was -8.1 for ER and -7.5 for IR, versus 2.7 for placebo (P=.0010 and P=.006). CGI-I responder rate was 37 percent for ER and 48 percent for IR, versus 12 percent for placebo (P=.0040 and P=.1207).

According to reports, approval of the ER formulation could come within a few months. However, in the next year, generic formulations of standard pramipexole could come to market, potentially challenging patients to weigh costs over convenience.

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**MS Therapy Focus Shifts to Oral Compounds**

Results of the 96-week, placebo-controlled Phase III CLARITY trial show that oral cladribine therapy reduced the rate of clinical relapses, disability progression, and brain lesions in patients with MS. According to data released at the AAN Annual Meeting last month by drug developer Merck KGaA, cladribine-treated patients had a statistically significant decrease in annualized rate of relapses compared to controls. In the high-dose group, 79 percent of patients experienced no relapse, similar to the 80 percent of patients that were relapse-free in the lower dose group. In the control group, 51 percent of patients did not have relapses.

Treatment reduced the risk of disability by more than 30 percent over two years. Cladribine is administered in either two or four four- to five-day courses per year.

Another agent also shows promise for relapsing-remitting MS, according to data released at the annual meeting and reported by Novartis AG. In a Phase III trial comparing fingolimod to interferon beta-1a, 80 to 83 percent of patients treated with fingolimod were relapse-free for one year compared to 69 percent of those receiving interferon. The company also reported results of an open-label Phase II extension study showing continued low relapse rates after four years of fingolimod therapy.
Tysabri Maker Presents New PML Data

The MS drug that always seems to find itself in the news is making headlines again, but this time the message may be relatively positive. Natalizumab (Tysabri, Biogen Idec) does not appear to carry the level of risk of progressive multifocal leukoencephalopathy (PML) previously estimated—and the infections are less deadly—according to new postmarketing surveillance data. Previous research said that the risk of developing PML was 1 in 1,000, but new data show it’s closer to 1.2 per 10,000 patients, according to Carmen Bozic, MD, vice president and global head of drug safety and risk management for Biogen Idec. Dr. Bozic delivered her remarks at the AAN’s 61st Annual Meeting.

The new data were taken from the Tysabri Outreach: Unified Commitment to Health (TOUCH) prescribing program and the Tysabri Global Observation Program in Safety (TYGRIS), according to Medical News Today. TOUCH is a mandatory prescribing program that ensures proper and educated use of natalizumab. TYGRIS is a global voluntary observational study evaluating the long-term safety of natalizumab in clinical practice. About three years after approval in the US and the European Union, approximately 52,000 patients had been treated with natalizumab in the postmarketing setting, more than 10 times the exposure in clinical trials, according to Dr. Bozic.

There is now a plethora of information about long-term exposure in the postmarketing setting, she said. To date, just shy of 25,000 patients have been taking the drug for 12 months or longer, 14,400 for 18 months or longer, and 6,800 for 24 months or longer. Some patients have taken the drug for more than 2.5 years, she added. The six patients who developed PML—three men and three women ranging in age from 37 to 59 years—used the drug as monotherapy for periods ranging from 12 to 31 months, a highly variable duration of treatment, Dr. Bozic noted.

Biogen and Elan also announced results from an ongoing, one-year longitudinal health outcomes study (n=1275) in which patients who received three infusions of natalizumab reported reduced fatigue, as well significant improvements in general and disease-specific measurements of quality of life (QoL) and cognitive function. The 12-item Short Form Scale Physical Component Summary (baseline 34.03 vs. 36.02 at the 3rd infusion; p<0.001) and the SF-12 Mental Component Summary Score (baseline 43.17 vs. 47.22 at the 3rd infusion; p<0.001) showed statistically significant improvements from baseline.

For the 29-item Multiple Sclerosis Impact Scale, there were statistically significant improvements from baseline for both the physical (baseline 48.25 vs. 40.19; p<0.001) and psychological (baseline 43.70 vs. 34.80; p<0.001) impact scores.

FDA has given the green light to a high-titer production process for Biogen Idec’s Tysabri, allowing the manufacturer to increase the production yield up to four-fold, according to a company statement.

FDA ACTIONS

**Dysport Approved.** The first neurotoxin approved for neurologic indications in several years, abobotulinumtoxin A (Dysport, Ipsen) has received FDA approval for the treatment for both cervical dystonia and glabellar lines. The drug will be available for aesthetic purposes in May or June and for cervical dystonia during the second half of 2009. Dysport was originally launched in the United Kingdom in 1991 and has marketing authorizations in over 70 countries. In accordance with their agreement, Medicis (which will handle cosmetic marketing) will now pay Ipsen approximately $75 million as a result of FDA approval, and Ipsen will receive a royalty based on sales and a supply price.

