

Program

Twenty First Annual Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement Disorders

Cosponsored by the Parkinson Study Group, Huntington Study Group, Dystonia Study Group, Myoclonus Study Group, Tourette Syndrome Study Group, Cooperative Ataxia Group, Tremor Research Group, and The *Movement Disorder Society*

To be held on Sunday, 7 October 2007, in the Cotillion Ballroom at the Marriott Wardman Park Hotel, Washington, D.C., 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) through joint sponsorship of The Movement Disorder Society and The Parkinson Study Group. The Movement Disorder Society is accredited by the ACCME to provide continuing medical education for physicians.

*The symposium will consist of peer-reviewed platform and poster presentations designed to communicate recent research advances in the field of Parkinson's disease, Huntington's disease, ataxia, dystonia, myoclonus, Tourette's syndrome, tremor and other Movement Disorders to professionals in neurology and related disciplines. Practitioners, educators, and researchers are invited to attend. Abstracts of platform and poster presentations representing original material will be published in the September 2007 issue of *Movement Disorders*.*

At the conclusion of this session, participants should be able to: 1) Identify by scholarly review, oral presentation and group discussion the current research into the diagnosis, prevention and treatment of Parkinson's disease and other Movement Disorders; 2) Identify the important advances in research and clinical treatments relating to a variety of Movement Disorders; 3) Discuss new pharmacological and non-pharmacological treatment options available for Parkinson's disease and other Movement Disorders; 4) Identify the mechanisms (genetic, environmental, pathophysiology, neurobiology) linked to Parkinson's disease and other Movement Disorders; and 5) Discuss the diagnostic approaches and tools available for Parkinson's disease and other Movement Disorders.

PARKINSON'S DISEASE SESSION:

8:15 AM – 10:15 AM

This session consists of a keynote speaker and 4 presentations by the following individuals with allotted time for questions and answers after each presenter.

8:15 AM-8:30 AM

Introduction and acknowledgements by Andrew Siderowf, MD, MSCE, Chair, PSG Symposia Committee

8:30-9:15 AM

KEYNOTE ADDRESS: Parkinson's Interrupted: Epidemiology and Disease Progression

Alberto Ascherio, MD, PhD. *Harvard School of Public Health, Boston, MA, USA.*

9:15-9:30 AM

Atomoxetine for the Treatment of Executive Dysfunction in Parkinson's Disease: A Pilot Open-Label Study

L. Marsh,¹ S.S. Bassett,¹ K. Biglan,² M. Gerstenhaber,¹ J.R. Williams.³ ¹*Johns Hopkins University School of Medicine, Baltimore, MD;* ²*University of Rochester School of Medicine, Rochester, NY;* ³*Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA.*

Introduction: Cognitive impairment in Parkinson's disease (PD) typically manifests as executive dysfunction (ED), including problems with distractibility, task incompleteness, and planning. While ED is often disabling and may represent a risk factor for PD-dementia, few studies have examined potential treatments. Similarities between PD-related ED and that observed in individuals with attention deficit disorder (ADD) raised the possibility that atomoxetine, a norepinephrine reuptake inhibitor used to treat ADD, may be a potential treat-

ment for PD-related ED. *Methods:* We conducted an 8-week pilot open-label, flexible dose clinical trial of atomoxetine in 12 patients with PD and clinically disabling ED. Outcome measures included the Clinical Global Impression-Change (CGI-C) Scale, behavioral measures of ED [Connors Adult Attention Deficit Disorder Rating Scale (CAARS), Frontal Systems Behavior Scale (FrSBE)], performance on a cognitive testing battery, psychiatric symptoms, motor deficits, and adverse effects. *Results:* Final atomoxetine doses ranged from 25 mg to 100 mg daily. Among primary outcomes, there was significant improvement ($p < .05$) in ED on the CGI-C (75% positive response rate; 95% CI: 43%-95%) and the self-rated FrSBE Executive Dysfunction and CAARS inattention/memory subscales. Other self-rated CAARS and FrSBE subscales and total scores also showed improved behavioral symptoms, but atomoxetine was not associated with significant changes in psychiatric, motor, or cognitive measures, except recognition memory. Adverse effects included disrupted sleep and gastrointestinal symptoms; one patient developed hypomania. Seven subjects remained on active treatment after the study. *Conclusion:* Atomoxetine appears to benefit clinical manifestations of executive dysfunction in PD and warrants further study in controlled trials.

9:30-9:45 AM

Montreal Cognitive Assessment (MoCA) Performance in Parkinson's Disease Patients with Intact Cognition by Mini-Mental State Examination (MMSE) Score

S. Nazem, P. Moberg, J. Duda, T. Ten Have, H. Hurtig, M. Stern, D. Weintraub. *University of Pennsylvania School of Medicine, Philadelphia, PA, USA.*

Background: The long-term prevalence of dementia in Parkinson's disease (PD) is up to 80%, and mild cognitive impairment (MCI) as a dementia precursor or non-progressive disorder is also common. Thus, screening for cognitive impairment in PD is important. The Montreal Cognitive Assessment (MoCA), a new brief screening tool for MCI, has been found to be more sensitive than the Mini-Mental State Examination (MMSE) for detecting MCI in non-PD patients. *Objective:* To examine MoCA performance in PD patients with intact global cognition by MMSE score. *Methods:* Outpatients at two movement disorders centers with idiopathic PD were administered the MoCA and MMSE as part of a depression study. Only patients with a MMSE score in the top 75th percentile (age- and education-corrected) were included in the analyses (N=72, 76% of original sample). As previously recommended in non-PD patients, a MoCA score <26 was used to indicate at least MCI. *Results:* Subjects were primarily male (82%) and white (96%), with the following mean (SD) values: age= 65.9 (10.1) years, duration of PD= 7.1 (5.8) years, and educational level= 16.1 (3.8) years. Mean (SD) MMSE and MoCA scores were 28.9 (1.1) and 25.0 (2.9), respectively. Over half (52.8%) of subjects had at least MCI by MoCA score. Increasing age ($r = -.43, p < .001$) and lower level of education ($r = .32, p < .01$) were correlated with lower MoCA score. *Conclusion:* Despite having similar MMSE scores as healthy elderly controls, approximately half of PD patients have MCI based on the recommended MoCA cut-off score. These results, which need to be validated in PD using formal MCI and dementia diagnostic criteria, suggest both that MCI is common in PD and that the MoCA is a more sensitive instrument than the MMSE for its detection.

9:45-10:00 AM

Combined Effects of Smoking, Coffee, and NSAIDs on Parkinson's Disease Risk

K. M. Powers,¹ D. M. Kay,² S. A. Factor,^{3,4} C. P. Zabetian,^{5,6} D. Higgins,⁴ A. Samii,^{6,7} J. G. Nutt,⁸ A. Griffith,⁹ B. Leis,⁹ J. W. Roberts,¹⁰ E. D. Martinez,^{5,6} J. S. Montimurro,² H. Checkoway,¹ H. Payami.² ¹University of Washington, School of Public Health and Community Medicine, Department of Environmental and Occupational Health Sciences, Seattle, WA; ²Genomics Institute, New York State Department of Health, Wadsworth Center, Albany, NY; ³Department of Neurology, Emory University School of Medicine, Atlanta, GA; ⁴Parkinson's Disease and Movement Disorder Clinic, Albany Medical Center, Albany, NY; ⁵Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle WA; ⁶Department of Neurology, University of Washington School of Medicine, Seattle, WA; ⁷Parkinson's Disease Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA; ⁸Department of Neurology, Oregon Health & Science University, Portland, OR; ⁹Booth Gardner Parkinson's Care Center, Evergreen Hospital Medical Center, Kirkland, WA; ¹⁰Virginia Mason Medical Center, Seattle, WA, USA.

