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PROGRAM

Fifth Annual Huntington Disease Clinical Research Symposium

Organized by the Huntington Study Group

To be held on Saturday, 5 November, 2011, in the Regency Ballroom at the Hyatt Regency Indianapolis, Indiana, USA.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The University of Rochester School of Medicine and Dentistry designates this educational activity for a maximum of 3.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The Symposium consists of three keynote speakers and four platform presentations by the following individuals with a panel discussion closing the session. In addition to the open panel, there will be allotted time for questions and answers after each keynote presenter.

8:00–9:00 AM
Poster viewing.

9:00–9:10 AM
INTRODUCTION—Introduction and acknowledgements by Andrew Feigin, MD, Chair, HSG Symposia Committee and Blair Leavitt, MD, co-Chair, HSG Symposia Committee.

9:10–9:40 AM
KEYNOTE ADDRESS—A Medical Career in the Shadow and Spotlight of Huntington's Disease.
Mary Edmondson, MD. *Duke University Medical Center, Durham, NC, USA.*

Mary Edmondson found herself involved in the cause of Huntington's disease patients and family members as a premedical college student. Inspired by Marjorie Guthrie, she organized the first meeting of North Carolina HD families at Duke University in 1981. After graduating from the UNC School of Medicine, and following residency and fellowship training in Internal Medicine at the University of Cincinnati, she taught and practiced for twelve years. In 2002 she completed a second residency in Psychiatry at Duke University. While in residence at Duke she established a genetic testing program for individuals at-risk for Huntington's disease and participated in the care of HD patients in the Duke Movement Disorders Clinic. Board Certified in both Internal Medicine and Psychiatry, she is uniquely experienced in managing the psychiatric, behavioral and medical complications of Huntington's disease. Huntington's Disease has shadowed Dr. Edmondson's professional career most of her life. After her father lost his battle with HD in 1995, Dr. Edmondson underwent predictive genetic testing. Fortunate to have tested negative for the gene, she embraced the care of HD patients and families, merging valuable lessons gained as a care-giving family member and at-risk individual with skills as a physician and activist. As the founder of the NC Center for the Care of Huntington's Disease, she brought together medical leadership from the major medical institutions in North Carolina to improve access to expert care for HD families. She provides ongoing psychiatric care to impoverished HD patients and their family members through a non-profit clinic, and participates in the HD clinics of both the Duke and Wake Forest University Medical Centers.

In the thirty years since the discovery of her father's illness, she has gathered funny, sad, and thought-provoking stories about Huntington's Disease, her journey through the health care system, and the demands of an inspired medical career. These experiences have informed her ideas about the comprehensive health care practices needed to meet the needs of HD patients and the dedicated physicians who provide their care.

9:40–10:10 AM

KEYNOTE ADDRESS—Understanding Changes in Behavior in HD.

Karen Anderson, MD. *University of Maryland, Baltimore, MD, USA.*

Behavioral changes are among the most common and disabling symptoms seen in people with Huntington's Disease (HD). Behavioral disturbances add greatly to the total burden of illness and may be a factor for long term care placement. They are seen in all stages of HD and may appear even before the onset of neurological illness.

This session will focus on understanding: depressed mood, apathy, irritability, delusions, anxiety, perseveration, and obsessive/compulsive behaviors. Sleep disturbances and changes in personality will also be described. Special emphasis will be placed on understanding suicidal behavior related to impulsivity, and how suicide attempts by people with HD may differ from those seen in the general population. Critical periods of increased risk for suicide in people with HD will be outlined, along with steps to help prevent attempts.

It is important for care partners to understand these symptoms for several reasons. For family members and others involved in a patient's daily life, it is helpful to know what types of behavioral symptoms can occur and how to describe them accurately when seeking professional help. It is particularly useful to understand how symptoms impact the family as a whole, and to specify which behaviors are more distressing to family members versus the affected individual.

For clinicians, understanding which symptoms are particular to people with HD is crucial to selecting proper treatment. Education of both families and clinicians about behavioral symptoms in people with HD is a vital part of treatment. Once behavioral changes are understood, extensive treatment with medications may not be needed; rather, family members may learn to work with patients to cope with symptoms more effectively. If treatment is needed, better understanding of behavioral symptoms allows for more precise treatment with fewer side effects. Behavioral changes are challenging, but can be managed with education and treatment.

10:10–10:20 AM

PLATFORM PRESENTATION—International Survey-Based Algorithms for the Pharmacological Treatment of Irritability and Perseverative Behaviors in Huntington's Disease.

M. Groves,[1] E. van Duijn,[2] K. Anderson,[3] D. Craufurd,[4] M. Guttman,[5] M. Edmondson,[6] D. van Kammen,[7] J. Giuliano,[7] S. Perlman,[8] J.-M. Burgunder,[9] N. Goodman,[10] and L. Goodman.[11] *[1]Beth Israel Medical Center, New York, NY, USA, [2]Leiden University Medical Center, Leiden, The Netherlands, [3]University of Maryland, Baltimore, MD, USA, [4]The University of Manchester, Manchester, UK, [5]University of Toronto, Toronto, ON, Canada, [6]Duke University, Durham, NC, USA, [7]CHDI Foundation, Inc, Princeton, NJ, USA, [8]University of California, Los Angeles, Los Angeles, CA, USA, [9]University of Bern, Bern, Switzerland, [10]Institute for Systems Biology, Seattle, WA, USA, and [11]Huntington's Disease Drug Works, Seattle, WA, USA.*

It is generally believed that treatments are available to manage behavioral symptoms such as irritability and obsessive-compulsive behaviors in Huntington's disease (HD). However, a recent Cochrane review of symptomatic treatments for HD concluded that no treatment recommendations could be made based on evidence from the research literature. In an effort to inform clinical decision-making, we surveyed an international group of experts to ascertain practice-based preferences for treatment of these symptoms. The irritability and obsessive-compulsive behaviors (OCBs) surveys were developed by a group of nine psychiatrists and neurologists drawn from the European Huntington's Disease Network (EHDN) and Huntington Study Group (HSG), and an HD family representative. The surveys were sent to 66 physicians from HD specialty centers in North America, Europe and Australia. Experts were selected by the core group as being knowledgeable in treating HD symptoms. Of the 55 expert respondents, 26 were from Europe, 23 from the United States, 4 from Canada, and 2 from Australia.

For irritability, the experts consistently endorsed an antipsychotic drug (APD) as first choice for treatment of urgent and aggressive behaviors. However, there was variation in practice patterns for treating less severe symptoms. Serotonin reuptake inhibitors (SSRIs) were endorsed as a first choice drug treatment by most respondents. Antiepileptic mood stabilizers (AEDs) were used by fewer respondents as first choice drug. For obsessive-compulsive/perseverative behaviors, survey results showed that behavioral therapy was utilized only for those with mild cognitive impairment. For pharmacologic treatment, there was agreement that a selective serotonin reuptake inhibitor (SSRI) was the first choice drug. However, clomipramine (CMI) was also cited as a monotherapy choice by experts familiar with its use. Antipsychotics (APDs) and (AEDs) were most often used as augmentation strategy.

Based on the survey results, we will present algorithm for the treatment of irritability and OCBs in HD.

