Abstracts from the ASENT 2007 Annual Meeting March 5–8, 2007

Poster Abstract #1: Passive and Active Functional Tasks Are the Main Reasons for Treatment of Upper Limb Spasticity in Post-Stroke Patients Among Neurologists, Psychiatrists, and Primary Care Physicians

Amanda M. VanDenburgh, Susan Abu-Shakra,
Mitchell F. Brin, and Frederick Beddingfield III
Allergan, Irvine, CA

Objective: To determine the major reasons for the treatment of upper limb spasticity in post-stroke patients among the leading three specialties that evaluate and manage these patients.

Methods: 523 physicians were contacted to participate in an Internet-based survey. A total of 50 neurologists, 50 psychiatrists (PM&Rs) and 300 primary care physicians (PCPs) fulfilled eligibility criteria and completed the survey. Physician demographics and patient population characteristics pertaining to post-stroke spasticity were collected.

Results: The average number of adult stroke patients evaluated per month was 23.8 for neurologists, 17.9 for PM&Rs, and 38.6 for PCPs. Approximately half of these patients had spasticity in the upper and/or lower limb (10.3, 10.0, and 12.5, respectively). A majority of the upper limb spasticity patients presented with a clenched fist. The main treatment goals in this population were: relief of pain/discomfort and improved access to the palm for hygiene purposes (passive function goals) or to improve the ability to grasp and hold objects (active function goals).

Conclusions: Physicians interviewed in this survey evaluate and treat a significant number of poststroke spasticity patients who suffer from passive and active functional consequences. Symptoms of hand pain/discomfort and inability to access palm for hygiene purposes (passive function symptoms) or inability to use hand for grasping/holding (active function symptoms) were the major reasons cited for treatment.

Allergan, Inc. (Irvine, CA), retained Beta Research Corporation, a market research firm (Syosset, NY). Beta Research programmed and hosted the survey, produced the data tabulations, and prepared the analysis.

Poster Abstract #2: A Cluster Analysis of Treatment Response in Acute Bipolar Mania

Ilya Lipkovich, John P. Houston, and Jonna Ahl
Eli Lilly & Company, Indianapolis, IN

Objective: Characterize treatment response in bipolar mania by identifying groups of patients with similar response profiles.

Methods: Patients ($n = 222$) were from a randomized, double-blind study of treatment with olanzapine or divalproex in bipolar I disorder, manic or mixed episode, with or without psychotic features. Hierarchical clustering based on Ward's distance was used to identify patient groups based on Young-Mania Rating Scale (YMRS) total scores at each of 5 assessments over 7 weeks. Logistic regression was used to identify baseline predictors for clusters of interest.

Results: Four distinct patient clusters were identified: Cluster 1 ($n = 64$) did not maintain a response (YMRS total scores $\leq$ d12); Cluster 2 ($n = 92$) responded rapidly (within less than a week) and response was maintained; Cluster 3 ($n = 36$) responded rapidly but relapsed soon afterwards (YMRS $\geq$ e15); Cluster 4 ($n = 30$) responded slowly ($\geq$ e2 weeks) and response was maintained. Predictive models using baseline variables found YMRS Item 10 (Appearance) and psychosis to be significant predictors for Clusters 1 and 4 versus Clusters 2 and 3, but none of the baseline characteristics allowed discriminating between membership in Cluster 1 versus 4. Experiencing a mixed episode at baseline predicted membership in Clusters 2 and 3 versus Clusters 1 and 4; more prominent baseline depressive symptoms and number of previous manic episodes were predictors for Cluster 3 versus 2.

Conclusions: Treatment response profiles were predicted by clinical features at baseline. The presence of these features may be potential risk factors for relapse in patients who have responded to treatment and should be considered prior to discharge.

Poster Abstract #3: Cognitive Status of Patients With Schizophrenia as Modulator or Mediator of Functional Outcome

Ilya Lipkovich*, Sara Kollack-Walker*, Bruce Kinon*,
Virginia Stauffer*, Haya Ascher-Svanum*, and
Richard Keefe†

*Eli Lilly & Company, Indianapolis, IN, and †Duke
University, Durham, NC

Objective: Evaluation of the impact of cognitive deficits at baseline and during early treatment on subsequent functional outcomes.