Inverse associations of Parkinson's disease (PD) with cigarette smoking, coffee drinking, and nonsteroidal anti-inflammatory drug (NSAID) use have been reported individually, but their joint effects have not been examined. To quantify associations with PD for the individual, two-way and three-way combinations of these factors, a case-control association study with 1186 PD patients and 928 controls was conducted. Subjects completed a structured questionnaire regarding smoking, coffee, and NSAID consumption. Odds ratios were calculated using unconditional logistic regression. Smoking, coffee, and over the counter NSAID use as individual factors exhibited significantly reduced risks of 20%-30%. The two-way and three-way combinations were associated with risk reduction of 37%-49%, and 62% respectively. Smoking and coffee exhibited significant inverse risk trends with increasing cumulative exposures, suggesting dose-response relations. With respect to the combination of all three exposures, persons who were at the highest exposure strata for smoking and coffee and used NSAIDs had an estimated 87% reduction in risk (OR=0.13, 95% CI=0.06, 0.29). No evidence for interaction was found. PD risk reduction due to smoking, coffee and NSAIDs were independent and cumulative, which if confirmed, implies these factors act on different pathways. Whether this finding reflects true biological protection needs to be investigated.

10:00-10:15 AM

LATE-BREAKING RESEARCH

Financial Anatomy of Parkinson Research

E.R. Dorsey,¹ J.P. Thompson,¹ S. Nicholson,² B. Fiske,³ T. Sherer,³ M. Frasier,³ ¹University of Rochester Medical Center, Rochester, NY; ²Cornell University, Ithaca, NY; ³Michael J. Fox Foundation, New York, NY, USA.

Objective: To determine the level and principal sources of recent funding for Parkinson disease (PD) research and to determine the current state of PD drug development. *Methods:* We evaluated the financing for PD research from 2003 to 2005 from the U.S. federal government, U.S. foundations, and global industry. We solicited data from government and foundation

sources in an anonymous manner. Using a proprietary pipeline database and published drug development costs, we estimated industry research and development PD expenditures. We determined biotechnology and pharmaceutical firm size from public and proprietary sources. **Results:** The National Institutes of Health, the Department of Defense, and five large PD foundations provided funding estimates. Funding for PD research grew from approximately \$1.1 billion in 2003 to \$1.2 billion in 2005. Industry accounted for 77% of expenditures in 2005. The number of drugs in development for PD grew from 66 in 2003 to 81 in 2005. Of the compounds in development for PD in 2005, 55% were supported by privately-held companies with indeterminate revenues or companies with revenue of less than \$10 million. An additional 20% were from companies with revenue between \$10 and \$100 million. In 2005, companies based outside the U.S. supported 64% of compounds in development. **Conclusion:** Current funding for Parkinson disease research is over \$1 billion and comes principally from industry. Three quarters of the compounds in development for Parkinson disease are supported by small companies, the majority from outside the U.S.

Financial support: This research was supported by the Michael J. Fox Foundation.

10:15-10:45 AM

BREAK/Poster viewing

OTHER MOVEMENT DISORDERS SESSION:

10:45 AM – 12:30 PM

This session consists of a keynote speaker and 4 presentations by the following individuals with allotted time for questions and answers after each presenter.

10:45-11:30 AM

KEYNOTE ADDRESS: Spinocerebellar Ataxia Type 10

Tetsuo Ashizawa, MD, *University of Texas Medical Branch at Galveston, Galveston, TX, USA.*

11:30-11:45 AM

Huntington's Disease Phenotype with CAG Expansion Less Than 36

H. Fadil, R. Zweig. *Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA.*

Huntington's disease (HD) is caused by an expansion of the trinucleotide CAG repeat on one of the IT15 alleles. According to ACMG/ASHG guidelines (Am J Hum Genet, 1998), allele sizes less than 36 "... have not been associated convincingly with an HD phenotype". We present a 79 year-old woman with a five year history of generalized choreiform movements. She denied dopamine antagonist exposure. In addition to chorea, neurological examination showed slow onset of saccades, difficulty sustaining lateral or vertical gaze, and mildly decreased balance. Brain MRI was unremarkable. Repeated genetic testing revealed IT15 allele CAG repeats of 35 and 18. Of the patient's four siblings, one sister died at age 86 with a diagnosis of HD, but without genetic confirmation. She reportedly had chorea for over ten years, and developed a severe gait disorder and depression. A brother reportedly had similar abnormal movements for 20 years before dying at age 80. We are aware of five additional cases of likely HD with IT15 allele expansion less than 36. Snell, et al (Nature Genetics, 1993) described 4 patients with 30-34 repeats, including an affected patient with

30 repeats on the likely inherited HD allele, based on haplotype analysis, from a family with seven other affected members with numbers "... well within the HD range". Kenney, et al (Movement Disorders, 2007) presented a patient with 29 CAG repeats with clinical and autopsy findings consistent with HD. Thus, although rare, allele sizes of less than 36 repeats can be associated with an HD phenotype.

11:45-12:00 PM

Brain Networks in Tourette's Syndrome With and Without OCD: An FDG PET Study

M. Pourfar, M. Carbon-Correll, N. Brown, C. Budman, D. Eidelberg, A. Feigin. *The Feinstein Institute for Medical Research, North Shore University Health System, Manhasset, New York, USA.*

Objective: To utilize FDG PET to identify regional changes in brain metabolism in patients with Tourette's Syndrome (TS). **Background:** TS is manifested by tics but is often associated with obsessive-compulsive disorder (OCD). We sought to identify changes in regional brain metabolism in TS subjects with and without OCD. **Methods:** 12 drug naïve adult TS patients (age 32.6 ± 10.4 [mean \pm SD]), and 12 age-matched control subjects (age 32.8 ± 7.2) underwent FDG PET imaging. All TS subjects were rated utilizing the Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive-Compulsive Scale (YBOCS). Three main imaging analyses were performed: 1) Voxel-based univariate analysis utilizing SPM; 2) Multivariate principal component analysis to identify a TS-related brain network; and 3) SPM analysis utilizing the clinical scores (e.g. tic and OCD severity) as covariates. **Results:** SPM revealed metabolic increases in cerebellum and motor and supplementary motor cortices in the TS subjects. Network analysis revealed a pattern of brain metabolism that discriminated between TS subjects and controls ($p < 0.001$), characterized by hypometabolism in striatum and orbitofrontal cortex covarying with hypermetabolism in motor cortices and cerebellum. YGTSS directly correlated with brain metabolism in BA 40 (supramarginal gyrus; $p < 0.001$), and YBOCS with metabolism in supplementary motor area ($p < 0.003$), cerebellum ($p < 0.006$) and inferior frontal cortex ($p = 0.01$). **Conclusion:** TS is characterized by a brain network involving decreases in striatal and orbitofrontal metabolism and increases in cerebellar and motor cortical metabolism. The heterogeneous clinical presentation of TS may relate to varying levels of activity within this network. Funded by the Tourette Syndrome Association.

12:00-12:15 PM

Huntingtin Aggregation in Motor Neurons: Two Huntington's Disease Patients Who Developed Motor Neuron Disease

E. Coon, P Kirby, W. Martin, M. Wieler, A. Osmand, H. Paulson. *University of Iowa Medical School, Iowa City, IA, USA.*

While preferential degeneration of striatal neurons is well established in the polyglutamine disorder Huntington's disease (HD), little attention has been paid to the possible involvement of motor neurons in this disease. We present two HD patients who developed clinical signs of amyotrophic lateral sclerosis (ALS). Both patients had a family history of HD and pathogenic CAG repeat lengths of 46 and 39. In both, clinical signs of motor neuron degeneration developed and the diagnosis of

ALS was confirmed. One patient with mild features of HD, including chorea, progressed rapidly to respiratory failure resulting in death. Autopsy revealed caudate atrophy, consistent with classic HD neuropathology, and profound motor neuron loss in the spinal cord. Remaining motor neurons, which contained Bunina bodies, were analyzed for the presence of polyglutamine recruitment foci. Recruitment foci correspond to microscopic polyglutamine aggregates and possibly toxic oligomers capable of further recruiting polyglutamine protein (*Osmund. Methods Enzymol.* 2006). Recruitment foci were detected in motor neurons and in cortical and striatal neurons, suggesting ongoing aggregation. We suggest that a minority of individuals with HD are predisposed to motor neuron loss through polyglutamine protein aggregation.