10:20–0:30 AM

LATE-BREAKING RESEARCH

PLATFORM PRESENTATION—Longitudinal Divergence between Subjects and Companion Assessments of Psychiatric Manifestations in Prodromal and Diagnosed Huntington Disease.

E. Epping,[1] J. Long,[1] D. Craufurd,[2] E. McCusker,[3] J. Paulsen,[1] and the PREDICT-HD Investigators and Coordina-

tors of the Huntington Study Group. [1]*Univeristy of Iowa, Iowa City, IA, USA,* [2]*Academic Unit of Medical Genetics and Regional Genetic Service, St Mary's Hospital, Manchester, UK, and* [3]*Westmead Hospital, Sydney NSW, Australia.*

Background: Behavioral changes are a core feature of Huntington Disease and often develop during the illness prodrome. Individuals with the HD mutation may exhibit decreased awareness of manifestations with illness progression. Annual assessments of psychiatric symptoms from participants and observation of changes from their companions in the prospective longitudinal PREDICT-HD study provide the ability to determine if differences exist between the two groups. Participants are enrolled prior to HD diagnosis, but a subset was diagnosed during follow-up, with assessments analyzed before and after diagnosis.
Methods: Psychiatric assessments from 821 individuals with the HD gene mutation, 233 gene mutation-negative participants, and companions from the PREDICT-HD study were analyzed up to 6 years from study entry. Assessments included the Frontal Systems Behavioral Scale (FrSBe), and the Symptom Checklist-90 Revised (SCL-90R), which contains global measures of psychopathology and symptom subdomains. The mutation-positive group was stratified based on CAG Length-Age Product (CAP) score into three groups (Low, Medium, High CAP). Higher CAP scores correlate with closer proximity to HD diagnosis. Linear mixed effects regression was used to identify changes in symptoms over time by CAP group in comparison to mutation-negative participants, and between participants and companions. 137 individuals were analyzed before and after HD diagnosis.
Results: In the high CAP group, symptoms reported at baseline were usually higher in participants than observed by companions, but this trend reverses over time, with companions reporting significantly more changes but participants often reporting less at later visits. This is also observed in the medium CAP group for a subset of measures. Differences were also observed in the diagnosed subset, with companion reports of change even more pronounced after diagnosis.
Summary: Companion assessment of psychiatric manifestations is critical in HD, as differences arise compared to HD individuals, possibly due to a decrease in awareness of symptoms.

10:30–10:50 AM
Break and poster viewing.

10:50–11:20 AM
KEYNOTE ADDRESS—The Role of Diet and Exercise in Huntington's Disease.
Karen Marder, MD, MPH. *Columbia University, New York, NY, USA.*

While we know that Huntington's disease (HD) is caused by an expansion of the CAG repeat in the HTT gene, the role of diet and exercise as potential modifiers of age at onset or disease course has received increasing attention. Individuals with HD have lower body mass index (BMI) than age-matched controls and higher CAG repeat length has been associated with faster weight loss over three years. In premanifest individuals participating in PHAROS, higher caloric intake, but not BMI, was associated with both higher CAG repeat length and 5 year probability of onset of HD suggesting that increased caloric intake may be necessary to maintain BMI in clinically unaffected individuals. In PHAROS participants, adherence to a Mediterranean-like diet was associated with a reduced risk of phenoconversion after adjustment for age and CAG repeat length. In another study, low plasma levels of branched-chain amino acids distinguished pre-manifest HD cases from controls, and these levels were correlated with weight loss and CAG repeat length. Though weight loss in HD may be related to decreased caloric intake from poor swallowing or increased energy expenditure due to physical activity (e.g. chorea and dystonia), these studies suggest a systemic metabolic defect, possibly leading to a hypermetabolic state that is present in the premanifest state and can be replicated in animal models. Therapeutic approaches including anapleurotic therapy with triheptanoin, and ketogenic diet have been used.
Whether exercise will delay onset or slow progression of HD is unknown. We do not know if exercise promotes neuronal plasticity and survival in premanifest and manifest HD, whether aerobic or strength training exercises will be beneficial, and what outcome should be measured, e.g. (neuroimaging, cognitive or motor). Acceptance of exercise as an intervention by HD families and whether exercise could be detrimental is unknown. In a small study, HD patients had a lower exercise tolerance (lower anaerobic threshold) and increased lactate production secondary to impaired skeletal muscle mitochondrial function during prolonged exercise. We need a better understanding of the response to exercise, and its relationship to energy expenditure and diet. Exercise mimetic agents or molecules that would activate PGC1 alpha may prove therapeutically valuable.

11:20–11:30 AM
PLATFORM PRESENTATION—The Transcriptional Modulator H2AFY Marks Huntington Disease in Blood and Brain, in Man and Mouse.
Y. Hu,[1] V. Chopra,[2] R. Chopra,[2] J.J. Locascio,[1,3] Z. Liao,[1] H. Ding,[1]B. Zheng,[1] W.R. Matson,[4,5] R. J. Ferrante,[6,7] H.D. Rosas,[3,8,9] S.M. Hersch,[2] and C.R. Scherzer.[1,10,11,12] [1]*Laboratory for Neurogenomics, Center for Neurologic Diseases, Harvard Medical School and Brigham and Women's*

Hospital, Cambridge, MA, USA, [2]Laboratory of Neurodegeneration and Neurotherapeutics, MassGeneral Institute for Neurodegenerative Disease, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA, [3]Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [4]Geriatric Research Education Clinical Center, New England Veterans Administration VISN 1, Bedford, MA, USA, [5]Neurology, Laboratory Medicine and Pathology, and Psychiatry Departments, Boston University School of Medicine, Boston, MA, USA, [6]Geriatric Research Educational and Clinical Center (00-GR-H), V.A. Pittsburgh Healthcare System, Pittsburgh, PA, USA, [7]Neurological Surgery, Neurology, and Neurobiology Departments, University of Pittsburgh, Pittsburgh, PA, USA, [8]Center for Neuroimaging of Aging and Neurodegenerative Diseases, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA, [9]Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA, [10]Harvard NeuroDiscovery Center Biomarker Program, Cambridge, MA, USA, [11]Partners Parkinson's Disease and Movement Disorders Center, Massachusetts General Hospital, MA, USA, and [12]Brigham and Women's Hospital, Boston, MA, USA.

Huntington's disease (HD) is a progressive neurodegenerative disease for which there are many potential molecular targets for disease modifying therapies. Biomarkers that can reliably measure disease activity and progression and therapeutic response are urgently needed to facilitate their development. Here we interrogated 119 human blood samples for transcripts associated with HD. We found that the dynamic regulator of chromatin plasticity, *H2Ahistone family, member Y (H2AFY)*, is specifically over expressed in the blood of patients with HD compared to normal controls and controls with other neurologic disorders. We independently replicated this finding in additional cross-sectional and longitudinal studies comprising 142 further subjects and found that the elevation of*H2AFY* expression in patient blood begins presymptomatically and is progressive with disease duration. To examine the relevance of *H2AFY* to neurodegeneration, we studied it in human postmortem brain tissue and in R6/2 fragment and CAG140 full-length mouse models of HD. *H2AFY*progressivelyaccumulates in brain, especially in neuronal nuclei in human HD and in the mouse models. Increased H2AFYin blood and brain is likely to be a component of an epigenetic response to mutant huntingtin. Histone deacetylase (HDAC) inhibitors that are neuroprotective in HD mouse models reduce levels of *H2AFY* in them as well as in the blood of human HD subjects enrolled in a randomized phase II clinical trial of the HDAC inhibitor phenylbutyrate (PHEND-HD). This study identifies the chromatin regulator *H2AFY* as a potential biomarker associated with disease activity and therapeutic response that may become useful for enabling disease modifying therapeutics for HD.