Methods: Data from 2 double-blind, randomized, active comparator clinical trials in patients with schizophrenia who completed 24 weeks of drug therapy ($n = 294$) were analyzed. Functioning was measured with the QLS Instrumental Role Functioning (QLS Instru) domain subscore, and cognitive impairment with the Brief Assessment of Cognition (BACS) scale. Cognitive status at baseline was categorized by BACS total z score (standard deviations from healthy controls) as severe ($z \leq -2$), moderate ($-2 < z \leq -1$), or mild to no impairment ($z > -1$). Patient characteristics, baseline functioning, psychopathology, cognitive impairment, and early changes (at 8–12 weeks) in cognition and psychiatric symptoms were evaluated for predicting good functioning (QLS Instru score > 3.5) at endpoint using logistic regressions. The significant predictors were used in modeling relationships within path analytic framework.

Results: Baseline cognitive status was predictive of subsequent functioning, with severe cognitive deficits having significant negative impact on the probability of good functioning (OR = 0.33, 95% CI: 0.14–0.77, $P = 0.01$). Other significant predictors included baseline functioning score, and early improvement in psychopathology. Path analyses suggested that cognitive impairment at baseline and early changes in psychopathology had a direct impact on subsequent functional out-

comes. Changes in cognition had an indirect effect on functional outcomes mediated via changes in psychopathology.

Conclusions: Severe cognitive impairment at baseline impacted functional outcome both directly and indirectly, whereas the effect of changes in cognition was indirect, mediated via changes in psychopathology.

Poster Abstract #4: Metabotropic Glutamate Receptor 5 Modulates Microglial Activity and Provides Neuroprotection

Kimberly R. Byrnes, Bogdan Stoica, and Alan I. Faden
Georgetown University Medical Center, Washington, DC

The microglial response has long been implicated in a number of acute and chronic inflammatory and neurodegenerative conditions, and research has begun to focus on methods of modifying microglial activity to reduce neuronal damage. Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptors that have been divided into three classes based upon signal transduction pathways and pharmacological profiles. Both group I mGluR (mGluR1 and mGluR5) and group II receptors modulate neurodegeneration in a number of *in vitro* and *in vivo* models. In general, activation of group II receptors is neuroprotective, whereas activation of group I receptors has more complex effects—mGluR1 enhances cell death and mGluR5 inhibits caspase-dependent neuronal apoptosis. Group II receptors also play a modulatory role on microglial function *in vitro*, whereas little is known about Group I receptors in this regard. To further investigate the role of mGluRs in microglial function, mGluR expression and activity was assessed in a purified microglial culture system. Expression of mGluR1, 2/3, and 5 was assessed before and after lipopolysaccharide (LPS) stimulation of microglia; mGluR2/3 and 5, but not mGluR1, were highly expressed in these cultures. Other microglial cultures were stimulated with LPS with or without pretreatment using the mGluR5 agonist CHPG. Remarkably, CHPG treatment completely inhibited LPS-induced activation of microglia, as measured by increases in proliferation, nitric oxide production, and TNF $\pm$ secretion. These effects were found to be mediated by both calcium and PKC³ dependent pathways, and could be blocked by addition of the mGluR5 antagonist MTEP. Co-culture of LPS-activated microglia with neurons resulted in neurotoxicity. Pretreatment of microglia with CHPG prior to LPS blocked such neuronal cell death. In separate studies, CHPG or vehicle were infused intrathecally to rats subjected to moderate spinal cord injury using the weight drop contusion method. At 7 days after injury, CHPG-treated spinal cord samples showed a marked reduction in microglial associated inflammatory factors including ED1 and p22phox. Collectively, these studies indicate that mGluR5 represents a novel target for attenuating microglial-related inflammation and associated neurotoxicity. This may have therapeutic applications to both acute and chronic neurodegenerative disorders in which neuroinflammation has been implicated.

Poster Abstract #5: NAIP-based Neuroprotection Drug Screening

Kazunori Tanaka*, Yoshinori Okada[†], Harumi Sakai[‡], and Asako Otomo[‡]

Additional authors: Shinji Hadano, Hitoshi Osuga, and Joh-E Ikeda

*Neugen Pharma, Inc.; [†]Laboratory for Structure and Function Research, and [‡]Department of Molecular Neuroscience, The Institute of Medical Sciences, Tokai University, Kanagawa, Japan