12:15-12:30 PM

LATE-BREAKING RESEARCH

The "Depression Phenotype" in Pre-Diagnosed Huntington's Disease

K. Duff,¹ J.S. Paulsen,¹ L.J. Beglinger,¹ J.C. Stout,² D.R. Langbehn,¹ C. Wang,¹ S. Queller,² N.E. Carlozzi,² & the PREDICT-HD Investigators of the Huntington Study Group. ¹University of Iowa, Iowa City, IA, USA; ²University of Indiana, Bloomington, IN, USA.

Depression is a common psychiatric co-morbidity in manifest Huntington's disease (HD), and it has been characterized by somatic and cognitive symptoms and increased suicide risk. Subsyndromal depression has also been reported in individuals with the gene expansion for HD but who had not reached clinical onset (pre-HD). To our knowledge, no studies have characterized the types of depressive symptoms that are most prominent in pre-HD. Using baseline data from the PREDICT-HD study, we examined correlations between individual items on the Beck Depression Inventory – II (BDI-II) and UHDRS Total Motor scores in 745 pre-HD individuals. Fourteen of the 21 BDI-II items significantly correlated with the Total Motor scores ($p < .05$, r 's ranged from 0.07 – 0.20). All correlations were positive, with higher BDI-II scores (i.e., worse depression) being related to higher Total Motor scores (i.e., greater motor abnormalities). The two strongest relationships were for "cognitive items" (e.g., item 13: indecisiveness, item 19: concentration difficulties). These results could be useful in several ways. First, clinical trials in pre-HD might focus on the depressive symptoms that are most prominent in these gene-expanded individuals, that is, the cognitive depression phenotype of pre-HD. Second, briefer assessment instruments might be developed that focus on the depressive symptoms in pre-HD. Future directions could include cross-sectional analyses between these symptoms and cognitive tasks and longitudinal analyses of these prominent depressive symptoms, both of which will be available from the PREDICT-HD study.

12:30-12:45 PM

Presentation of best abstract awards and closing remarks by Jang-Ho Cha, MD, PhD, Chair, HSG Symposia Committee.

POSTER SESSION: 12:45-1:45 PM

LUNCH FOR ATTENDEES

This session consists of guided tours of the posters by Dr. Andrew Siderowf, Chair of the PSG Symposia Committee and

Dr. Jang-Ho Cha, Chair of the OMD Symposia Committee with abstract authors presenting their research.

Poster 1 (OMD)

Effects of Dopamine Agonist Treatment on Spinal Cord Excitability in Patients with Restless Legs Syndrome

W. Bara-Jimenez,^{1,2,3} M. Aksu,^{1,4} F.E. Leon-Sarmiento,^{1,5} M.F. Malone,¹ R.Y.K. Lai,⁶ B.A. Chizh,⁷ K. Maltby,⁷ M. Hallett,² T.N. Chase.¹ ¹Experimental Therapeutics Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA; ²Human Motor Control Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA; ³Bethesda Neuroscience Clinic, Bethesda, MD, USA; ⁴Neurology Department, Erciyes University, Kayseri, Turkey; ⁵Uniciencia Research Group, Universidad Nacional/Fundacion Santa Fe, Bogota, Colombia; ⁶Neurology Centre of Excellence for Drug Discovery, GlaxoSmithKline, Harlow, Essex, UK; ⁷Cambridge Clinical Unit, GlaxoSmithKline, Cambridge, Cambridgeshire, UK.

Objective: To test the hypothesis that dopaminergic mechanisms are involved in the abnormal spinal cord excitability of primary Restless Legs Syndrome (RLS). **Methods:** In this double-blind, placebo-controlled, parallel-group study, 24 patients with primary RLS and 22 healthy controls received a once-daily, dose-escalating regimen of ropinirole, 0.25–2.0mg/day for patients and 0.25–0.5mg/day for controls, or placebo. Treatment duration was 23 days for patients and 8 days for controls. Clinical severity scales and overnight periodic limb movements (PLMS) recordings (polysomnography) were assessed. To evaluate spinal excitability, threshold and spread of early (FR1) and late (FR2) spinal flexor reflex responses were investigated, in awake and sleep states. Ropinirole effects were assessed on Day 6 and 23 (patients only). Dopaminergic blockade effects were examined on Day 8 by administering intravenous metoclopramide, 10mg, just prior to testing. **Results:** Ropinirole reduced RLS and PLMS severity, in accordance with previous reports. Although both FR1 and FR2 responses showed substantial variability, RLS patients treated with ropinirole generally had greater increases in FR1 and FR2 thresholds compared with those receiving placebo on Days 6 and 23. Awake FR2 threshold increase by ropinirole was significant on Day 6 ($p < 0.05$), an effect blunted by metoclopramide. Threshold increases on Day 23 were not statistically significant. Ropinirole did not affect FR responses in controls. **Conclusion:** Ropinirole reduced some measures of spinal FR excitability in patients, supporting a role of dopaminergic pathways on dysfunctional spinal FR mechanisms in primary RLS. This might be relevant for ropinirole's clinical effects, particularly its reduction of PLMS.

Poster 2 (OMD)

Histones Associated with Downregulated Genes are Hypo-Acetylated in Huntington's Disease Models

G. Sadri-Vakili,¹ B. Bouzou,² C.L. Benn,¹ M.-O. Kim,¹ P. Chawla,¹ R.P. Overland,¹ K.E. Glajch,¹ E. Xia,¹ Z. Qiu,¹ S.M. Hersch,¹ T.W. Clark,² G.J. Yohrling,³ J.-H.J. Cha.¹ ¹MassGeneral Institute for Neurodegenerative Disease, Department of Neurology, Massachusetts General Hospital, Charlestown, MA; ²Center for Interdisciplinary Informatics, MassGeneral Institute for Neurodegenerative Disease, Charlestown, MA;

³Johnson & Johnson Pharmaceuticals, Research & Development, L.L.C., Spring House, PA, USA.

Transcriptional dysregulation plays a major role in the pathology of Huntington's disease (HD). However, the mechanisms causing selective downregulation of genes remain unknown. Histones regulate chromatin structure and thereby control gene expression; recent studies have demonstrated a therapeutic role for histone deacetylase (HDAC) inhibitors in polyglutamine diseases. This study demonstrates that despite no change in overall acetylated histone levels, histone H3 is hypo-acetylated at promoters of downregulated genes in R6/2 mice, ST14a and *STHdh* cells, as demonstrated by *in vivo* chromatin immunoprecipitation. In addition, HDAC inhibitor treatment increases association of acetylated histones with downregulated genes and corrects mRNA abnormalities. In contrast, there is a decrease in mRNA levels in wild-type cells following treatment with a histone acetyltransferase inhibitor. Although changes in histone acetylation correlate with decreased gene expression, histone hypo-acetylation may be a late event, as no hypo-acetylation is observed in 4 week old R6/2 mice. Nevertheless, treatment with HDAC inhibitors corrects mRNA abnormalities through modification of histone proteins and may prove to be of therapeutic value in HD.