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11:30–11:40 AM

PLATFORM PRESENTATION—Refining the diagnosis of Huntington disease: The PREDICT-HD study.

K. Biglan,[1] Y. Zhang,[2] M. Geschwind,[3] A. Juhl,[4] G. Kang,[3] A. Killoran,[1] W. Lu,[2] E. McCusker,[5] J. Mills,[4] L. Raymond,[6] C. Testa,[7] J. Wojcieszek,[8] J. Paulsen,[4] and the PREDICT-HD Investigators of the HSG. *[1]Department of Neurology, University of Rochester, Rochester, NY, USA, [2]Department of Biostatistics, University of Iowa, Iowa City, IA, USA, [3]Department of Neurology, University of California San Francisco, San Francisco, CA, USA, [4]Department of Psychiatry, University of Iowa, Iowa City, IA, USA, [5]Department of Neurology, Westmead Hospital, University of Sydney, Sydney, Australia, [6]Division of Neurological Sciences, University of British Columbia, Vancouver, BC, Canada, [7]Department of Neurology, Emory University, Atlanta, GA, USA, and [8]Department of Neurology, Indiana University, Indianapolis, IN, USA.*

Objective: To evaluate the clinical diagnosis of Huntington disease (HD) in prodromal HD using both a motor diagnosis and a multidimensional diagnosis.

Background: The clinical diagnosis of HD is traditionally based on the identification of characteristic motor abnormalities in an individual at-risk for HD. However, HD is a multidimensional disease and the focus on motor diagnosis may be misleading.

Design/Methods: Participants with the gene expansion for HD but not yet diagnosed were evaluated annually. Motor diagnosis was defined as a diagnostic confidence level (DCL) of 4 (unequivocal motor signs, ≥99% confidence) on the Unified Huntington Disease Rating Scale (UHDRS). Multidimensional diagnosis was defined as answering yes on question 80 (Q80) of the UHDRS, ≥99% confidence of manifest HD based on the *entire* UHDRS. We used Kaplan-Meier curves to estimate the temporal relationship of DCL to Q80. UHDRS motor, cognitive, and behavioral measures at first diagnosis were compared between participants diagnosed via Q80 prior to DCL and participants who were diagnosed simultaneously using t-tests. K-mean cluster analysis was used to identify clusters based on UHDRS motor, cognitive, and behavioral scores. Differences in

functional, motor domains, and rater type were explored between the identified clusters and controls using ANOVA, Kruskall-Wallis and Fisher's Exact Tests.
Results: 186 participants received a diagnosis of HD during a maximum of 7 years (mean 3.1) of follow up. In 108 (58.1%) the diagnosis by Q80 and DCL occurred simultaneously, and 69 (37.1%) diagnosis by Q80 occurred prior to DCL. Participants who were diagnosed by Q80 prior to DCL; were less impaired on motor (12.2±6.7 vs 22.4±9.3, $p<0.0001$), cognitive (42.2±14.4 vs 34.6±11.7, $p=0.0002$, for verbal fluency), but not behavioral measures (16.3±21.2 vs 18.6±22.1, $p=0.49$) at the time of first diagnosis when compared with those diagnosed simultaneously. Cluster analysis identified 3 clusters that represented primarily cognitively impaired, behavioral, and cognitively preserved phenotypes at diagnosis.
Conclusions: A multidimensional method results in an earlier diagnosis at a time with less motor and cognitive impairment than a diagnosis based on the motor examination. This may have implications for designing preventive trials where disease onset is an outcome.

11:40 AM–12:30 PM
PANEL DISCUSSION—Question and answer session between the day's speakers and the audience.

POSTER SESSION
Posters will be staffed from 8:00–9:00 AM and 10:30–10:50 AM in the Regency Ballroom.

Poster 1
Cognitive Improvement in Patients with Huntington's Disease after Successful Interventions to Obtain Financial Benefits.
B. Hennig, R. Kaplan, and D. Miner. *University of Connecticut Health Center Huntington's Disease Program, Farmington, CT, USA.*

Introduction: Although there is no known cure for Huntington's disease (HD) pharmacological and psychosocial interventions can improve quality of life. One on one support, coordination of information to be submitted to Social Security Administration and advocacy can lead to patients with HD obtaining disability benefits. Security of income often reduces distress. If distress is reduced and quality of life is improved one logical outcome might be improved cognitive function. This study examined the change in neuropsychological test scores before and after participants were approved for Social Security Disability Income.
Participants and Methods: Nine adult HD patients aged 23–61 (M=48.8, SD=8.0) completed a neuropsychological test battery, including the RBANS, Trail Making Test, Stroop Test and Beck Depression Inventory prior to and following approval for SSDI. Paired T-tests were used to compare cognitive changes.
Results: Using the RBANS to control for age, participants showed an overall improvement in their Total Index Score ($t=-2.92$, $df=8$, $p<.05$) and Attention Index ($t=-4.07$, $df=8$, $p<.01$). There was also a trend improvement in Immediate Memory ($p<.10$). Performances on measures requiring executive functioning and speed of information processing did not significantly change. Depression scores were also unchanged.
Conclusion: Based on the results of this small study one can conclude that with appropriate case management, quality of life, including the ability to stabilize the financial well-being of a person with HD, will improve. This improvement will in turn lead to a reduction in distress which can result in improvement of cognitive function.

Poster 2
Project AWARE: Assessing Awareness, Willingness and Ability of the Huntington disease Community to participate in Huntington disease clinical trials.
S. Kinel,[1] L. McCarthy,[1] E. Kayson,[1] E.R. Dorsey,[2] S. Noonberg,[3] L. Vetter,[4] and L. Goodman.[5] *[1]University of Rochester, Rochester, NY, USA, [2]Johns Hopkins University, Baltimore, MD, USA, [3]Medivation, Inc., San Francisco, CA, USA, [4]Huntington's Disease Society of America, New York, NY, USA, and [5]Huntington's Disease Drug Works, Lake Forest Park, WA, USA.*

Objective: Project AWARE examined barriers, preferences and knowledge regarding clinical trial participation for people affected by Huntington disease (HD) through a survey. Results will guide initiatives to improve awareness, willingness and ability for participation in trials.
Background: Current HD trials face difficulty recruiting an adequate number of participants. Little data has emerged since a small pilot project survey was offered in the US Pacific Northwest assessing HD families' levels of awareness, interest and knowledge regarding clinical research[1].
Methods: The pilot survey was expanded to broadly examine the HD community's: 1) level of awareness of trials; 2) communication preferences; 3) motivations and barriers towards participation; and 4) knowledge regarding research. Demographics were also addressed. The survey was conducted online and the results were anonymous.
Results: 618 respondents primarily women (75%), care partners (43%) and well-educated (55% college degree or higher) completed the survey. Other individuals included 22% at-risk, 15% pre-manifest gene carriers, and 10% with manifest HD. 72% requested information on HD trials, although 66% indicated they do not have enough information. Individuals primarily received information from the

internet (27%) and less from their doctor (3%). The preferred mode of contact about clinical trials was e-mail (51%), phone (38%) or letter (36%) followed by support groups (13%) and doctor's offices (13%). The greatest barriers included personal expenses (34%), side effects (34%), travel distance (32%), and drug safety (27%). Motivating factors included home/web assessments (43%), travel reimbursement (33%) and Saturday visits (32%). Overall, the majority was knowledgeable about the research process; however, most were unaware of the currently recruiting HD trials.