Oxidative stress appears to play an important role in neurodegenerative diseases. A previous study on neuronal apoptosis inhibitory protein (NAIP) demonstrated that NAIP 1) selectively suppresses oxidative stress-induced cell death, 2) rescues motor neurons and CA1 neurons from death after peripheral nerve axotomy and bilateral common carotid artery occlusion, respectively, in mice by its ectopic expression, 3) preserves nigrostriatal dopaminergic function in the intrastriatal 6-OHDA rat PD model, 4) promotes motor neuron survival through the intracellular GDNF signaling, 5) is induced under hypoxia, and 6) results in the reduction of cell damage/death in cerebral ischemia and myocardial ischemia. Based on these findings, we hypothesize that NAIP-upregulatable anti-oxidative stress drugs could delay and/or prevent the onset of neurodegeneration and ischemic heart diseases. To clarify this hypothesis, we established the NAIP double sandwich ELISA system to identify the NAIP-upregulating compounds. Thirty compounds that upregulate endogenous NAIP were identified by the screening of 935 neurotropic compounds. Among these compounds, L-745870 exerted the strongest cell protective competence against oxidative stress-induced cell death. Intriguingly, an oral administration of L-745870 rescued hippocampus CA1 neurons from damage after bilateral common carotid artery occlusion in gerbil, and was efficacious against neurodegeneration in SOD1 ALS mouse model. These studies provide a preclinical proof-of-concept on the therapeutic feasibility of neurodegenerative diseases and cerebral and myocardial infarction. Further, the NAIP-based drug screening in conjunction with computer-aided pharmacoscreening will identify more promising compounds to treat such diseases.

This work was supported by the Ministry of Health, Labor, and Welfare of Japan.

Poster Abstract #6: Age-Related Motor Impairment in Mice Lacking Vg1037, an Orphan GPCR Localized to Brain Motor Systems

Richard Torres*, J. Vercollone*, K. D. Anderson*, and S. D. Croll^{†‡}

Additional Authors: G. D. Yancopoulos, S. J. Wiegand, and A. J. Murphy

*Regeneron Pharmaceuticals, Tarrytown, NY; [†]Queens College of CUNY, Flushing, NY; and [‡]Neuropsychology and Neuroscience, Graduate Center of CUNY, New York, NY

Using Velocigene[®] technology, mutant mice were made in which the VG1037 gene (GPR139) was replaced with the reporter gene LacZ. Staining for the LacZ product revealed extensive, but specific, localization of VG1037 to the nervous system, with a preferential localization to motor systems, including lateral striatum, globus pallidus, inferior olivary complex, and the cerebellar deep nuclei. In addition, marked LacZ expression was observed in the vestibular nuclei, spinal cord, and dorsal root ganglia. Mice were behaviorally evaluated for motor function using runway and open field gait analyses, Rotarod, and balance beam. At 2 months of age, mice showed no impairment in any of these behaviors. However, starting at 5 months of age, mice lacking the VG1037 gene displayed a significant impairment in balance, manifested as a decreased latency to fall on the Rotarod and less movement on the balance beam. In addition, the older null mutants showed significantly abnormal lateral placement of their forepaws when turning corners on the open field, but normal forepaw placement on a straightaway. Therefore, VG1037-null mutants appear to have a primary age-related motor deficit. The most parsimonious explanation for this profile of deficits is that VG1037-null mice

develop a balance deficit consistent with the localization of this gene to the motor and vestibular systems.

Poster Abstract #7: Anticonvulsant Effects of a Synthetic Progestin, Norethindrone, But Not Its A-Ring Reduced Metabolite in Mice

Rafal M. Kaminski*, Scott P. Runyon[†], Herbert Marini[‡], and Michael A. Rogawski[§]

*Epilepsy Research Section, NINDS, NIH, Bethesda, MD;

[†]Research Triangle Institute, Research Triangle Park, NC;

[‡]University of Messina, Messina, Italy; and [§]University of California, Davis, Davis, CA

It has been well established that the anticonvulsant effects of progesterone, an endogenous progestin, are mediated by allopregnanolone, its A-ring reduced neurosteroid metabolite. Moreover, it is believed that withdrawal of allopregnanolone accompanying the fall in progesterone at the time of menstruation is a major factor in catamenial seizure exacerbations in women with epilepsy. This view is supported by evidence that progesterone supplementation during the luteal phase of the menstrual cycle can reduce the incidence of catamenial seizures. There are anecdotal reports of beneficial effects of synthetic progestins in catamenial epilepsy. In the present study, we have attempted to ascertain whether a synthetic progestin, norethindrone, has anticonvulsant properties in an animal seizure model. Since norethindrone enters the same metabolic pathway as progesterone, we also examined whether its A-ring reduced metabolite 3 α -hydroxy-5 α -norethindrone is anticonvulsant. Norethindrone, at 100 mg/kg, elevated the pentylenetetrazol (PTZ) seizure threshold in mice for up to 120 min, indicating that it has prolonged anticonvulsant actions comparable in potency to progesterone. In contrast, 3 α -hydroxy-5 α -norethindrone was completely devoid of activity, unlike allopregnanolone, which dramatically elevates the PTZ seizure threshold. Furthermore, norethindrone was inactive in progesterone receptor knockout (PRKO) mice bearing a targeted null mutation of the progesterone receptor gene that eliminates the A and B isoforms of the progesterone receptor in the brain and in peripheral tissues. We have previously reported that the anticonvulsant activity of progesterone against PTZ seizures is actually enhanced in PRKO mice. Together, the data indicate that activation of progesterone receptors rapidly induces seizure protection. It will be of interest to determine whether norethindrone, acting via progesterone receptors and not its reduced metabolite, also has protective effects in an animal model of catamenial epilepsy.

