

AAN Annual Meeting: Video Coverage, Study Highlights, and More

Last month, thousands of members of the international neurology community convened in Vancouver for the Annual Meeting of the American Academy of Neurology (AAN). *Practical Neurology*[®] magazine covered the meeting through many channels, such as live Twitter updates from the lecture hall, breaking news from the meeting posted on NeurologyWire.com, and video coverage featuring interviews with thought leaders (available on PracticalNeurology.com), hosted by Dr. Michelle Dougherty. Ahead are highlights from this year's meeting:



Rates of Fertility Found to Be No Different In Women with Epilepsy

Findings from a prospective study indicated that women with epilepsy seeking conception have comparable likelihood of achieving pregnancy, time to achieve pregnancy, and pregnancy outcomes, compared to a group of healthy peers. "There's a lot of research showing that patients with epilepsy—men and women—do not conceive children at the same rate as those without epilepsy," said study co-author Cynthia Harden, MD. "We were trying to prove or disprove the long-held idea that women with epilepsy have greater rates of infertility." An app was designed for the investigators to keep track of menstrual cycles, sexual activity, as well as seizure activity; participants included patients with epilepsy and healthy controls who were trying to conceive for no less than six months. "The primary outcomes showed that the fertility rates were basically the same," she said. Studies are currently underway to examine the influence of ovulatory rates and frequency of intercourse on outcomes, as well as AED and seizure factors within the epilepsy group. But according to Dr. Harden, these initial findings should reassure women with epilepsy and clinicians when counseling these patients who are planning pregnancy.

Data for Investigational Levodopa for Subcutaneous Infusion Impresses in Presentation

NeuroDerm showcased promising new data for its investigational levodopa/carbidopa agent administered by subcutaneous infusion. The Phase 2a data, presented at the "Invited Science: Movement Disorders" session, demonstrated that NeuroDerm's subcutaneously administered levodopa and carbidopa (LD/CD), ND0612H, led to clinically-

significant plasma levodopa levels. These results suggest that ND0612H, which is intended to maintain high, consistent, and stable levodopa plasma levels in patients with severe Parkinson's disease through simple sub-cutaneous delivery, may provide a safe and effective alternative to the current treatment options that require surgery in a majority of these patients. According to Oded Lieberman, PhD, MBA, CEO of NeuroDerm, ND0612H will fill a unique need in the market. "We are offering the same benefits of levodopa/carbidopa administered by enteral suspension without surgery," he observed. The solution that NeuroDerm has designed and patented, according to Dr. Lieberman, "has the ability to continuously administer levodopa not through surgery but simply, subcutaneously." According to Dr. Lieberman, this will be a particular benefit for patients with severe Parkinson's disease for whom the therapeutic window has become so narrow. Dr. Lieberman noted that the company plans to submit NDAs for both the high-dose and low-dose versions of the drug by the end of 2017.

Study Assesses Real-World Impact of Rebif in Relapsing MS

EMD Serono presented data showing the real-world and clinical impact of Rebif (interferon beta-1a) for people with relapsing multiple sclerosis. According to Frederick Munschauer, MD, study co-author and Vice President of Medical Affairs for Neurology and Immunology at EMD Serono, using real-world data allows physicians to gain insights into a drug's effectiveness beyond the controlled conditions of clinical trials. "Real-world data, in which you take all patients, all comers and look how they did when exposed to a given therapy, allows us to get some insights into comparative effectiveness as well as safety, tolerability, and, importantly, the burden of care both to patients and

physicians,” observed Dr. Munschauer. “You don’t know whether the result of a randomized clinical trial is indeed generalizable to a broader population of patients with disease where drug will be utilized.”

The findings showed that, after controlling for patient demographics and clinically meaningful measures of disease severity, patients initiating Rebif had a lower likelihood of experiencing surrogates for relapse in the first year than patients initiating dimethyl fumarate or teriflunomide. “This gives the practicing neurologists insights into how drugs that have been around for some time would compare to some of the newer drugs, and that’s where we think the power of this methodology will advance the clinical practice of neurology over subsequent decades,” Dr. Munschauer explained.

Investigational Inhaled Levodopa Shows Promise as Rescue Therapy

Acorda presented poster data from its Phase 2b study of CVT-301, a novel, self-administered inhaled levodopa therapy currently in Phase 3 development for the treatment of “off periods” in Parkinson’s disease. Inhaled CVT-301 bypasses the digestive system, reaching the brain quicker than oral medications, so off periods may be treated more quickly.

In the study, CVT-301 demonstrated rapidly improved motor function during during off-periods, according to investigator Peter LeWitt, MD, Director of the PD and Movement Disorders Program at Henry Ford Hospital in Detroit. “The novelty here is that you have a rapid onset of effect for what is essentially a rescue therapy during ‘gaps’ throughout the day in which patients experience a loss of treatment effect,” said Dr. LeWitt. “The goal is not to produce a constant effect, but to get someone out of an ‘off state.’” Dr. LeWitt believes that CVT-301 may fill a very important need for patients and help relieve any stress or worry about leaving the house and having an attack. “What this agent can be for patients is a confidence builder,” he noted.