**Botulinum Toxin Black Box.** The FDA will require all botulinum toxin products to contain a boxed warning about adverse effects that could occur if the effects of the toxin extend outside the injection site. According to an agency statement, FDA took the action, “because of reports that the effects of the botulinum toxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism, including unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids.” FDA also has mandated a Risk Evaluation and Mitigation Strategy (REMS) be put in place for all botulinum toxin products. Botox (Allergan), Dysport (Ipsen), and Myobloc (Solstice) are affected. Reportedly, most reports of distant spread of the toxin happened in adult patients who received Botox or Myobloc for unapproved use in spasticity or for cervical dystonia, an approved use.

May 2009

Practical Neurology
**Epilepsy Costs and Conversation**

Total costs of epilepsy care may extend well beyond those associated with primary management of the condition, new data presented at the AAN Annual Meeting confirm. Costs for management of comorbidities, including mental health disorders, can significantly increase the overall costs to third-party payors and employers.

A 12-month retrospective analysis of costs associated with epilepsy found higher rates of mental disorders, substance abuse, and other neurological and physical disorders among patients with epilepsy compared to those without the condition. On average, the analysis showed, direct costs for third-party payors (medical, pharmaceutical costs, etc.) were nearly three times higher for patients with epilepsy versus those without. Interestingly, expenses related to health issues other than epilepsy accounted for 80 percent of insurers’ total annual costs for epilepsy patients.

In a second study investigating indirect costs associated with epilepsy, costs were also three times higher—or about $6,400 higher per patient—for individuals with epilepsy versus others.

The study was sponsored by Johnson & Johnson Pharmaceutical Services, Inc. in conjunction with Ortho-McNeil Neurologics. The latter also sponsored and presented a study analyzing dialogue between neurologists and epilepsy patients.

According to results of the study, topics of mood and behavior were not generally discussed during epilepsy patients’ visits with neurologists, while one out of four visits lacked discussion of AED side effects.

The study involved audio- and video-recording of office visits as well as surveys of physicians and patients assessing what they discussed in office visits. Only 13 of 60 visits (22 percent) included discussion of mood and behavior, 57 percent of patients reporting irritability, depression, anxiety, hyperactivity, or other mood effects in post-visit surveys. Many neurologists admitting post-visit that they are uncomfortable addressing mood/behavior, believing they are the domain of other physicians.

Discussion of mood and behavior may be especially important now, in light of recent FDA mandate of class-wide label changes for AEDs. Last month, FDA updated its order that manufacturers, “Update product labeling to include a warning about an increased risk of suicidal thoughts or actions and...develop a Medication Guide to help patients understand this risk.” The only drugs excluded from the rule are those indicated only for short-term use.

In April, the agency approved label changes for all of the following: Carbatrol, Celontin, Depakene, Depakote ER, Depakote sprinkles, Depakote tablets, Dilantin, Equetro, Felbatol, Gabitril, Kepra, Kepra XR, Klonopin, Lamictal, Lyrica, Mysonine, Neurontin, Peganone, Stavzor, Tegretol, Tegretol XR, Topamax, Tranxene, Tridione, Trileptal, Zarontin, Zonegran, and generics. For more information, log on to: www.fda.gov/CDER/Drug/infopage/antiepileptics/default.htm.

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**FDA ACTIONS**

**Fampridine NDA Accepted.** An oral therapy for MS could receive FDA approval by year’s end. After announcing early this spring that the FDA had refused a new drug application (NDA) for fampridine-SR, Acorda Therapeutics earlier this month said that the agency had accepted a revised NDA and given it Priority review status. Sustained release fampridine has been shown in studies to improve walking ability of patients with MS, according to the company.

**Glioblastoma Drug Cleared.** While glioblastoma is still considered incurable, FDA approval of Avastin (bevacizumab, Genentech/Roche) makes the condition treatable. The agency approved the indication earlier this month based on data from clinical trials showing that about a quarter of treated patients experienced tumor response, which lasted for about four months. Avastin is also approved for metastatic colorectal cancer and breast cancer.

**AD Trial Approved.** Blanchette Rockefeller Neurosciences Institute (BRNI) will launch as Phase II trial of Bryostatin for the treatment of Alzheimer’s disease patients following FDA approval of the trial design last month. Bryostatin, originally created as an anti-cancer chemotherapy, has shown evidence of efficacy against AD in rodent models. The human trials should begin this summer.