Poster 3 (OMD)

Suppression of Polyglutamine Neurotoxicity by C-terminus of Hsp70 Interacting Protein (CHIP) Supports an Aggregation Model for Polyglutamine Disease Pathogenesis

A.J. Williams,¹ T.M. Knutson,¹ V.F. Colomer Gould,² A.P. Osmund,³ H.L. Paulson.¹ ¹University of Iowa, Iowa City, IA; ²Johns Hopkins University, Baltimore, MD; ³University of Tennessee-Knoxville, Knoxville, TN, USA.

It remains unclear both how misfolded proteins damage neurons and how cellular protein quality control (PQC) systems handle aggregated proteins. Two important PQC pathways are the molecular chaperone system and the ubiquitin-proteasome system which regulate protein folding and protein degradation, respectively. The co-chaperone and ubiquitin ligase, CHIP, acts as a triage factor for both pathways. To explore its role in polyglutamine diseases, we bred mice deficient in CHIP to transgenic mice expressing the Spinocerebellar Ataxia Type 3 (SCA3) disease protein, ataxin-3. Whereas SCA3 mice with normal CHIP levels remain normal, CHIP-haploinsufficient mice develop age-dependent motor deficits and mice lacking CHIP display severe gait abnormalities and early mortality. When CHIP is reduced or eliminated, ataxin-3 microaggregates and aggregation recruitment foci (which are distinct from inclusions) accumulate in brain, but not elsewhere, demonstrating a direct correlation between microaggregate levels and phenotypic severity. Finally, further cell-based studies suggest CHIP does not act primarily by mediating ataxin-3 degradation. We conclude that CHIP acts to enhance polyQ protein solubility and prevent polyQ aggregation into toxic species, and may generally protect against polyQ neurotoxicity.

Poster 4 (OMD)

Anterocollis: Classification, Clinical Phenotype, Treatment Outcomes and Risk Factors

A. Tuchman, C. Sengun, A. Russell, C. Singer, S. Papapetrooulos. Department of Neurology, University of Miami, Miller School of Medicine, Miami, FL, USA.

Anterocollis (AC) is a form of cervical dystonia (CD) that produces patterned, repetitive muscle contractions that result in neck flexion. Little is known about AC since cases are usually excluded from clinical trials and there are limited reports on the subject. In this study we describe the demographics, phenotypic characteristics, treatment outcomes and risk factors for the development of anterocollis (AC). We performed a review of consecutive CD patients seen in our Division over a 15-year period. Out of 399 CD patients 27 (6.8%) had clinical features of AC (mean age 67.0 ± 5.43 , mean duration 21.1 ± 4.71). Patients with AC also suffered from laterocollis (72.7%) or torticollis (77.3%). Pain in the cervical region was very frequently reported among patients (~55%). AC was associated with neuroleptic exposure (9.1%) and a history of head or neck trauma (13.7%). Of the patients injected with botulinum toxin type A or B 13.3% reported excellent, 33.3% good, 26.7% mild and 26.7% no response to injections (mean duration of effect 3.1 ± 0.93 months). Oral antidystonic medications had limited contribution to symptom relief. AC is not an uncommon form of primary CD with good response to botulinum toxin therapy and should therefore be further studied.

Poster 5 (OMD)

Mutant Huntingtin-Mediated Histone Monoubiquitylation Induces Transcriptional Dysregulation in Huntington's Disease

M.O. Kim, P. Chawla, R.P. Overland, E. Xia, G. Sadri-Vakili, and J.H. Cha. MassGeneral Institute for Neurodegenerative Disease, Department of Neurology, Massachusetts General Hospital, Charlestown, MA, USA.

Although transcriptional dysregulation is a critical pathogenic mechanism in Huntington's disease (HD), little is known about how mutant huntingtin (Htt) mediates it. Here we show that disrupted interaction of Htt with Polycomb group protein Bmi-1 contributes to general increase in monoubiquityl histone H2A at lysine 119 (uH2A) in R6/2 mouse brain. Increased uH2A is found only at promoters of downregulated genes, mRNA levels of which are rescued by Ring2 knockdown-mediated reduction of uH2A, which also decreases heterochromatin protein 1 α and methylation of histone H3 at lysine 9. In contrast, global levels of monoubiquityl histone H2B at lysine 120 (uH2B) are decreased in R6/2 mouse brain, but only downregulated genes have decreased uH2B at their promoters. Reduction of uH2B by hBrel knockdown recapitulates the pattern of transcriptional repression and decreases histone H3 methylation at lysine 4. These findings demonstrate that mutant Htt mediates transcriptional repression by affecting histone monoubiquitylation and heterochromatin proteins.

Poster 6 (PD)

Does the Burden of Psychiatric Symptoms Vary Across Stages of Parkinson's Disease?

K.E. Anderson,¹ A.L. Gruber-Baldini,² J. Mullins,³ P.S. Fishman,³ S.G. Reich,³ W.J. Weiner,³ L.M. Shulman.³ ¹University of Maryland, Department of Neurology, Maryland Parkinson's and Movement Disorders Center, Baltimore, MD & University of Maryland, Department of Psychiatry, Baltimore, MD; ²University of Maryland, Department of Epidemiology & Preventive Medicine, Baltimore, MD; ³University of Maryland, Department of Neurology, Maryland Parkinson's and Movement Disorders Center, Baltimore, MD, USA.

Objective: To examine whether psychiatric symptoms vary in severity across stages of Parkinson's disease (PD). **Background:** Prevalence of depression in PD has been shown to vary by Hoehn & Yahr (H&Y) stage. It is not known whether anxiety and somatization (physical symptoms associated with psychological distress) show similar changes across disease stages. **Methods:** The Brief Symptom Inventory (BSI-18) assessed self-reported emotional symptoms (depression, anxiety, somatization) in a cross-sectional sample of 761 PD patients (64% male, average age 66.5 ± 10.6 yrs). Unpaired t tests were used to compare adjacent H&Y stage BSI scores. An ANOVA was used to compare later to early stages. **Results:** Comparisons of PD patients in H&Y Stages 3 vs. 2.5 did not differ significantly from one another with respect to any BSI indices ($p < .05$). Stage 2.5 vs. 2 patients showed greater levels of psychiatric symptoms on all 3 BSI measures ($p < 0.003$). Stage 4 vs. 3 patients reported higher levels of anxiety ($p = 0.011$). Stage 2 vs. 1 and Stage 5 vs. 4 patients reported more severe depressive symptoms ($p = 0.049$; $p = 0.002$, respectively). Psychiatric symptoms were significantly more severe on all 3 BSI measures in later compared to early disease stages ($p < 0.001$). **Conclusions:** The burden of psychiatric symptoms tends to increase with PD progression. The transition from H&Y 2 to 2.5 may be a particularly crucial point in the genesis of psychiatric symptoms, representing a significant increase in the severity of emotional distress. Similar to depressive symptoms, anxiety and somatization may be more severe in later stage PD.

Poster 7 (PD)

Treatment of Nocturnal Symptoms of Parkinson's Disease Using Rotigotine Transdermal Patch

R. Chaudhuri,¹ J. Jankovic,² C. Trenkwalder,³ B. Boroojerdi,⁴
¹King's College Hospital, London, UK; ²Baylor College of Medicine, Houston, TX, USA; ³Paracelsus-Elena Hospital, Kassel, Germany; ⁴SCHWARZ Biosciences, Monheim, Germany.