Acorda is currently enrolling for its Phase 3 trial and is planning to file an NDA with the FDA in early 2017.

Zinbryta Shows Benefit for Cognition in Relapsing MS Patients

New data presented by Biogen showed that the investigational therapy Zinbryta (daclizumab HYP) provides improvements on cognitive outcome measures in people living with

relapsing forms of multiple sclerosis (RMS). A post-hoc analysis of exploratory efficacy endpoints from the Phase 3 DECIDE study comparing Zinbryta to Avonex (interferon beta-1a intramuscular injection) showed treatment with Zinbryta led to significant improvements across cognitive outcome measures. New 144-week data show mean improvements from baseline on the Symbol Digit Modalities Test were +6.30 for Zinbryta-treated patients versus +3.09 for Avonex-treated patients.

According to Christopher Hotermans, MD, PhD, Vice President of Global Medical Therapeutic Areas for Biogen, these results are significant, given the impact of MS on cognition. “We know that roughly 52 to 70 percent of patients with relapsing MS have cognitive issues and that these can present very early on,” said Dr. Hotermans. “These data show that patients on Zinbryta have significant improvement over the active comparator over 96 and 144 weeks,” observed Dr. Hotermans. “To the best of my knowledge, that’s first time a drug is showing significant effect on cognition.”

Modeling Data Predict Strong Efficacy with Aptiom Monotherapy for Partial-Onset Seizures

Researchers successfully predicted the efficacy of conversion to eslicarbazepine acetate (ESL, Aptiom) monotherapy at 800mg QD for partial-onset seizures through the use of modeling and simulation of the exposure-response relationship, according to a poster study sponsored by Sunovion. The results indicated that ESL 800mg QD reduces seizure-related exits compared with the historical control in patients who convert from either one or two previous AEDs. “In this study, we identified a number of factors that affect the success of monotherapy conversion,” said study co-author and Executive Medical Director of Sunovion Dr. David Blum. “We found that patients who convert from one drug are likely to achieve success at 800mg on Aptiom.”

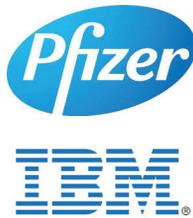
Regarding the use of pharmacokinetic-pharmacodynamic modeling to predict efficacy outcomes, Dr. Blum noted that simulations may help researchers extrapolate findings beyond the scope of traditional trials. “When you run a clinical trial, you answer very closely defined questions within specific contexts.” With this modeling, he says, “We can expand that context and ask different questions.” ■

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Pfizer and IBM Team Up On Remote Monitoring Project for Parkinson's Disease

Pfizer Inc. and IBM are joining forces to develop remote monitoring solutions aimed at transforming how clinicians deliver care to patients suffering from Parkinson's disease. The experimental approach will rely on a system of sensors, mobile devices, and machine learning to provide real-time, around-the-clock disease symptom information to clinicians and researchers. The ultimate goal is to obtain a better understanding of a patient's disease progression and medication response to help inform treatment decisions and clinical trial design, while also speeding the development of new therapeutic options. "We have an opportunity to potentially redefine how we think about patient outcomes and 24/7 monitoring, by combining Pfizer's scientific, medical and regulatory expertise with IBM's ability to integrate and interpret complex data in innovative ways," said Mikael Dolsten, MD, PhD, President of Pfizer Worldwide Research and Development, in a release.

The collaboration seeks to create a holistic view of a patient's well-being by seeking to accurately measure health indicators, including motor function, dyskinesia, cognition,



sleep, and daily activities such as grooming and eating. Insights from these data could help clinicians understand the effect of a patient's medication as the disease progresses, enabling them to help optimize the patient's treatment regimen. Data generated through the system could also arm researchers with the insights and real-world evidence needed to help accelerate potential new and better therapies.

"The key to our success will be to deliver a reliable, scalable system of measurement and analysis that would help inform our clinical programs across important areas of unmet medical need, potentially accelerating the drug development and regulatory approval processes and helping us to get better therapies to patients, faster," said Dr. Dolsten.

The two companies project that the system will move into initial clinical testing quickly. Pfizer and IBM will convene an external advisory board of patient groups, advocacy organizations, clinicians, and neuroscientists for guidance on the use of technology, medical devices, data management, and research protocols, and to ensure the needs of patients guide the program.

Investigational Progressive MS Agent Decreases Disease Progression in Phase 3 Trial

An investigational agent for the treatment of primary progressive multiple sclerosis has shown considerable promise in new phase 3 data presented at the recent AAN Annual Meeting. The study demonstrated evidence of the efficacy and safety of MD1003, a highly concentrated pharmaceutical-grade biotin administered at a dose of 300mg per day in the treatment of primary and secondary progressive MS. The primary endpoint was met in the intent to treat population, with 12.6 percent of patients in the MD1003 arm showing an improvement of EDSS or TW25 at Month 9, confirmed at Month 12, compared to none of the patients in the placebo arm. According to manufacturer medDay Pharmaceuticals, the data represent the first time a drug has decreased the rate of disease progression in addition to improving a significant proportion of patients with the progressive MS primary endpoint met.