Poster Abstract #8: PARP Inhibitors Attenuate Secondary Neuronal Cell Death and Improve Neurological Dysfunction After Traumatic Brain Injury

Bogdan A. Stoica, Kimberly R. Byrnes, and Alan I. Faden
Georgetown University Medical Center, Washington, DC

Traumatic brain injury (TBI) causes neuronal apoptosis through activation of caspase-like proteases as well as through caspase-independent mechanisms. Although inhibition of caspase-3 reduces post-traumatic apoptosis and improves functional outcomes in clinically relevant animal models, improvements are partial and limited. As neuronal cell death still occurs, albeit without the classical (caspase-dependent) apoptotic phenotype, such observations suggest that caspase-independent pathways may play an important role in delayed cell death.

Recent work shows that apoptosis inducing factor (AIF) contributes to caspase independent apoptosis after TBI. Moreover, unlike caspase activation, AIF translocation can occur under low energetic conditions, in association with activation of poly-ADP-ribose polymerase 1 (PARP-1) and reduction of NAD⁺. We used a well-established mouse controlled cortical impact (CCI) model of TBI to investigate the extent of caspase-dependent and independent apoptosis in relation to bioenergetic status. We also examined the connection between PARP activation and AIF-dependent neuronal cell death. Our results show that AIF translocation is detectable in the central regions of post-traumatic lesion sites at which cellular bioenergetic state is substantially compromised—whereas caspase-3 activation is generally more intense toward the periphery of the lesion where the bioenergetics are better preserved. Treatment with the specific PARP-1 inhibitor PJ34 at 3 hours after injury attenuates AIF translocation and secondary neuronal cell death, markedly reduces lesion volume and significantly improves functional outcomes (cognitive and motor) after CCI. These findings indicate that caspase-independent apoptosis contributes to secondary cell death, especially within the more central regions of the posttraumatic lesion where ATP is reduced, and that delayed pharmacological treatment with a selective PARP inhibitor limits AIF-related apoptosis and considerably improves posttraumatic outcome. The ability to limit cell death in the lesion core, and the effectiveness of more clinically relevant delayed treatment to improve posttraumatic outcome, underscores the therapeutic potential for this approach in human head injury.

Poster Abstract #9: Implementing Data Standards: Challenges from the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Common Data Elements Project

Selma C. Kunitz

KAI Research, Inc., Rockville, MD.

To accelerate and streamline clinical trials data collection in neurological studies, NINDS-NIH, together with KAI Research, Inc. (KAI), initiated a Common Data Element (CDE) project.

Goals of the CDE Project are to eliminate reinventing the wheel in clinical trials and to

- Create easily accessible tools
- Achieve data independence
- Facilitate aggregation of data

Development steps included identification of core data elements that are critical across clinical studies and to review other data standards projects (e.g., NIH Roadmap Initiative and CDISC) to ensure compatibility with other efforts.

Implementation included:

- Review of data collection forms and definitions from studies funded by NINDS to identify a set of "core" data elements relevant across neurological studies.
- Review of literature to identify recent clinical studies and the data used to present results as an empirical test of the data elements contained in the core data set.

Products include:

- Data structure, XML tags and CDISC tags, definitions
- Interactive Web site to access CDE data elements, data dictionary, study forms, and Manual of Procedures (MOP) at www.nindscommondataelements.org

Ongoing steps include development of disease spokes to compile CDEs for specific neurological disease areas. The talk will address the lessons learned in implementation of the CDE, including gap analysis for NINDS studies and some of the difficulties merging existing standards in new disease areas.