Conclusions: Enhancing online communication channels, including social media, while developing relationships between individuals, their physicians and support groups through education, may expand participation. Travel reimbursement, distance to study sites, telemedicine and Saturday visits are important factors that must be considered when designing future trials.

Veatch Goodman L, Guiliano J and Lovecky D. **Survey of Clinical Trial Interest and Literacy in Huntington Support Groups: Northwest Pilot Project.** *Neurotherapeutics* 2009; 6:204.

Poster 3

National Institute of Neurological Disorders and Stroke Huntington's disease Common Data Elements Project.

W.R. Galpern, on behalf of the NINDS HD CDE Working Group. *NINDS/NIH, Bethesda, MD, USA.*

Objective: The National Institute of Neurological Disorders and Stroke (NINDS) Huntington's disease (HD) Common Data Elements (CDE) Project aims to develop content standards to enable clinical investigators to systematically collect, analyze, and share data across clinical research studies in HD (http://www.commondataelements.ninds.nih.gov/).

Background: The NINDS initiated the CDE Project in an effort to facilitate clinical research across a variety of neurological disorders including HD. By identifying CDEs in a standardized format and by developing common documentation and case report forms, the NINDS hopes to facilitate HD clinical research studies.

Methods: An external working group of nearly 60 international experts has been assembled to develop the HD CDE recommendations. This Working Group is divided into eleven Subgroups: Motor, Cognitive, Behavior/Psychiatry, Imaging Biomarkers, Biochemical Markers, Genetics, Pathology, Functional Outcomes/Patient Reported Outcomes, Epidemiology/Environment, Statistics and Scale Metrics, and Operations. The Subgroups will meet over the course of a year to review the elements commonly collected in current HD clinical studies, to develop a series of recommendations for standardized data collection, and to incorporate feedback.

Results: The final products from each subgroup will include a list of standardized instruments with explanations regarding recommended use, template case report forms, and data dictionaries which define CDE names, definitions, and permissible values.

Conclusions: It is anticipated that the HD CDE recommendations will be available for public review and comment in early 2012, and they will be posted to the NINDS CDE Website in the spring of 2012 for use by investigators. The HD CDEs will be reviewed and updated periodically to accommodate new tools and incorporate revised recommendations.

Poster 4

Pridopidine – Modulating the Direct and Indirect Pathways Controlling Movement.

S. Waters,[1] D. Klamer,[1] J. Tedroff,[1] H. Pontén,[1] C. Sonesson,[1] B. Gronier,[2] and N. Waters.[1] *[1]NeuroSearch Sweden AB, Gothenburg, Sweden and [2]Faculty of Health and Life Sciences, De Montfort University, Leicester, United Kingdom.*

Introduction: Motor symptoms of Huntington's disease (HD) are associated with abnormalities in glutamate and dopamine transmission within the cortico–striatal pathways. Pridopidine belongs to a class of compounds that normalize psychomotor activity in animal models of aberrant dopamine or glutamate neurotransmission. *In vitro*, pridopidine displays fast-off competitive dopamine type 2 (D2) receptor antagonism.

Methods: In this study, the effects of pridopidine on the expression of the immediate early gene Arc, a measure of *N*-methyl-d-aspartic acid (NMDA) receptor activity, was assessed by qPCR. Furthermore, *in vivo* electrophysiological recordings were performed to investigate the effects of pridopidine on the firing of prefrontal cortex pyramidal neurons in urethane-anaesthetized rats.

Results: Pridopidine dose-dependently increased cortical and striatal Arc expression. Accumulating comparative data on other dopaminergic and NMDA receptor ligands suggest this effect is related to a combination of subcortical D2 receptor antagonism and indirect activation of cortical D1 receptors. The unselective NMDA receptor antagonist MK-801 displayed opposite effects, while memantine, which preferentially blocks extrasynaptic NMDA receptors, had pridopidine-like effects. Pridopidine also dose-dependently increased the firing of pyramidal cells in the prefrontal cortex *in vivo*. This indicates that pridopidine may have the ability to enhance synaptic NMDA receptor signalling.

Conclusion: Motor symptoms in HD are associated with abnormalities in glutamate and dopamine transmission within the cortico–striatal pathways. The dopaminergic stabilizing profile of pridopidine, in combination with increased activity

in cortico–striatal NMDA receptor-mediated communication, provides a mechanistic rationale to support the beneficial effects of pridopidine on motor symptoms of HD. Negative motor symptoms of HD may be improved with pridopidine through activation of the direct pathway (D1/NMDA receptor-mediated), while inhibition of D2 receptor-mediated transmission, strengthening the indirect pathway, may improve hyperkinetic features such as dystonia and chorea.

Poster 5

The Feasibility of PREQUEL: A Study of Coenzyme Q10 in Pre-Manifest Huntington's disease.

A. Killoran,[1] K.M. Biglan,[1] E. Julian-Baros,[1] N. Yoritomo,[2] and C.A. Ross[2] for the Huntington Study Group PREQUEL Investigators. *[1]University of Rochester, Rochester, NY, USA and [2]Johns Hopkins University, Baltimore, MD, USA.*

Background: PREQUEL is a safety and tolerability study evaluating three doses of Coenzyme Q10 (CoQ) in pre-manifest (prior to motor diagnosis) individuals with the gene expansion for Huntington's disease (HD). PREQUEL represents the first multi-center interventional study in this population. Enrollment began in February 2010.
Objective: We report an update on the blinded tolerability of CoQ and the provisional feasibility of enrolling and retaining participants with pre-manifest HD in an interventional clinical trial.
Methods: PREQUEL is a double blind, 20 week, parallel group, multi-center trial with participants pre-manifest for HD randomized to receive 600 mg, 1200 mg or 2400 mg/day of Coenzyme Q10. The primary outcome measure is tolerability, defined as the ability to complete the 20 weeks of follow up on the original treatment assignment. Secondary tolerability outcomes included premature withdrawals, drug suspensions, dosage reductions and adverse events. Feasibility was assessed by evaluating enrollment activity and trends.
Results: Seventy-five participants have enrolled at 14 sites, as of June 24, 2011. Eighty-four percent were referred by site staff, 9.3% by an off-site doctor, 8% by the HDSA, and 1.3% each from family/friend, HDTrials.org and the site's website. Fifty-one participants have completed the study and 17 remain active. Two dose reductions have occurred, with one being successfully re-challenged. There have been seven premature withdrawals and 89 participants have had 97 adverse events, most commonly due to mild to moderate (93%) gastrointestinal complaints (n=29). There was one serious adverse event that was unrelated to the study drug.
Conclusion: Clinical trials in a population pre-manifest for HD are feasible. Preliminary data suggest that CoQ is well tolerated in this population. Continued follow-up will identify a dosage of CoQ that is tolerable for use in future preventive trials.

Poster 6

Burden of Huntington's disease in the USA.