Purpose: The rotigotine transdermal patch (Neupro®) is a broad-spectrum dopamine receptor agonist, which is approved in Europe and the U.S. for the treatment of idiopathic Parkinson's disease (PD). Given the stable 24-hour plasma levels achieved with this system, beneficial effects on nocturnal and early morning PD symptoms were expected and are reported here. **Methods:** The effect of rotigotine on sleep was analyzed from data collected in 3 double-blind, placebo-controlled trials and one open-label extension of an early morning motor and sleep specific trial in patients with advanced PD. The following questionnaires were used: 15 item Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), UPDRS Part IV, and the nocturnal akinesia, dystonia, and cramps score (NADCS). **Results:** A total of 1032 patients were included in this analysis, 727 treated with rotigotine and 305 with placebo. Compared to baseline, the status on awakening improved to "on without troublesome dyskinesia" by 24.1%, 15.6%, and 25.5% with rotigotine and by 8%, 4.3% and 11.5% with placebo in the 3 double-blind trials. In the open-label trial, the mean change from baseline (9.4) in overall PDSS score was 11.6 ($p < 0.001$). ESS sum score improved from 7.3 to 6.1 ($p < 0.0027$). 58% of patients who had sleep disturbances at baseline according to UPDRS Part IV were free of symptoms at the end of the treatment phase. There was also a significant reduction in NADCS with Neupro® treatment (-2.13 total score, $p < 0.0001$). **Conclusions:** In these four trials, rotigotine signif-

icantly improved nocturnal and early morning PD symptoms without increasing daytime sleepiness.

Poster 8 (PD)

Lipids and Alpha-Synuclein Aggregation in Parkinson's Disease

K. Broersen, B. Davletov. *Medical Research Council Laboratory of Molecular Biology, Cambridge, UK.*

α -Synuclein is a small cytosolic protein involved in the pathogenesis of Parkinson's disease and other neurodegenerative disorders. Recent studies suggested a lipid-related function for this brain-enriched protein. Since the brain carries a high content of docosahexaenoic acid (DHA) and since α -synuclein gene expression increases in response to DHA intake, we have investigated the interaction of α -synuclein with this essential omega-3 fatty acid. We show that α -synuclein allows DHA to be present in a soluble rather than micellar form. Upon interaction with DHA, the normally unstructured α -synuclein rapidly adopts an α -helical conformation. Prolonged exposure to DHA, however, gradually converts α -synuclein into amyloid-like fibrils. These results identify a potential biological function for α -synuclein and define an omega-3-linked pathway leading to α -synuclein aggregation.

Poster 9 (PD)

Concentrations of Tetrahydroisoquinolines in Common Fruits and Vegetables

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Epidemiological studies suggest that environmental factors contribute to the pathogenesis of Parkinson's disease (PD). A diverse collection of neurotoxins can produce Parkinsonism in humans and animal models. The discovery of MPTP, in particular, led to a search for structural analogs that could also contribute to degeneration of dopaminergic neurons. The tetrahydroisoquinolines (TIQs) are structurally similar to MPTP, inhibit complex I of the respiratory chain and can initiate apoptosis in cultured dopaminergic neurons. Using enantiomeric-selective high performance liquid chromatography with electrochemical detection (HPLC-EC) and liquid chromatography-mass spectrometry (LC-MS), the concentrations of TIQ, 1-benzyl-TIQ, (R/S) salsolinol (SAL), N-methyl-(R/S)SAL, norsalsolinol (NorSAL) and N-methyl-NorSAL were determined in those fruits (N = 20) and vegetables (N = 20) most commonly consumed in the United States. Several TIQ derivatives were detected in all fruits and vegetables. N-methyl-(R/S)SAL and (R/S)SAL were detected as racemic mixtures with no evidence of stereoselective synthesis. In general, hydroxylated and methylated derivatives were present at higher concentrations than their parent TIQ. In contrast, TIQ was present at much higher concentrations than its benzylated derivative, 1-benzyl-TIQ. Bananas, citrus fruits, strawberries, potatoes, onions, celery, tomatoes and mushrooms were found to have particularly high concentrations of one or more TIQs. Our data may provide a link between dietary risk factors and the pathogenesis of PD.

Poster 10 (PD)

The Pivotal Role of Nitric Oxide in 6-OHDA-induced Dopaminergic Neurotoxicity: Neurochemical Evidences in Rats

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The present study was undertaken to explore the involvement of nitric oxide (NO) in 6-OHDA experimental model of Parkinson's disease in rats. The effect of pharmacological manipulation of NO system was evaluated on striatal dopamine (DA) levels decrease produced by the toxin. In the *control-lesioned* group (n = 7), 6-OHDA (5 μ g) was infused in the left substantia nigra pars compacta (SNc). A second lesioned group (n = 7), 50 mg/kg i.p. of the NO synthase (NOS) inhibitor, 7-nitroindazole (7-NI), was administered 1 h before the toxin. A third lesioned group, 40 mg/kg i.p. of molsidomine (MOL), a NO donor, was injected 1 h before the toxin. In a fourth group (n = 7), 7-NI and MOL were co-injected 1 h before the toxin. Four sham groups (n = 7, each) received similar pharmacological treatment, nil, 7-NI, MOL, 7-NI+MOL. After a week from the lesion, rats were sacrificed and their brains removed and the striatum of both sides was collected. The samples were analyzed by reversed-phase HPLC with electrochemical detection. The levels of DA in the left striata were $-90.6 \pm 9.5\%$ in the *control-lesioned* animals, $-35.3 \pm 4.4\%$ in the *7-NI lesioned* group, $-91.5 \pm 6.4\%$ in the *MOL lesioned* group and $-88 \pm 5.1\%$ in the *7-NI+MOL* group. In the same groups 7-NI and MOL did not affected DA striatal levels. Thus a crucial role of NO in 6-OHDA induced neurodegeneration is suggested as well of a protective benefit for inhibitors of NOS in the treatment of Parkinson's disease.

Poster 11 (PD)

Re-evaluating Dose Conversions When Switching Between Dopamine Agonists: A Post Hoc Analysis of Subjects Initiating Rotigotine Therapy after Prior Maintenance on Ropinirole

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Introduction: Switching between dopamine agonists (DAs) in Parkinson's disease (PD) may be an option to enhance treatment benefit in individual patients; however, switching regimens for DAs are not well studied. To evaluate outcomes in rotigotine-treated subjects previously maintained on ropinirole, a post hoc analysis of an open-label extension to a double-blind placebo- and comparator-controlled rotigotine trial (SP513) was performed. **Methods:** Subjects randomized to the active-comparator (ropinirole ≤ 24 mg/day) in the 6-month, double-blind trial who elected to enroll in an open-label extension with rotigotine were evaluated. Following double-blind maintenance, ropinirole was tapered and rotigotine then titrated weekly in 2mg/24hour increments up to an optimal dose (≤ 8 mg/24h). For this post hoc analysis, subjects were divided into three groups based upon previous daily ropinirole dose (≤ 9 mg, >9 mg to ≤ 18 mg, or >18 mg). UPDRS(II+III) scores were used to assess patient outcome, defined as improvement (≥ 5 -point decrease), worsening (≥ 5 -point increase) or no

change. **Results:** Most patients (115/160;72%) were titrated to the maximum rotigotine dose allowed (8mg/24h). The percentage of patients with improvements or no change in UPDRS did not directly correlate with previous ropinirole dose (80%, 65%, and 73% for the ≤ 9 mg[n=56], >9 mg to ≤ 18 mg[n=34], and >18 mg groups[n=63], respectively). Subject withdrawal for lack of efficacy (6%) did not show bias towards prior ropinirole dose. **Conclusions:** In this post hoc analysis, prior ropinirole dose was not highly predictive of therapeutic outcome following switch to rotigotine in early PD patients, suggesting that a beneficial outcome was possible with rotigotine across a broad range of previous doses of ropinirole.