Poster Abstract #10: Preliminary Experience With Functional MRI (fMRI) Detects Altered Neural Networks Subserving Executive Function and Attention in Subjects With Partial Ornithine Transcarbamylase Deficiency (OTC)

Andrea Gropman*, Ayichew Hailu[†], Rebecca Seltzer[‡], Stanley Fricke[‡], and John van Meter[‡]

*Children's National Medical Center, Washington, DC;

[†]Georgetown University, Washington, DC; and [‡]Urea Cycle Rare Disorders Consortium

Objective: Ornithine transcarbamylase deficiency, an X-linked disorder, is the most common of the urea cycle disorders. Patients with neonatal onset present in the first few days of life with lethargy progressing to hyperammonemic coma, whereas the manifestations of partial deficiency are more variable with respect to age of onset and neurological symptoms. Preliminary neurocognitive assessment in women heterozygous for OTC have demonstrated weaknesses in attention/executive function. fMRI is based on the principle that the MRI signal changes in response to changes in the magnetic character of the intravascular contents. Since deoxygenated hemoglobin is more paramagnetic than oxygenated hemoglobin, it acts as an endogenous intravascular paramagnetic contrast agent. During increased neural activity, there is an elevation of cerebral blood flow, which is greater than that required by local oxygen consumption. On a magnetic susceptibility T2*-weighted image, this results in increased signal intensity, which, as in positron emission tomography (PET), allows estimation of task-related neural activation when compared with a baseline image. fMRI has been used extensively to examine neural networks subserving attention memory, and language in patients with epilepsy, ADHD, Alzheimer disorder, and TBI, but rarely as a tool to assess alterations in neural networks that may underlie cognitive changes seen in inborn errors of metabolism.

Methods: Ten adult subjects with partial OTC (8 females, 2 males) and eight controls consented to participate in this IRB-approved study. Subjects performed a modified flanker task which probes frontal lobe function, executive function and attention. All data were acquired on a Siemens Trio 3.0T scanner using echo-planar imaging sequences. Data was spatially normalized and corrected for head motion and artifacts. A fixed effects model was used to analyze activation maps. Statistical parametric analysis was used, with a *P* value of <0.05 considered significant.

Results: Activation maps revealed decreased activation in the frontal lobes, compared with controls. OTC subjects demonstrated parietal lobe activation suggesting recruitment of additional brain areas to compensate for perturbation of neural networks involved in frontal lobe function.

Conclusions: Although preliminary, this study suggests that subjects with OTC exhibit differential activation patterns compared with controls when performing a task that probes executive function. This is in agreement with earlier cognitive testing. Additionally, this study suggests that fMRI may be a useful tool to monitor the cognitive and neurological consequences of inborn errors of metabolism and may provide a

biomarker for early recognition of neurological damage and potential response to therapies.

Poster Abstract #11: A Research Network for the Experimental Therapeutics of Rare Neurologic Disorders

Barbara E. Herr*, Rachel Richesson[†], and Robert C. Griggs*; the CINCH Consortium

*Department of Neurology, University of Rochester Medical Center, Rochester, NY, and [†]University of South Florida College of Medicine, Tampa, FL

Rare neurologic diseases require multicenter, multinational collaboration for recruitment of sufficient numbers of participants for clinical trials. CINCH (Clinical Investigation of Neurologic Channelopathies) is an NIH-funded consortium, one of ten in the Rare Disease Clinical Research Network (RDCRN). CINCH is investigating episodic ataxias (incidence < 1/500,000), Andersen-Tawil syndrome (incidence < 1/1,000,000), and nondystrophic myotonias (incidence uncertain; estimated < 1/100,000). CINCH goals include longitudinal phenotype characterization, outcome measure development, quality of life assessment, molecular characterization, and pilot trials. CINCH explores pathways for developing orphan products.

RDCRN structure supports research and biostatistical design, informatics, data standards, information technology tools, adverse event handling, image transmission, and facilitated links with patient advocacy organizations and GRCs. A shared NIH-funded Data and Safety Monitoring Board provides oversight. A Data and Technology Coordinating Center (DTCC) provides technical support and informatics tools including a public website, with a public registry to request customized study information, and a member website, hosting Internet-based protocol management. The public English/Spanish website offers links with established patient support sites, patient-directed educational content, clinical trial information, and contact information for RDCRN-affiliated domestic and foreign sites. The member website includes tools for secure, rapid, high-quality data collection and review. CINCH has established a training program in experimental therapeutics for patient-oriented researchers committed to rare disorders focusing on study design for small numbers of subjects, recruitment strategies, grant strategies, and working with advocacy groups. CINCH has supported/mentored 21 trainees in its initial 3½ years.

Funded by NIH awards 8U54 NS059065, from the National Institute of Neurological Disorders and Stroke, and 7U54-RR019259, from the National Center for Research Resources, under the aegis of the Office of Rare Diseases.