J. Dorey,[1] J. Cohen,[2] M. Mraidi,[1] D. Urbinati,[1] and M. Toumi.[3] *[1]Creativ Ceutical SA, Paris, France, [2]Tufts University Center for the Study of Drug Development, Boston, MA, USA, and [3]UFR d'Odontologie, University Claude Bernard Lyon I, Villeurbanne, France.*

Introduction: Little is known about the burden of illness of Huntington's disease (HD). This study aims to assess the burden of illness from various perspectives (health insurance, patient and caregiver), including quality of life (QoL).
Materials and Methods: The study is being performed using online patient and caregiver self-reported questionnaires, which collected data for self-reported clinical assessments, QoL, resource utilization and caregiver burden. The study has been made possible by the Huntington's Disease Society of America, who are managing data collection.
Results: So far, 158 patients and 341 caregivers have been included. Of these patients, mean (± SD) age is 49.0 (13.0) years and 67% are female. HD symptoms started at a mean (± SD) age of 41.0 (15.0) years, and on average, patients were diagnosed 1 year later. Genetic testing for HD has been performed in 84 % of patients.
Results from the EuroQoL 5D reveal severe problems in a large proportion of patients: mobility (100%), self-care (33.33%), usual activities (57.15%), pain/discomfort (35.71%) and anxiety/depression (76.36%). Average (± SD) health utility is 0.34 (0.33). The mean number of monthly visits to a physician ranges from 0.74 (0.88) for GPs to 0.88 (0.93) for specialists. Consultations with other healthcare professionals ranges from 2.51 (6.30) to 8.33 (29.68) visits/month. Caregivers spend more than 6 hours/day caring for patients and their monthly expenses amount to $1252.45.
Conclusion: This study is ongoing, but data received to date confirm the tremendous burden of HD on society, patients and caregivers. This highlights the need for patient and caregiver support. Intense research should be supported by authorities to identify agents that would alleviate symptoms or slow HD progression.

Poster 7

The Movement Disorder Society Health Professional Alliance Project.

T. Pretto,[1] C. Moskowitz,[2] and the Health Professional Leadership of the Movement Disorder Society.[3] *[1]Rush University, Chicago, IL, USA,[1] Columbia University, New York, NY, USA,[2] and Movement Disorder Society, Milwaukee, WI, USA.[3]*

Objective: To expand health professional involvement in MDS as an inter-disciplinary forum dedicated to research, education

and collaboration between the Health Professional (HP) and physician members of the Movement Disorder Society.
Aim: To enrich and broaden the scope of care, management and research initiatives in movement disorders.
Background: The majority of MDS membership is neurologists; 3415 neurologists vs. 122 health professionals (3%). Previous attempts at integrating educational offerings for Health Professionals were not well-endorsed due to limited membership, sparse offerings, disinterest, lack of employer support, cost. A webpage started in 2009 where the 2010 survey of other HPs was posted. The MDS has made this expansion a strategic goal 2010–2013.
Methods: Based upon previous work of the MDS HP web-site initiative, *The 2010 needs survey* was developed to document demographics, culture of learning in country of practice, multi-disciplinary team learning attitudes and unmet educational needs. The survey was conducted via the MDS web-site. Web-page advertisement was also conducted via The European Huntington Disease Network (www.ehdn.org) and Parkinson Study Group (www.parkinson-study-group.org).
Results: 1) 57% of respondents were not MDS members. 2) The majority of responders were nurses and physical therapists. 3) Consensus: Multi-disciplinary treatment is a better approach to care. 4) Cost and time are the biggest deterrents to continuing education. 5) Multi-disciplinary team members should include: Psychologists, Psychiatrists, Neurologists, Nurses, OT, PT, Nutritionists, SLPs and Social Workers. 6) Educational needs are as diverse as the various disciplines; however, the most common desire is to learn more about multi-disciplinary based care.
Conclusion: ***Outreach*** to potential members is for improved patient outcomes. ***Interdisciplinary research*** is needed to support a multi-disciplinary model. ***Education*** models need to be developed to allow professional learning with minimal cost and time commitment. This *expansion project is possible* in conjunction with web-site development through e-learning/virtual society participation.

Poster 8

The Behavioural and Psychological Symptoms of Huntington's Disease - A practical guide to assist in caring for a person with HD.

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Huntington's disease (HD) is presently incurable, so the current goal is to allow affected individuals to live as well as possible with the illness, to maximise functional independence and quality of life for the person with HD and their carers and family members. The Behavioural and Psychological Symptoms of HD (BPSHD) have been considered the presenting symptoms of HD in up to half of all people with HD, and can precede the classical motor symptoms by up to a decade. BPSHD are often the most distressing part of the condition and thus a good understanding of these are crucial to good clinical practice, and so that those involved can be effectively informed how to manage these stressful but common symptoms. A more thorough understanding of the BPSHD is also essential as they are often amenable to targeted treatment and intervention, which can lead to a better quality of life for the people living with HD and also for family members and carers, and also potentially dramatically delay institutionalisation and reduce healthcare costs. A booklet was written to provide a much-needed and accessible resource, designed to raise the profile and improve the recognition, understanding and management of the BPSHD. It is written for people affected by HD, including family members, friends, caregivers, and professionals who give advice and care to these communities. Copies of the booklet will be available, in order to contribute to the improved management and quality of life for those affected by HD.

Poster 9

Assessment of Kinematic Changes with Ambulatory Device Use in Patients with Huntington's Disease.

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Purpose/Hypothesis: Individuals with Huntington's disease (HD) experience balance and walking impairments that worsen with disease progression and contribute to higher fall risk. To improve mobility and prevent falls, ambulatory devices (ADs) are often prescribed. The purpose of this study was to determine the effects of using ADs on lower extremity joint kinematics during comfortable walking.
Subjects: Individuals with a diagnosis of HD (n=21, mean age 49.3±11 years, mean UHDRS 40.4±14.4) who could walk 10 meters without assistance volunteered for this study.
Methods: Reflective markers were attached to the iliac crest, greater trochanter, lateral femoral condyle, and lateral malleolus of the tibia. Subjects were videotaped using various ADs [standard walker (SW), 2 wheeled walker (2WW), 3 wheeled walker (3WW), 4 wheeled walker (4WW), standard cane and no AD]. Sagittal hip and knee mean angular excursion values for early and late stance and swing phases of gait were obtained using the Peak Motus motion analysis system. Data were analyzed using repeated measures ANOVA with LSD post-hoc comparisons to detect differences across devices.
Results: Preliminary analysis revealed that 4WW use significantly increased ($p<0.05$), while SW use decreased

mean hip angular excursions compared to the no AD condition in both late stance and swing phases. Knee angular excursion data were consistent with these findings.
Conclusions: When compared to no AD and SW, greater mean hip angular excursions with 4WW use in late stance phase suggest greater terminal hip extension. Greater hip excursions in swing phase with 4WW use may underlie improved velocity and stride length measures that were previously reported by our lab in the same subjects. Based on these findings, we recommend that clinicians consider 4WW prescription for gait impairments and fall prevention for individuals with HD.
Clinical Relevance: This research represents the first study to provide an evidence-based approach to AD prescription.

Poster 10

Characterization and Correlates of Change in the Mini Mental Status Exam Score in Huntington's Disease.