Poster 12 (PD)

Predicting Falls in Parkinson's Disease using Functional Reach

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Individuals with Parkinson's disease are at increased risk of falls and these may result in injuries. There are no standardized methods to determine which patients are at increased risk of falling. We evaluated 366 patients with Parkinson's disease on their first clinic visit using the "Functional Reach" (FR) measure. All patients were evaluated by a single physician. The Functional Reach involves the patient standing with their feet together and right arm parallel to the ground. The patient reaches along a ruler or tape measure mounted on the wall until they begin to fall or need to take a step. The excursion of a point on the hand is the functional reach. Age, height, weight and gender were also included in a logistic regression model designed to discriminate falling risk. A logistic regression model was highly significant ($p < 0.0001$) in predicting falling status. Persons only able to reach 20 cm had approximately an 80% chance of being a faller.

Poster 13 (PD)

Rotigotine Transdermal Patch is Effective in the Treatment of Idiopathic RLS: Results of a 6-Month, Multi-Center, Double Blind, Placebo-Controlled Trial in the USA

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Objective: To evaluate efficacy and safety of rotigotine transdermal patch in patients with moderate to severe idiopathic RLS over a period of 6 months. **Methods:** Multi-center, randomized, double-blind, placebo-controlled, 5-arm parallel-group trial with 4 fixed doses of rotigotine 0.5-3mg/24h (2.5-15cm²). The co-primary efficacy parameters were the IRLS sum score and the CGI item I. **Results:** A total of 505 patients (52 \pm 13 years, 61% female) were randomized at 58 sites in the US. The mean baselines scores were: IRLS 23.3 ± 5.0 and CGI 4.7 ± 0.7 . The improvement net effects versus placebo at 6 months were -2.2 ± 1.2 , -2.3 ± 1.2 , -4.5 ± 1.2 ($p < 0.001$), and -5.2 ± 1.2 ($p < 0.001$) in the IRLS and -0.35 ± 0.19 , -0.32 ± 0.19 , -0.65 ± 0.19 ($p < 0.001$) and -0.90 ± 0.19 ($p < 0.001$) in CGI item I for rotigotine 0.5, 1, 2, and 3mg/24h, respectively. At least 1 adverse event was reported by 84 % of patients on placebo and 88% on rotigotine. Most common side effects were application site reaction(27.2%), nausea(21.5%), headache(17.6%) and

somnolence(12.6%). AEs were usually mild to moderate in intensity and transient. *Conclusion:* Therapy with rotigotine transdermal patch in doses of 2 and 3 mg/24h over a period of 6 months resulted in a statistically significant and clinically relevant reduction in the IRLS score and CGI item I compared to placebo and was well tolerated.

Poster 14 (PD)

Voxel-Based Morphometry and Diffusion Tensor Imaging in Parkinson's Disease

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Background: Parkinson's disease (PD) is characterized by motor abnormalities; however there are neurocognitive changes that are not sufficiently evaluated with PD rating scales or with standard magnetic resonance imaging (MRI). *Objective:* To determine if there are structural or microstructural MRI abnormalities in PD as compared to age-matched healthy control subjects. *Methods:* Thirteen control and twelve non-demented PD subjects underwent 3T MRI voxel-based morphometry (VBM) and Diffusion Tensor Imaging (DTI). Patients were evaluated with a variety of neurocognitive measures and the Unified Parkinson Disease Rating Scale (UPDRS) OFF and ON their antiparkinsonian medications. *Results:* The PD participants, as to be expected had dopa-responsive features as ascertained by the UPDRS off and on medications but did not have substantially neurocognitive differences from control subjects. Decreased fractional anisotropy (FA) was observed in PD subjects bilaterally in the frontal lobes, including the supplementary motor area (SMA), the pre-SMA and the cingulum. There were no significant differences in mean diffusivity, or gray and white matter density between PD and controls. *Conclusion:* VBM analysis of DTI shows microstructural white matter changes in frontal areas without volume loss. These findings may relate to underlying motor deficits and appear to precede the development of clinically significant neurocognitive impairments.

Poster 15 (PD)

Assessing Apathy with the UPDRS: Comparison to the Apathy Evaluation Scale

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Background: The Apathy Evaluation Scale (AES) has been found to be reliable and valid in assessing apathy in PD (Starkstein, 1992). Despite this, current practice often assesses apathy with a single item from the Unified Parkinson's Disease Rating Scale (UPDRS, item 4). The relationship between this item and the "gold standard" AES scale is unknown. The purpose of this study was to evaluate UPDRS

item 4 in relation to the AES. *Methods:* We administered the AES and the UPDRS to 301 PD patients, comparing UPDRS item 4 to the standard AES classification of ≥ 14 as apathetic. A "receiver operating characteristics" (ROC) curve was obtained and logistic regression was used to determine sensitivity, specificity, positive and negative predictive power for UPDRS item 4. *Results:* As a group, PD patients were 67.9 years old (SD=10.4), well educated, in moderate stages of disease severity (UPDRS motor=29.5), with a mean AES of 13.68 (range 0-33) and item 4 of 1.14 (range 0-4). The ROC curve showed area under the curve as .75 (best = 1.0, worst = .5). Item 4 correctly classified only 69% of patients. Sensitivity was only 52.3%, while specificity was 87.2% with positive predictive power of 64.2% and negative predictive power of 73%. Over 1/4 PD patients with a zero score on Item 4 of UPDRS scored in the clinically apathetic range on the AES. *Conclusion:* These findings suggest item 4 is not an adequate screening tool for apathy in PD. It has poor sensitivity in relation to the Apathy Evaluation Scale.

Poster 16 (PD)

The Relationship Between Non-motor Symptoms, Disease Severity, and Motor Subtype in Parkinson's Disease

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Introduction: Non-motor symptoms (NMS) in Parkinson's disease (PD) have become increasingly recognized; however, little is known about the relationship between NMS, disease severity, and motor subtype. *Methods:* 91 veterans with idiopathic PD underwent a structured evaluation including the NMSQuest (a 30-question instrument regarding non-motor symptoms in PD) in addition to Hoehn and Yahr (HY) staging, Unified Parkinson's Disease Rating Scale (UPDRS), Mini-Mental Status Examination (MMSE), and the Epworth Sleepiness Scale (ESS). Patients were stratified by disease stage (HY) and motor subtype [tremor dominant (TD) versus postural instability and gait difficulty (PIGD)] using the classification devised by Jankovic et al (1990). *Results:* We found that NMS were highly prevalent and that they increased with disease severity ($p=0.005$). Genitourinary and gastrointestinal symptoms predominated in this VA population; however, difficulty remembering things (56%) and sleep disorders (>40%) were also highly prevalent. When stratified by HY stage, there were highly significant differences with regard to mean UPDRS II ($p<0.001$), UPDRS III ($p<0.001$), UPDRS total ($p<0.001$), and NMSQuest ($p=0.005$) scores with advancing disease. Although a statistically significant difference was seen between TD and PIGD groups on the NMS Quest ($p=0.03$), this difference disappeared with controlling for UPDRS II, UPDRS III, UPDRS total, or HY stage. *Conclusions:* NMS in PD are frequent at all disease stages but increase in prevalence as motor disease progresses. In addition, although NMS appear to be more frequent in subjects with the PIGD clinical subtype, it may be that this increased prevalence is related to advanced disease severity.

*Poster 17 (PD)***The Washington Parkinson Disease Registry (WPDR): A State-Wide Research Registry**

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Introduction: The recruitment of adequate numbers of Parkinson's disease (PD) patients for research participation can be a significant problem for investigators, and PD patients often complain that they are unaware of studies for which they might be eligible. To address these issues, we have collaborated with regional advocacy groups to develop a State-wide registry of PD patients that are willing to be contacted for research participation. **Methods: Recruitment.** Advertisement through the local chapter of the APDA and the Northwest Parkinson Foundation are utilized, along with regional educational programs, radio, TV interviews and PSAs. **Screening.** Potential registrants undergo an initial screening using a previously published telephone questionnaire (Tanner et al., 1990). **Data Acquisition.** Personal and detailed medical information relating to PD will be collected by telephone interview. **Tier System.** Registrants are stratified based on likelihood of a correct diagnosis of PD. **WPDR Access.** Study protocols are reviewed by the WPDR executive board. Study subjects will be selected based upon submitted inclusion/exclusion criteria and will be given contact information for the proposed study. Enrollment into the WPDR is ongoing. **Discussion:** The primary goal of the WPDR is to develop a large registry of individuals with PD and an interest in participating in research. This will serve as a regional and national resource to speed up recruitment of PD patients, facilitate research, and improve access to studies for patients. Due to obvious selection bias, the WPDR is not intended to be an epidemiologic sample, unlike other registries in other regions of North America.