**Dissolvable Lamotrigene Green-lighted.** A formulation of Lamictal (GlaxoSmithKline) that dissolves on the tongue earned FDA approval this month. Lamictal ODT will be available in 25mg, 50mg, 100mg and 200mg formulations, according to the company.
SHORT TAKES

Arm of AD Study Cancelled. Elan Corporation and Wyeth will discontinue the highest of three dosing regimens (2.0mg/kg) in the two ongoing Phase III studies of bapineuzumab in patients with mild to moderate Alzheimer’s disease who do not carry the ApoE4 allele. The decision was made after its review of vasogenic edema (VE) in the Phase III trial. During a Phase II trial, VE was observed more frequently in patients who were carriers of the ApoE4 allele and was more likely to occur at higher doses of bapineuzumab. The companies will continue testing in two other ongoing studies, which are testing a single 0.5mg/kg dose in patients with ApoE4 allele. The study’s Safety Monitoring Committee also had no concerns over the 1.0mg/kg dose.

Bucking Migraines. In efforts to raise $1 million for headache research, the National Headache Foundation has kicked off the Migraine Million campaign. The organization says 82 cents from every dollar it receives goes directly to research, programs, and services. Donations can be made online at headaches.org.

Diet Pills. If adding an AED onto the ketogenic diet for a pediatric patient, consider zonisamide. A retrospective study of 217 consecutive children who started the diet from 2000 to 2007 found that a greater than 50 percent reduction in seizures was significantly less likely for patients taking phenobarbital but was significantly more likely for those taking zonisamide. (Epilepsia, early view, April 20, 2009)

Spine Study Commences. A novel protein-based therapy for low back pain is now under investigation, according to DePuy Spine, Inc. (a Johnson & Johnson company), which is developing the treatment in collaboration with Advanced Technologies and Regenerative Medicine, LLC. The genetically engineered human protein, intradiscal rhGDF-5, injected into the lower spine may relieve pain and could slow or even reverse early stage degenerative disc disease, the company says.

Another J&J company and member of the DePuy family, Codman Neurovascular (formerly Cordis) has been established and may become familiar to neurologists. The company markets neurovascular coils, catheters, liquid embolics, and vascular reconstruction devices for minimally invasive treatment of aneurysms and cerebral arteriovenous malformations.

DBS in Children. Globus pallidus internus-deep brain stimulation offers an effective and safe therapy in children suffering from primary dystonia, according to a study presented during the 77th Annual Meeting of the American Association of Neurological Surgeons. In this study, results and long-term follow up data (36 to 85 month range) were analyzed in a group of five patients, age 16 or younger, suffering from primary generalized dystonia. All patients had cases of dystonia that were resistant to conservative approaches.

The entire patient group experienced significant improvement in symptoms as early as the first week, which further improved in the months to follow: The mean improvement in the Burke-Fahn-Marsden movement score was 67.4 percent (range 47 percent to 87.5 percent), 75.4 percent (range 61.5 percent to 91.7 percent), and 83.5 percent (range 72 percent to 93.3 percent) at three months, 12 months, and long-term follow-up, respectively.

Two patients experienced problems with the implanted devices: electrode dislocation and breakage of extension cable in one, and imminent perforation of extension cable in another. There was very mild dysarthric speech disturbance in two patients with no other therapy-related morbidity noted.

Stimulating Depression Treatment. Researchers have investigated cortical stimulation in patients with medically refractive major depression. The results of a study, Long Term Follow-up of Cortical Stimulation to Treat Major Depressive Disorder, were presented May 5 at Harvard Medical School. For the study, 12 patients were randomized to single blind active or sham stimulation for eight weeks; all subjects then received active stimulation. One patient was excluded from analysis due to a protocol deviation. Outcome assessments included the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS), and the Global Assessment of Functioning (GAF).

Improvements were seen: At 8 weeks, HDRS decreased by 22 percent (active: n=6) versus 3 percent (sham: n=5). MADRS decreased 22 percent (active) versus 8 percent (sham). GAF increased 23 percent (active) versus 12 percent (sham). In all patients, continued improvement was seen at 6 months (average HDRS: 20 percent) and 12 months (average HDRS: 33 percent).

At 12 months, patients whose electrodes were implanted <20 mm from the precentral sulcus averaged a 59 percent improvement in HDRS compared to a 12 percent improvement in patients (n=6) with electrodes <20mm from the precentral sulcus.

Epilepsy Surgery in Babies. Surgery is relatively safe for babies and toddlers with epilepsy and effective in controlling seizures, according to a study in Epilepsia (e-pub Jan. 2009). Further, the study says surgery may aid the brain development of the child. Researchers reviewed epilepsy surgeries in children three years old and younger between 1987 and 2005. Across Canadian pediatric neurosurgical centers 82 percent of 116 children started suffering from seizures this first year of life. And the surgeries themselves were notable. Children typically underwent major brain operations, including doctors removing or disconnecting half of the brain. Despite the seriousness of the surgery there few complications and only one death. Prior to surgery, the children experienced an average of 21 seizures per day. About 67 percent were seizure free and 14 percent had a better than 90 percent improvement one year after surgery. Only 7.5 percent saw no benefit from surgery.