Biomarker Analysis of Phase 2 Data Shows Potential for ALS Agent for Patients with Systemic Inflammation

Secondary analysis of Neuraltus Pharmaceuticals' Phase 2 clinical trial of its investigational treatment, NP001, for amyotrophic lateral sclerosis (ALS), suggest that increased levels of a biomarker for systemic inflammation, C-reactive protein (CRP), may indicate which patients are more likely to have a positive response. NP001 is designed to regulate inflammatory cell activity, as measured by CRP. In the Phase 2 study, Neuraltus prospectively measured CRP levels in participating patients. CRP is easily measured and high levels are recognized as indicating systemic inflammation.

According to the company, the additional pre-defined analysis of the Phase 2 data involving CRP, in conjunction with other independent research in ALS patients, make it a credible biomarker for enriching patient selection in future studies of NP001.

THE FDA FILE



New Drug Class Established as Nuplazid Receives FDA Approval for Parkinson's Disease Psychosis

The FDA has approved Nuplazid (pimavanserin) from Acadia Pharmaceuticals for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis, which affects roughly 40 percent of patients with Parkinson's disease. The first FDA-approved medicine for this indication, Nuplazid preferentially targets 5-HT_{2A} receptors (which are thought to play an important role in Parkinson's disease psychosis) while not interfering with patients' dopaminergic therapy and thus not impairing motor function. According to Acadia, Nuplazid's novel pharmacology establishes a new class of drug: a selective serotonin inverse agonist (SSIA).

In a pivotal Phase III study published in *The Lancet*, Nuplazid significantly reduced the frequency and severity of psychotic symptoms compared to placebo on the Scale for Assessment of Positive Symptoms – Parkinson's Disease (SAPS-PD). The most common adverse reactions in this study were peripheral edema (seven percent for Nuplazid-treated patients versus three percent for those on placebo) and confusional state (six percent in Nuplazid-treated patients versus three percent in the placebo group).

Acadia plans to make Nuplazid commercially available to patients suffering from hallucinations and delusions associated with Parkinson's disease psychosis in the US in June.



Marinus Pharmaceuticals Receives FDA Orphan Drug Designation for Ganaxolone IV to Treat Status Epilepticus

The FDA has granted Orphan Drug Designation to the intravenous (IV) formulation of a CNS-selective GABA_A modulator, ganaxolone, for the treatment of status epilepticus from Marinus Pharmaceuticals. A Phase 1 clinical trial evaluating the safety, tolerability and pharmacokinetics of ganaxolone IV is expected to initiate in the first half of 2016. "Status epilepticus is a life-threatening condition, associated with high mortality and if not treated immediately, can result in brain damage, cognitive impairment and death," remarked Christopher M. Cashman, Chief Executive Officer of Marinus Pharmaceuticals, in a release. "We are pleased to receive the Orphan Drug Designation for ganaxolone IV in this difficult to treat seizure disorder with limited treatment options."

Skin Disorder Tied to Increased Risk of Alzheimer's Disease

A new study has uncovered an increased risk of dementia—in particular Alzheimer's disease—in patients with rosacea, a chronic inflammatory skin disease. The risk may be highest in older patients and in patients where rosacea was diagnosed by a hospital dermatologist, according to the findings published in the April 2016 edition of the *Annals of Neurology*.

Rosacea is characterized by elevated expression of certain proteins—including matrix metalloproteinases and antimicrobial peptides—that are also involved in various neurodegenerative disorders such as Alzheimer's disease and other forms of dementia. A Danish research team explored this link further, reviewing cases of more than 82,000 patients with rosacea from 1997 to 2012. After adjustments for potential confounding factors, patients with rosacea were estimated to have had a seven percent increased risk of dementia and a 25 percent increased risk of Alzheimer's disease compared to individuals without rosacea. Women had a 28 percent increased risk of Alzheimer's disease and men had a 16 percent increased risk if they had rosacea, while the risk of Alzheimer's disease was only significantly increased in individuals older than 60 years (who had a 20 percent increased risk). When analyses were limited to patients with a hospital dermatologist diagnosis of rosacea only, the increased risks of dementia and Alzheimer's disease were 42 percent and 92 percent, respectively. ■

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Migraine Prevention Drug Shows Potential in Phase 2b Trial

An investigational agent from Alder BioPharmaceuticals has shown promise for migraine prevention. In a Phase 2b study, ALD403, a monoclonal antibody that targets calcitonin gene-related peptide (CGRP), acted rapidly and prevented migraine over a 12-week period, meeting both primary and secondary efficacy endpoints. Researchers randomized patients to receive a single intravenous infusion of 10mg, 30mg, 100mg, or 300mg of ALD403 or placebo, and found that the 300 mg and 100mg dose levels of ALD403 met the primary efficacy endpoint of 75 percent response rate in 12 weeks in 33 percent and 31 percent of patients, respectively.

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