*Poster 18 (PD)***Diagnosing Depression in Parkinson's Disease: BDI Screening versus DSM-IV-TR Criteria**

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Depression is the most common neuropsychiatric complaint in Parkinson's disease (PD), with an estimated prevalence of around 40% of all patients who undergo formal screening. The ability to diagnose and treat depression is important since it is associated with poor treatment compliance, caregiver distress and reduced quality of life. The Beck Depression Inventory (BDI) is a widely used screening tool to detect depression in PD. The BDI-II closely parallels DSM-IV-TR depression criteria, by assessing whether symptoms have been present for two or more weeks. We evaluated 133 PD patients with a battery of neuropsychological measures, including the BDI-II, as part of a presurgical evaluation for Deep Brain Stimulation (DBS) surgery. Based on BDI-II scores, 61 patients (45.9%)

were identified as having clinically significant depressive symptoms (BDI-II = 14). Within this subgroup 23 (37.7%) and 14 (23.0%) patients met DSM criteria for Major Depressive Disorder and Minor Depressive Disorder, respectively. Twenty-three patients (37.7%), who were classified as depressed based on BDI-II scores, did not meet diagnostic criteria for either disorder. While it is possible that these patients may represent what has been referred to as Subsyndromal or Sub-threshold Depression, their complaints could not be clearly dissociated from their disease symptomatology (anhedonia, fatigue, sleep disturbance). These findings underscore the importance of evaluating depression in PD in the context of disease symptoms and suggest that the BDI-II should not be used alone to diagnose depression, especially when making treatment decisions. Longitudinal studies are needed to further define long-term sequelae of depression in PD.

*Poster 19 (PD)***Neuropsychological Deficits in Parkinson's Disease Patients Without Global Cognitive Impairment**

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Purpose: Dementia occurs in up to 80% of Parkinson's disease patients over time, but relatively little is known about initial cognitive changes in PD. We report on the frequency and characteristics of neuropsychological impairment in PD patients without global cognitive impairment. **Methods:** A battery of neuropsychological tests was administered to a cohort of PD patients without significant global cognitive impairment (on the basis of having an age- and education-adjusted Mini-Mental State Examination (MMSE) score in the top 75th percentile). Standardized tests of memory (Hopkins Verbal Learning Test-Revised [HVLTR]), executive function (Stroop Color-Word Test [STRP]), verbal fluency, and Tower of London-Drexel [TOL-DX]), and attention (Digit Span) were administered, for a total of 9 standardized scores. Patients who scored ≥ 1.5 or > 2 standard deviations (SDs) below the mean on a measure were considered to have a score that was borderline or impaired, respectively. **Results:** Of 141 subjects who were assessed with the battery, 117 (83%) patients met our MMSE criterion (mean [SD] MMSE score = 28.9 [1.2]). Borderline or impaired scores on neuropsychological measures were common: HVLTR (15.4-24.8%); STRP (12.0%); Verbal Fluency (8.5%); TOL-DX (5.2-25.9%); and Digit Span (0.0%). Approximately half of patients had either an impaired (41.9%) or borderline (12.0%) score on one or more neuropsychological measure. **Conclusions:** Impairment in different cognitive domains is common in PD, even among those who have intact global cognitive functioning on the basis of a standardized screening instrument. In contrast with some previous reports, we found that memory impairment is more common than executive and attentional impairment, the latter being unimpaired in our population. These results suggest the need to use sensitive neuropsychological instruments covering a range of cognitive domains to detect mild cognitive impairment in PD.

*Poster 20 (PD)***Perceived Driving Ability of Drivers with Parkinson's Disease**

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Objectives: To determine if perceived driving ability among patients with Parkinson's disease (PD) differed from drivers without PD. **Background:** Automobile drivers generally adapt their driving patterns to compensate for decreased abilities (e.g., avoiding night time driving). These compensatory strategies tend to improve driving safety. Whether one makes adjustments is dependent on their confidence level, which is directly related to perceived ability. A driver must recognize deficits in order to employ compensatory behaviors. **Methods:** Nineteen random subjects with idiopathic PD, recruited from the University of Florida's Movement Disorder Center (MDC), were referred to a driver rehabilitation specialist to determine safe driving ability, regardless of the clinician's perception of their driving competence. In addition to undergoing an on-road driving test, participants reported driving habits and confidence levels which were compared to an age-matched control group. **Results:** Nineteen PD patients (78% males) with a mean age of 75 years (SD 6.07), UPDRS mean motor score of 25.9 (6.9) on medication and 34.2 (9.9) off medication were analyzed and compared to an age-matched control group (n=96). Although 44% of the PD group failed the on-road test (vs. 20% for the control group), 88.8% of the drivers with PD rated their driving ability as "good" or "excellent" (vs. 93.7% for the control group). **Conclusions:** Drivers with PD may be overconfident in their driving abilities leading to decreased employment of compensatory behaviors and thereby increasing their crash risk.

Poster 21 (PD)

Rotigotine Patch is Effective in the Treatment of Idiopathic RLS: Results of a 6-Month, Multi-Center, Double Blind, Placebo Controlled Trial in Europe

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Purpose: To evaluate efficacy and safety of rotigotine transdermal patch in moderate to very severe idiopathic RLS patients with moderate to very severe idiopathic RLS over a period of 6 months. **Methods:** Multi-center, randomized, double-blind, placebo-controlled, fixed-dose, 4-arm parallel-group trial with rotigotine 1, 2, and 3mg/24h (5-15cm²). Primary efficacy parameters were IRLS and CGI item 1 (severity of illness) scores. Secondary parameters included RLS-6 and QoL-RLS scores. **Results:** 458 patients (58 ± 11 years, 73% female) were randomized at 49 sites in 8 European countries. Forty-two percent of placebo and 28% of rotigotine patients withdrew from the study. The mean baseline IRLS score was 28.1±6, and the mean baseline CGI score was 5.0±0.8. Improvement from baseline in IRLS scores was significantly greater than placebo in all 3 rotigotine groups. The net effects versus placebo of the improvements after 6 month were (-5.1, -7.5, and -8.2, p<.0001). CGI item 1 scores were also significantly improved versus placebo (-0.76, -1.07, and -1.21, p<.0001). Comparable effects were observed in the RLS-6 and QoL-RLS. Fifty-five percent and 78% of patients on placebo and rotigotine, respectively, reported at least 1 adverse event. The most common side effects were application site reaction (1.7%, 42.5%), nausea (5.1%, 16.4%), headache (9.4%, 15.8%), and dizziness (2.6%, 5.8%) for placebo and rotigotine, respectively. AEs were usually transient and mild to moderate in intensity. **Conclusion:** Six-month therapy with rotigotine

transdermal patch (1, 2, and 3 mg/24h) was significantly superior to placebo and well tolerated.