Poster Abstract #12: Continuous Subcutaneous Apomorphine as an Aid in Regaining Consciousness After a Severe Traumatic Brain Injury

Esteban Fridman*, Ben-Zion Krimchansky[†], Tatiana Galperin[‡], Elkan Gamzu[‡], and Mariana Bonetto

*FLENI-Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia, Argentina; [†]Lowenstein Rehabilitation Hospital, Israel; and [‡]NeuroHealing Pharmaceuticals, Newton, MA

Objective: To investigate continuous subcutaneous apomorphine to accelerate the recovery of patients in a vegetative state (VS) or minimally conscious state (MCS) due to severe traumatic brain injury (TBI).

Design: Open-label, two-center study of subcutaneous continuously administered apomorphine via an external pump for 12 hours/day, at doses from 1 to 8 mg/hour for 84 days in closed-head TBI patients in VS or MCS for 1–4 months post injury. Apomorphine is a strong dopamine agonist with favorable pharmacokinetics.

Results: 3 male and 3 female patients (aged 18–41 at baseline) with TBI secondary to vehicular accidents from 46 to 104 days earlier were enrolled. Baseline CNCS (Coma-Near Coma Scale) ranged from 20 to 41. All but one had been treated with, and failed to respond to, other dopaminergic agonists. Four of the six patients recovered consciousness (CNCS = 0 in three cases, and 2 in one patient still under treatment). One patient improved from CNCS = 36 to CNCS = 26 over 47 days, but died from a non-drug-related subdural hemorrhage. The sixth patient improved from CNCS = 36 to CNCS = 24 by day 14 and is still under treatment. The first patient has returned to work. In all cases, the rate of improvement was faster than expected (2 weeks or less) and was sustained after apomorphine was discontinued. Drug-related side effects were mild, transient, and expected based on the long-term use of apomorphine.

Conclusion: These preliminary data suggest that continuous subcutaneous apomorphine may accelerate the emergence of consciousness following TBI, a hypothesis to be tested in a double-blind, placebo controlled trial.

Pt	Age, Gender	Dx*	Stimulant Rx Prior to NH001 Rx	OAI (MRI)	Treatment		CNCS Scores	
					Start of Rx (days post of Rx)	Duration of Rx (days)	At Baseline	Day 180 (after NH001 start)
1	25, m	MCS	Methylphenidate, II	104	190	20	0	0
2	41, f	VS	Amantadine, Methylphenidate	II–III	70	47	36	26
3	30 f	VS	—	II	46	84	33	8
4	18 m	VS	L-dopa/carbidopa, Amitriptyline	II–III	57	84	41	2
5	18 m	VS	Amantadine, L-dopa	III	62	60 [†] (ongoing)	38	2 [†] (ongoing)
6	22 m	VS	L-dopa/carbidopa	III	68	40 [†] (ongoing)	36	24 [†] (ongoing)

*Diagnosis: MCS, minimally conscious state; VS, vegetative state. [†]On Rx as of January 19, 2007.

Poster Abstract #13: Possible Role of Primidone in the Treatment of Restless Leg Syndrome (RLS)

Krishna Mettu, Mandeep Garewal, Manjamali Sivaraman, and Pradeep Sahota

University of Missouri-Columbia, Columbia, MO

Introduction: RLS is a serious distressing sensorimotor complex disorder characterized by an urge to move legs usually with dysesthesias, begins or worsens during periods of rest or inactivity, is relieved with movement, and follows a circadian pattern with symptoms more intense in the evening hours. It can be either primary with familial component or secondary, occurring in conjunction with several medical conditions, such as iron deficiency anemia, end-stage renal disease, or pregnancy. Current pharmacological treatment medications which are being used so far include benzodiazepines, dopamine agonists, narcotics, levodopa/carbidopa, anticonvulsants, and iron replacement. We report a case in which primidone markedly improved the symptoms of RLS.

Case Report: A 49-year-old female presented with tremor in her upper extremities for evaluation. She had prior history suggestive of RLS with symptoms of uncomfortable creeping, crawling sensation in legs at rest especially in the evenings, constant urge to move legs and relieved with movements. This led to difficulty in initiation and maintenance of sleep, secondary to leg movements. She had been prescribed other medications including clonazepam without benefit. Dopamine agonists were not tried secondary to bipolar disorder. Past medical history was significant for hypertension, depression, bipolar disorder, anxiety. Neurological exam was remarkable for essential tremor in upper extremities for which she was started on treatment with primidone.

Results: Following the initiation of primidone for essential tremor, patient incidentally reported a marked improvement of RLS symptoms, sleep, and quality of life.