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Objective: To characterize the rate of change in the Mini Mental Status Examination (MMSE) score and its subcomponents in patients with Huntington's disease (HD) compared to controls, and to analyze the rate of change in MMSE scores by CAG repeat length, predominant symptom at disease onset, and Total Functional Capacity score.
Background: Cognitive dysfunction is a core feature of HD. The rate of decline and its correlation with other clinical features of the disease remain largely unknown.
Methods: The Cooperative Observational Huntington's Research Trial (COHORT) is an international prospective, observational study designed to collect longitudinal data from participants with HD and their family members and caregivers. The rate of change in MMSE scores was calculated using a linear mixed effects model with a random slope for each subject. Additional analyses were performed using multiple linear regression models, controlling for age, gender, and education level. The rate of change by symptom type was analyzed using F-tests followed by Tukey post-hoc tests for all pairwise comparisons.
Results: A total of 1276 patients with manifest HD and 650 controls (53.7% F, mean age 51.6 y) were included in the analysis. Total MMSE score and all subscores declined significantly faster in the HD group than in controls. For subjects with HD, the rate of change in MMSE scores was significantly correlated with CAG repeat length. The rate of decline of the recall subscore was slower in the group presenting with psychiatric symptoms. The rate of change of the total MMSE score and all subscales were significantly correlated with rate of change of TFC scores.
Conclusions: This study validates the use of MMSE as a measure of cognitive function in patients with HD. Changes in rate of decline in the MMSE score can serve as a useful outcome measure in HD clinical trials.

Poster 11

The Effect of Video Game-Based Exercise on Dynamic Balance, Mobility and UHDRS Neuropsychiatric Test Scores in Individuals with Huntington's Disease.

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Huntington Disease (HD) is associated with neurodegeneration of striatal neurons. Recent MRI studies suggest the abnormalities extend to white matter (WM) tracts both in advanced and early HD stages. The anatomical Corpus Callosum (CC) structure can mirror different aspects of HD pathogenesis. We recruited 17 patients, 17 preHD subjects and healthy age-matched controls (HC). All MRI data were acquired on a 3T scanner. Combining Region of Interest analysis, Voxel-Based Morphometry and Diffusion Tensor Imaging (DTI), we investigated callosal WM thickness, density and Fractional Anisotropy (FA), Radial (DR) and Axial (DA) Diffusivity. Compared with HC, preHD subjects showed reduced thickness, WM density and FA, and increased DR in the isthmo. Similarly, patients revealed a reduced callosal thickness in the whole CC, WM density in splenium, isthmo and part of the body and FA, and increased DR in whole CC, DA in isthmus and body. Compared with preHD subjects, patients showed a callosal WM density reduction in splenium, isthmo, rostrum and FA, and increased DR in whole CC and DA in the body. We found preHD changes in CC isthmo, then rostrally extended to the body, in patients. Diffusion data suggests that changes in isthmo is most likely caused by a damage of myelin sheaths, thus worsen by axonal body-CC damage. Since a little amount of isthmo fibers arise from cortico-striatal neurons, our data suggests that myelin breakdown of early and heavily myelinated axons in CC could be related to neuronal degeneration other than in striatum.

Poster 12

Analysis of TGFbeta1 in glial cells, neurons and peripheral macrophages to seek Huntington disease biomarkers.

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We have recently reported abnormal TGFbeta1 production in HD. TGFbeta1 is a pleiotropic cytokine with an established neuroprotective function as well as a powerful anti-inflammatory role. We tested immortalized human astroglial cell lines (SVGp12) expressing wild-type (25Q) and mutant (72Q) Htt-exon1 and neuron cell lines (STHdhQ7/Q7 and STHdhQ111/Q111), HD mouse model (R6/2 brain and macrophages), HD-subject cell lines (blood cells and macrophages) and brain samples (from subjects at different HD stage), to relate the abnormal TGFbeta1 production to the disease progression. We analyzed the levels of TGFbeta1 by flow cytometry; Real-Time RT-PCR, Western blot analysis and Immunocytochemistry. All HD subjects were clinically and genetically evaluated and age matched with health controls. Cell lines expressing the HD mutation showed reduced TGFbeta1 levels. TGFbeta1 decreases in preHD macrophages and then it progressively increases in further HD stages in cell lines obtained from HD subjects and HD mice, compared with controls. We confirmed the same progressive, stage-related increase in the HD mouse brain, in autoptic human HD brain. The relative cytokine increase in human peripheral macrophages correlates with the HD stage, disease burden, UHDRS scores, TFC and HD progression. While confirming a TGFbeta1 related dysfunction in peripheral and brain tissues in HD, we remark the potentiality for seeking novel markers of HD progression, by testing TGFbeta1 in peripheral human tissues.

Poster 13

Correlation between Burden of Pathology Scores and Cognitive and Functional Symptoms in Huntington's Disease.

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The Huntington's disease (HD) Burden of Pathology (BOP) Score is derived from an equation utilizing CAG repeat length and current age. Some investigators have suggested that BOP scores can be used as an index of disease severity for individuals with preclinical, and possibly mild, HD; however, studies are limited. The present study sought to determine if there is a relationship between BOP score and specific cognitive and functional measures in preclinical and manifest HD. We used a convenience sample of up to 148 preclinical and manifest HD subjects followed at one academic center. The mean age of disease onset for the cohort was 41.34 (SE=1.06) years and the mean age at their initial testing was 46.41 (SE=1.02) years. Mean education was 13.90 (SE=.21) years and mean CAG repeat length was 45.13 (SE=.39). Using Pearson r, we found significant correlations between BOP and all cognitive and functional scores. The strongest correlation occurred for the Functional Assessment (r=−.52, p<.001), followed by the UHDRS Total Functional Capacity (r=−.51, p<.001), Independence Scale (r=−.49, p<.001), Total Motor Score (r=.41, p<.001), and Dementia Rating Scale (r=−.37, p<.001). These results suggest that there is at least moderate correlation between BOP score and a number of cognitive and functional measures in not only preclinical, but also mild to moderate, manifest HD. Further studies will be needed to confirm and extend these findings.

Study supported by: UCSD HDSA COE and UCSD ADRC NIH P50 AG 005131.

Poster 14

Assessing Visuospatial Functioning in Huntington's disease (HD) using the Judgment of Line Orientation (JLO) Test.

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Objective: To examine visuospatial ability in Huntington's disease (HD) using the Judgment of Line Orientation (JLO) Test.

Background: Although previous studies have described visuospatial deficits in subcortical dementias, few have examined these deficits in HD. The Benton JLO Test, commonly used to assess visuospatial ability, requires minimal motor involvement. It has demonstrated sensitivity to visuospatial deficits in PD; however, to our knowledge, no one has examined performance on the JLO in HD.

Methods: A global cognitive measure, the Mattis Dementia Rating Scale (DRS) was used to stratify subjects as mild vs. moderate-severe. Forty-seven mild (DRS ≥ 128) and 31

moderate-severe (DRS < 128) HD subjects were administered the JLO. UHDRS Total Motor and HD Burden of Pathology (BOP) Scores were used as measures of disease severity. We examined the relationships between JLO, DRS, UHDRS Total Motor, and HD BOP scores utilizing Pearson r correlations.