Conclusion: This case illustrates a possible role of primidone in the management of RLS. The exact mechanism of action of primidone is not known. It is thought to act as a gamma aminobutyric acid-receptor (GABA) agonist. Primidone is used to treat essential tremor and seizures. Further randomized controlled studies need to be performed in a larger patient population to assess the efficacy and role of primidone in treatment of RLS. This also suggests a possible role of GABA in the pathophysiology of RLS.

No financial support was received for this study and the authors do not have any personal financial interest.

Poster Abstract #14: Recruiting Older Diverse Populations into Studies of Parkinson's Disease: A Mixed Methods Approach to Development of an Intervention

Barbara C. Tilley, Arch Mainous, Dan Smith, and Jordan Elm

Medical University of South Carolina, Charleston, SC

Objective: To present development of an intervention for recruiting diverse participants into PD treatment trials.

Background: NET-PD (NINDS Exploratory Trials in Parkinson's Disease) conducted two pilot studies of PD treatments. Of 413 participants, 91% were Caucasian non-Latino, despite evidence suggesting a similar prevalence of PD across race/ethnic groups.

Methods: We used mixed methods (patient focus groups, interviews of older diverse community members, and The Trust in Medical Research Scale (TIMRS) administered in a sample of community physicians) to identify recruitment issues.

Results: Community physicians showed a higher level of trust on TIMRS than a general population sample, but similar differentiation by race/ethnicity. The recruitment intervention, developed from the data, incorporates a recruitment coordinator familiar with the diverse community near the study site, an approach to community physicians, and training for the recruitment coordinator in approaches to participants once they are referred. NET-PD sites have been randomized to an intervention trial of the recruitment intervention.

Limitations: TIMRS has not been validated in physician populations. The effectiveness of the new intervention cannot be evaluated until the conclusion of the randomized trial.

Conclusions: Based on a mixed-methods approach, an intervention was developed for recruiting diverse participants into the NET-PD long-term trial. The process used to develop the intervention provides insights about PD patients and about

the usefulness of TIMRS for future studies, regardless of the success of the recruitment intervention.

Funded by NIH/NIA 5 P30 AG21677 and NIH/NINDS U01NS043127 and U01NS43128

Poster Abstract #15: Preliminary Experience With MRS at 3T in Urea Cycle Disorders Detects Altered Metabolism in Partial Ornithine Transcarbamylase Deficiency

Andrea Gropman*, Ayichew Hailu[†], Rebecca Seltzer[‡], Stanley Fricke[†], John van Meter[‡], Mark Batshaw[‡], and Mendel Tuchman[‡]

*Children's National Medical Center, Washington, DC;

[†]Georgetown University, Washington, DC; and [‡]Urea Cycle Rare Disorders Consortium

Objective: To utilize 1H MRS at 3T to assess the extent of biochemical variations in glutamine, myo-inositol and NAA in symptomatic and asymptomatic female subjects heterozygous for ornithine transcarbamylase deficiency (OTCD) and hemizygous males with late-onset disease.

Methods: Single-voxel 1H MRS was performed on 10 subjects (8 females, 2 males) and 10 controls (8 females, 2 males) using PRESS sequence at TE 30 msec. Data were corrected for partial volume and analyzed with LCModel, a user-independent linear combination quantification software package, to yield absolute metabolite concentrations. All subjects also underwent IQ testing and dietary history analysis, and subjects had blood drawn for ammonia and plasma amino acids.

Results: All subjects were imaged in stable medical state. IQ scores were similar in subjects and controls. Two females with more severe disease manifested IQ in the low average range. Dietary protein intake was in the range of 0.6 mg/kg in subjects and 1.4 mg/kg in controls. Several biochemical changes identified subjects *versus* controls. Glutamine elevations were observed in thalamus of all subjects, compared with controls ($P < 0.05$). Myo-inositol depletion was evident in subjects *versus* controls in the parietal white matter ($P < 0.05$).

Conclusions: Impaired metabolism as seen by 1H MRS was common in subjects with partial OTCD, even those who are asymptomatic. The findings are important in that they confirm previous studies, but moreover demonstrate abnormal metabolism in asymptomatic females, which may provide an explanation of previous neurocognitive testing demonstrating impaired domains in females with OTC *versus* controls. This study also demonstrates the ability to use 1H MRS to assess biomarkers that differentiate patients from controls, which may be used to noninvasively assess disease course, response to therapy, and mechanisms of neural injury.