Results: Mild HD subjects (mean DRS=135.2) had a mean age of 45.8 years and mean CAG repeat length of 45.2. Moderate to severe HD subjects (mean DRS=117.4) had a mean age of 49.7 years and mean CAG repeat length of 44.8. One sample T-tests revealed that only moderate to severe, but not mild, HD subjects scored significantly lower ($p<0.001$) on the JLO compared to normative data (Woodard, 1998). JLO performance significantly correlated with Total DRS and Motor scores for both mild ($p<0.01$; $p<0.01$, respectively) and moderate-severe ($p<0.01$; $p<0.05$, respectively) HD subjects. There were no statistically significant correlations between JLO and BOP scores for either group.

Conclusion: Our results suggest that visuospatial ability declines over the course of HD; however, the JLO may not be a useful measure for detecting this impairment in the earliest stages. Further studies are needed to confirm and extend these findings.

Study supported by: UCSD HDSA COE and UCSD ADRC NIH P50 AG 005131.

Poster 15

Cognitive Impairment in Prodromal Huntington disease: Longitudinal Data from PREDICT-HD.

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It is well established that cognitive changes are detectable prior to diagnosis in prodromal Huntington disease (prHD). How cognition declines over time is less well understood. If rates of cognitive decline vary over time, this may help to identify targets and critical periods for intervention. Previous longitudinal studies have examined short periods of time, have not had sufficient power to examine differences in rates of change over time, and/or have failed to stratify their samples based on estimated proximity to diagnosis, thereby obscuring differences between cases and controls.

Participants with prHD and controls completed a cognitive battery as a part of their participation in PREDICT-HD. Samples analyzed range from 417 to 1050 participants with durations (current age- age at study entry) from 0–6 years. The prHD individuals were stratified into High, Medium, and Low groups based on cumulative genetic toxicity at study entrance. Linear mixed effects regression examined the intercept and longitudinal trend for 29 cognitive variables. All models controlled for age at study entry, years of education, and gender. Models were evaluated using Akaike's information criterion and likelihood ratio test. Annualized rates of change were obtained.

Nearly all tasks revealed baseline (intercept) differences between cases and controls. Controls and participants in the Low group demonstrated improvements over time on most tasks. While some tasks captured insidious cognitive decline, tests of facial perception, emotion recognition, odor identification, verbal fluency, information processing speed, inhibition, reaction time, tapping speed and accuracy, and visual scanning also indicated differences in rates of change as estimated proximity to diagnosis increased.

In multiple areas of cognition, the rate of deterioration varied as a function of cumulative genetic toxicity at study entry, with faster deterioration associated with greater severity. Practice effects were also evident. Findings may help inform interventions in HD as well as other neurodegenerative disorders.

Poster 16

Measures of Growth in Children at risk for Huntington Disease.

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Research on Hungtinton Disease (HD) has conventionally focused on the proposed mechanism of a toxic gain of function of the mutant huntingtin protein, leading to neurodegeneration later in life. Mutant huntingtin is, however, present throughout the life span and expressed ubiquitously across the body. The role of abnormal development in the pathophysiology of HD is gaining significant scientific support. In addition, abnormalities in metabolic processes are being considered as important mechanisms for both brain and systemic manifestations of the disease. In this study we examined the effect of mutant huntingtin on human development by evaluating measures of growth in children (7–18 years of age) at risk for HD. Children at risk for HD are tested for gene-expansion for research purposes only and are enrolled only if they are currently not manifesting symptoms of the disease (no juvenile HD children included). Measurements of growth (height, weight, body mass index or BMI, and head circumference) in children tested as gene-expanded (n= 20, CAG repeats≥39) were compared to those of a large database of healthy children (n=152, 7–18 years of age).

Gene-expanded children had significantly lower measures of head circumference, weight and BMI. Head circumference was abnormally low even after correcting for height suggesting a specific deficit in brain growth rather than a global growth abnormality. The results indicate that children who are decades ahead of HD diagnosis have significant differences in development compared to controls and suggest that mutant huntingtin may play a role in abnormal growth, and in particular, brain development. Understanding the pathogenesis by investigating early manifestation of symptoms, shown as affected growth measurements in the current study, is important for finding novel biomarkers which could lead to development of new interventions.

Poster 17

Temporal Order Memory Deficits in Manifest Huntington's Disease.

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The identification of novel cognitive deficits is important for the assessment of Huntington's disease (HD). The findings from previous lesion and neuroimaging studies suggest that the frontal lobes play a critical role in memory for the temporal order of items in a sequence. Since HD results in frontostriatal circuit dysfunction, temporal order memory may be particularly sensitive to neuropathological degeneration associated with HD. In the present study, patients with manifest HD and normal controls were administered a visuospatial temporal order memory task on a computerized radial eight-arm maze. On the study phase of each trial, participants were presented with a random sequence of circles shown one at a time at the end of each of the eight arms. On the choice phase, participants were presented with a circle at the end of two of the study phase arms, and were asked to choose the circle that occurred earliest in the sample phase sequence. In order to vary temporal interference, manipulations of the temporal metric were carried out by systematically changing the temporal distance between the two circles in the choice phase. Research suggests that there is more interference for temporally proximal stimuli relative to temporally distal stimuli. We found that HD patients demonstrated significant impairments, relative to controls, across all temporal distances. These results indicate that temporal order memory is impaired in HD patients even when temporal interference is minimal. The present findings identify a fundamental, yet relatively unexamined, processing deficit that may affect the execution of various daily living skills in individuals diagnosed with HD.

Poster 18

Run-In Practice Effects for Cognitive Tests Used in HD study of Citalopram.

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Introduction: In HD, cognitive changes due to disease-progression or treatment are potentially confounded by "practice effects"—systematic improvement due to increasing familiarity in the first few test administrations. A practice run-in was used in a recent HD citalopram trial. We analyzed cognitive measures from these pre-treatment repetitions for evidence of practice effects.

Methods: Non-depressed adults (N=32) with mild to moderate HD-related cognitive deficits participated in in a clinical trial to examine the efficacy of citalopram to enhance cognition. Cognitive tests were administered at three visits, approximately two weeks apart, before active treatment randomization. Some tests were also administered at screening. Therefore 3–4 pre-treatment repetitions were available. We tested for systematic test improvement using repeated-measures ANOVA.

Results: The *Symbol Digit Modalities Test* showed significant improvement over the first 3 repetitions. Performance stabilized at the fourth repetition despite introduction of a potential placebo effect. *Stroop Interference* showed a modest, statistically significant improvement over the first 3 repetitions. There was substantial additional improvement at the fourth administration. It is unclear if this was due to additional practice or to introduction of placebo at the previous visit. *Stroop Word* and *Color* tasks showed no evidence of practice effects. *Verbal Fluency* results were inconclusive. Among non-UHDRS cognitive tests, the *Hopkins Verbal Learning Test (HVLT)* and Letter-*Number Sequencing* test showed patterns consistent with possible mild practice effects, but these were not statistically significant. The *Trail Making Test: Parts A and B* showed notable instability if subjects' baseline values were markedly impaired. The Trails tests may be unsuitable for subjects with moderate or severe disease. Because of this volatility, practice analyses for the Trails tests were inconclusive.

Conclusions: Some commonly used cognitive tests showed short-term practice effects, even after multiple sessions. Practice run-in periods may help minimize the impact of such effects in HD clinical trials.

Poster 19

International Survey-Based Algorithms for the Pharmacological Treatment of Irritability and Perseverative Behaviors in Huntington's Disease.