Poster Abstract #16: Building Patient Trust in Clinical Research: The Parkinson's Disease Experience

Robin Elliott and Veronica Todaro

Parkinson's Disease Foundation, New York, NY

Fewer than 1% of people with Parkinson's disease (PD) currently participate in Parkinson's clinical trials, far less than is required by large-scale studies that will be recruiting patients over the next several years. There are several reasons for this low level of participation, but one of the most important is the lack of trust within the PD patient community about clinical trials. To address this obstacle, the Parkinson's Disease Foun-

dation (PDF) facilitated a one-day meeting in January 2007 with 24 leaders representing diverse constituencies within the PD community. Participants at this roundtable included researchers, clinicians, government representatives, industry sponsors, advocacy organizations, and patients who are committed to the acceleration of Parkinson's therapies. Speakers included experts from both outside and inside the PD community.

We believe that this was one of the first meetings of its kind to bring together all stakeholders in the Parkinson's community and ask them to focus on the reasons why those who live with the disease do not participate more widely in clinical studies.

This gathering was educational and insightful for attendees. Topics included ways to engage the PD community in the clinical research process; ideas for enhancing the informed consent process and mechanisms for encouraging Parkinson's clinical research data translation and transparency. In addition to paving the way to increased understanding, dialogue, and partnership throughout the PD community, the roundtable offered hope for identifying and addressing key barriers to clinical trial participation in a way that will ultimately advance treatments and therapies and bring us closer to a cure for Parkinson's disease.

This roundtable was supported by Vernalis Pharmaceuticals and Teva Pharmaceuticals Industries.

Poster Abstract #17: Double-Blind Randomized Treatment of Poststroke Depression With Nefiracetam

Robert G. Robinson*, Ricardo E. Jorge*, and Sergio E. Starkstein[†]

*Department of Psychiatry, University of Iowa, Iowa City, IA; [†]Department of Psychiatry, University of Western Australia, Perth, Australia

Background: Although prior studies have shown effective treatments for poststroke depression, further trials utilizing novel treatments are needed. Nefiracetam is a nootropic agent with anticonvulsant, neuroprotective, and cognitive enhancing effects that appeared to show to improve mood in previous clinical trial.

Methods: A total of 159 patients within 3 months following stroke who met DSM-IV criteria for major depression were enrolled in a randomized, placebo-controlled, double-blind 12-week trial of 600 or 900 mg of nefiracetam or placebo.

Results: Repeated-measures ANCOVA failed to show a significant time by treatment interaction using either intention-to-treat or efficacy analysis. Response rates were greater than 70% and remission rates were greater than 40% for both nefiracetam and placebo, but no significant treatment differences were found. However, when examining the efficacy of nefiracetam among patients within the upper quintile of baseline HAM-D scores (i.e., those with more severe depression) we found a significant time by treatment interaction ($F = 3.24$, $df = 6, 46$, $P = 0.010$). Individual post hoc group comparisons showed that the 900-mg group had significantly lower HAM-D scores at 12 weeks of treatment than the 600-mg group and the placebo group.

Conclusion: Previous studies have shown that active antidepressant treatment following stroke may improve long-term mood as well as recovery in activities of daily living and cognitive function. The potential utility of nefiracetam in the management of patients following stroke remains to be determined.

**Poster Abstract #18: National Institutes of Health
Rapid Access to Interventional Development
(NIH-RAID) Pilot Program**

D. Badman, T. Jackson, and T. Miller

*National Institute of Neurological Disorders and Stroke,
National Institutes of Health, Bethesda, MD*

Background: The NIH Roadmap established the NIH-RAID Pilot Program to make available, on a competitive basis, certain critical resources needed for the development of new small molecule therapeutic agents. The NIH-RAID Pilot is not a grant program. Successful projects will gain access to the government's contract resources, as well as assistance of the NIH in establishing and implementing a product development plan.

Resources: Synthesis in bulk of small molecules and oligonucleotides; chemical synthesis of small peptides (GMP and non-GMP); scale-up production from lab scale to clinical-trials

lot scale; development of analytical methods for bulk substances; isolation and purification of pharmacologically active entities from natural sources; development of pharmacology assays; conduct of pharmacology studies with a predetermined assay; development of suitable formulations; physicochemical characterization of formulations developed, including tests of stability, disintegration, dissolution, and lot-to-lot variability; range-finding initial toxicology; IND-directed toxicology, with correlative pharmacology and histopathology; and product development planning and advice in IND preparation.

Eligibility: The NIH-RAID Pilot is intended for use by academic laboratories and not-for-profit organizations. The NIH-RAID Pilot also is open to non-U.S. applicants. Ideas arising solely from a corporate source without academic collaborators are not eligible. However, it is recognized that partnerships with for-profit entities are critical in the development process, and products may be licensed to for-profit partners and still be eligible for the NIH-RAID Pilot.