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Please see Keynote Presentation above for abstract body.

Late-Breaking Research

Poster 20

An International Survey-based Algorithm for the Pharmacologic Treatment of Chorea in Huntington's Disease.

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It is generally believed that treatments are available to manage chorea in Huntington's disease (HD). However, lack of evidence prevents the establishment of treatment guidelines. In an effort to inform clinical decision-making, we surveyed an international group of experts to obtain practice preferences. Survey results showed that patient stigma, physical injury, gait instability, work interference, and disturbed sleep were indications for a drug treatment trial. However, the experts did not agree on first choice of chorea drug, with the majority of experts in Europe favoring an antipsychotic drug (APD), and a near equal split in first choice between an APD and tetrabenazine (TBZ) among experts from North America and Australia. All experts chose an APD when comorbid psychotic or aggressive behaviors were present, or when active depression prevented the use of TBZ. However, there was agreement from all geographic regions that both APDs and TBZ were acceptable as monotherapy in other situations. Perceived efficacy and side effect profiles were similar for APDs and TBZ, except for depression as a significant side effect of TBZ. Experts used a combination of an APD and TBZ when treatment required both drugs for control of chorea and a concurrent comorbid symptom, or when severe chorea was inadequately controlled by either drug alone. The benzodiazepines (BZDs) were judged ineffective as monotherapy but useful as adjunctive therapy, particularly when chorea was exacerbated by anxiety. There was broad disagreement about the use of amantadine for chorea. Experts who had used amantadine described its benefit as small and transient. In addition to selected survey results, this report reviews available chorea studies; we present an algorithm for the treatment of chorea in HD based on expert preferences obtained through this international survey.

Poster 21

Genetic Privacy Concerns and Knowledge of GINA Among Those Affected by Huntington Disease.

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Background: Privacy and genetic discrimination are important issues to individuals affected by genetic disorders such as Huntington disease (HD). Signed into law on May 21, 2008 and implemented on November 21, 2009, the Genetics Information Nondiscrimination Act (GINA) was designed to address potential genetic discrimination in employment and obtaining health insurance.
Objectives: To assess the privacy concerns of individuals from families affected by HD with respect to genetic, medical, and financial information and to evaluate the understanding of GINA among these individuals.
Methods: From July 2009 to June 2010, individuals from families affected by HD who were enrolled in a longitudinal observational study (COHORT) at 23 sites in Australia, Canada, and the United States were given a cross sectional survey with questions pertaining to their privacy concerns and experiences with genetic discrimination. Respondents were asked to rate their level of concern over privacy on a Likert scale from 1 (very concerned) to 4 (not at all concerned). Respondents living in the U.S. were also asked questions specific to GINA and as a control the Health Insurance Portability and Accountability Act (HIPAA).
Results: More than half of the COHORT study members who were provided with a survey responded (51%; 580 members; 46% manifest HD, 9% pre-manifest HD, 21% at risk, and 24% control). Overall, respondents were more concerned about the privacy of their financial information (Likert scale score=2.0) than the privacy of their genetic information (score=2.3; $p<0.0001$). U.S. participants had greater familiarity with HIPAA (65% slightly, somewhat

familiar or very familiar) than with GINA (40% slightly, somewhat or very familiar; p<0.0001).
Conclusion: Individuals in families affected by HD were more concerned about privacy of financial information than privacy of genetic information. In addition, among individuals at risk for genetic discrimination, knowledge of GINA is low.

Poster 22

Randomized, Double-Blind, Placebo-Controlled Study of Dimebon in Individuals with Mild-to-Moderate Huntington disease.

HORIZON Investigators of the Huntington Study Group and European Huntington's Disease Network (K. Kieburtz, presenting author). *University of Rochester, Rochester, NY, USA.*

Introduction: In an earlier Huntington disease study, dimebon was safe and well tolerated and provided a potential signal of benefit on cognition. This larger trial sought to determine its efficacy in mild-to-moderate Huntington disease.
Patients and Methods: This was a six-month, randomized, double-blind, placebo-controlled study of dimebon (60 mg/day) at 64 sites in Australia (n=3), Europe (n=28), and North America (n=33). Participants were over 30 years old with confirmed HD and cognitive impairment (Mini-Mental State Exam [MMSE] scores 10 to 26). Co-primary outcomes were cognition (MMSE change from baseline) and global function (Clinician's Interview-Based Impression of Change, plus caregiver input [CIBIC-plus]; range 1 = markedly improved, 4 = no change, 7 = marked worsening). Secondary outcomes were measures of behavior, daily function, motor ability, and safety outcomes.
Results: The study enrolled 403 participants. The mean change in the MMSE at Week 26 for those receiving dimebon (1.5 point improvement) did not differ significantly from the mean change for those receiving placebo (1.3 point improvement; P=0.39). Similarly, the mean CIBIC-plus score at Week 26 did not differ significantly in those receiving dimebon compared to placebo (4.1 v. 4.0; P=0.84). On the secondary efficacy outcomes, no significant differences were observed. The incidence of adverse events was similar between those randomized to dimebon (69%) and placebo (68%).
Conclusion: Over six months in individuals with mild-to-moderate Huntington disease and evidence of cognitive impairment, dimebon was safe and well-tolerated but did not improve cognition or global function relative to placebo.
Sponsor: The HORIZON study was sponsored by Medivation, Inc and Pfizer Inc.
References: 1. Kieburtz K, McDermott MP, Voss TS et al. A randomized, placebo-controlled trial of latrepiridine in Huntington disease. Arch Neurol 2010;67:154–60.

Poster 23

Longitudinal Divergence between Subjects and Companion Assessments of Psychiatric Manifestations in Prodromal and Diagnosed Huntington Disease.

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Poster 24

Abnormal Brain Structure in Gene-Expanded Children Greater Than Estimated 30 Years from Onset.

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Introduction: There has been growing evidence that the etiology of Huntington's Disease (HD) has an important component of abnormal brain development. To assess this, the current study was designed to evaluate brain structure in children at risk for HD.
Methods: Children ages 6–18 years who have a parent with HD are enrolled in the study only if they are currently not manifesting symptoms of the disease. Participants are tested for gene-expansion for research purposes only. The sample included 13 children who were gene-expanded (CAG repeat range 39–54, mode 42) and an average age of 14.6 years. The gene non-expanded group included 18 children, average age 14.5. Both groups were compared to a large sample of normal healthy control children (n=80, average age 13.1, range 8.2-18.9 years). All participants underwent a brain MRI scan with a 3T magnet using the same protocol. To eliminate effects of outliers, non-parametric methods were used to evaluate brain morphology between groups. Age and height were controlled for when evaluating total brain tissue volume. All regional brain measures controlled for age and total brain volume.
Results: Gene-expanded children had substantially smaller total brain tissue volumes (a decrease of roughly 5%) compared to controls. After controlling for total brain tissue, the cortex was still decreased in volume and this was most prominent in the parietal lobe. The striatum and cerebellum were of normal size after controlling for total brain volume. The gene non-expanded children had no abnormalities compared to the controls.
Discussion: In this sample of children who are gene expanded yet greater than an estimated 30 years from onset, the volume of the brain, and in particular the cortex, is abnormal supporting the notion that aberrant brain development may play an important role in the pathophysiology of the disease.