Poster 22 (PD)

Adjunctive Ropinirole 24-hour Prolonged Release Reduces "Off" Time and Improves the Cardinal Symptoms of Tremor, Rigidity, and Bradykinesia in Patients with Advanced Parkinson's Disease (PD)

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Introduction: Ropinirole is effective in treating PD and a 24-hour prolonged-release formulation offers a convenient, once-daily treatment option. The efficacy of ropinirole 24-hour on the motor cardinal symptoms of PD was evaluated in patients with advanced PD not optimally controlled with L-dopa. **Methods:** The EASE-PD Adjunct study (101468/169) randomized patients with PD not optimally controlled with L-dopa to adjunctive ropinirole 24-hour (n=202) or placebo (n=191), once daily for 24 weeks. Initial dose: 2.0mg/day, titrated to a maximum of 24.0mg/day. At 8.0mg/day and at each subsequent increase, L-dopa dose reduction was required. Primary endpoint: mean change in daily "off" time at Week 24 last observation carried forward (LOCF). Analyses (*post-hoc*) assessed mean changes from baseline in the tremor, rigidity, and bradykinesia components of the Unified PD Rating Scale (UPDRS) at Week 24 LOCF. **Results:** Ropinirole 24-hour prolonged release significantly reduced daily "off" time, compared with placebo at Week 24 LOCF (adjusted mean treatment difference [AMTD]: -1.7; 95%CI: -2.3, -1.1; p<0.0001). At Week 24 LOCF, significantly greater improvements were seen with ropinirole 24-hour compared with placebo, for change from baseline in tremor (AMTD: -0.9; 95%CI: -1.3, -0.4; p=0.0001); rigidity (AMTD: -0.9; 95%CI: -1.4, -0.4; p=0.0003); bradykinesia (AMTD: -1.8; 95%CI: -2.5, -1.0; p<0.0001). Mean dose (SD) of ropinirole 24-hour at last visit was 18.8 (6.3) mg/day. **Conclusions:** Once-daily ropinirole 24-hour prolonged release significantly reduces "off" time and significantly improves the motor cardinal symptoms of tremor, rigidity, and bradykinesia in patients with advanced PD not optimally controlled with L-dopa.

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Poster 23 (PD)

A Rating Instrument for Hallucinations in Parkinson's Disease: The University of Miami Hallucinations Questionnaire (UMHQ.v1)

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Hallucinations occur in any form and severity in up to 40% of Parkinson's disease (PD) patients. They have been associated with increased caregiver burden, nursing home placement, and increased mortality. Absence of a uniform classification and lack of PD-specific rating instruments for hallucinations have contributed to conflicting reports and have limited clinical trial outcomes. Here we present quantitative and qualitative data on hallucinations in PD systematically collected through a

symptom-specific instrument that could be used to improve clinical research outcomes and monitor progression. We prospectively administered the 21-item questionnaire (UMHQ.v1) to 95 patients seen in our department during an 18-month period. The questionnaire consists of a 2 parts: Part I (Items 1-6, quantitative part that measures severity with scores 0-18) and part II (items 7-21, qualitative part). We identified 21 (24.7%) patients (15M/6F, mean age 63.7±9.3yrs, mean disease duration 10.4±6.3yrs mean MMSE 24.4±5.4) with hallucinations. Detailed neuropsychological evaluation was also performed. Patients scored a mean of 12.3±3.0 in part I of the UMHQ. Part II identified 12 patients (57.1%) with one type of hallucinatory modality (9 pure visual and 3 pure auditory) and 9 (42.9%) with various combinations. The majority reported very frequent (>once/day) hallucinatory experiences of prolonged (>10s) duration. Only 5 (23.8%) of patients believed that their hallucinations were real. Surprisingly, there was no correlation between reality testing and MMSE scores. Using a sensitive disease-specific scale we quantitatively and qualitatively characterized hallucinations in PD patients. The UMHQ should be further tested as an end-point in clinical research.

Poster 24 (PD)

Anxiety Disorders in Parkinson's Disease

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Introduction: Previous studies indicate that about 40% of patients with Parkinson's disease (PD) have at least one clinically significant anxiety syndrome, while the prevalence rate in the general population is only 9% - 18%. Despite this, anxiety in PD is under-diagnosed. One reason for under-recognition of anxiety in PD may be that many of the anxiety syndromes in PD do not fit into discrete diagnostic categories. *Methods:* Subjects with idiopathic PD based on UK Brain Bank Criteria (n=107, 70 Men, 37 Women) were recruited from the practices of three community-based movement disorder specialists to take part in an ongoing study on screening for mood disorders in PD. Subjects underwent a comprehensive diagnostic psychiatric exam in addition to the Structured Clinical Interview for Diagnosis (SCID) using DSM-IV-TR criteria to determine whether conditions fulfilled criteria for major DSM diagnoses. Final diagnoses were established by an "expert panel" of 5 psychiatrists using best-estimate diagnostic procedures. *Results:* Participants were 67.3 (10.9) years old, 93% Caucasian, 4% African American, 1% Asian, and 2% other, and had PD duration = 7.9 (5.8) years (n=102). There were 50 (47%) of the 107 subjects diagnosed with at least one anxiety disorder. However, the majority of anxiety disorder diagnoses (32/50, 64%) did not fit into a discrete DSM category and were classified as Anxiety disorder not otherwise specified. *Conclusions:* These findings suggest that anxiety disorders occur more frequently in PD than in the general population and that further characterization of anxiety disorders in PD is needed.

Poster 25 (PD)

Sitting Apraxia in Progressive Supranuclear Palsy

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Objective: To demonstrate "sitting apraxia" in PSP. *Background:* Difficulty arising from a chair affects almost all patients with parkinsonism. Much less common is impaired sitting, termed "sitting apraxia," which appears to be more common in parkinsonian syndromes, particularly PSP. *Methods:* Case presentations with video. *Results: Patient 1.* A 69 year old woman had a three year history of imbalance and falls. On examination, speech was nearly unintelligible but she could understand. She had the applause sign (Dubois B, et al. *Neurology* 2005). She could arise from a chair by pushing off, but on her feet spontaneously fell backwards. There was supranuclear vertical ophthalmoplegia (SVO). When attempting to sit, she aligned herself properly in front of the chair and appropriately grasped the handles. She made several attempts to sit, only to resume a standing posture before eventually lowering herself into the chair after 45 seconds. *Patient 2.* A 74 year old man presented with a three year history of imbalance and falls. Examination demonstrated impaired balance, the applause sign, and SVO. Similar to patient 1, he was able to align himself in front of a chair and grasp the handles, made several aborted attempts to sit, and after 20 seconds, plopped into the chair. *Conclusions:* The difficulty sitting demonstrated by our patients with PSP does not appear to adequately account for by axial rigidity or akinesia suggesting that the inability to sit represents a unique disorder of motor control of the trunk, justifying the term "sitting apraxia."

Poster 26 (PD)

Association of Mid-Life Physical Activity with Risk of Future Parkinson's Disease

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Objective: to examine the association of mid-life physical activity with risk of future Parkinson's disease (PD). *Background:* Results of studies investigating the association of physical activity (PA) and PD risk are inconsistent with recent prospective studies indicating that greater exercise is associated with lower risk. Confirmation of this finding could lead to trials of physical exercise as a potential disease modifying therapy. *Methods:* An estimate of 24-hour habitual PA was collected from 5,377 Japanese-American men, aged 45 to 65 years, participating in the longitudinal Honolulu Heart Program baseline exam from 1965 to 1968. To avoid the possibility that early PD could affect PA, follow-up for PD was initiated 12 years after baseline. Incidence of PD was calculated within quartiles of a PA index derived from baseline data. *Results:* 118 men developed PD. Average time from baseline to diagnosis was 23 years (range 12.8-34.7). Age adjusted incidence of PD/10,000 person years was 18.4 in the lowest PA index quartile decreasing to 14.7, 10.5, and 9.1 in the 2nd, 3rd, and 4th quartiles

respectively (P value for trend was 0.012). Using the highest PA quartile as the reference group, the relative hazards and 95% confidence intervals for PD after adjusting for age, and other potential confounders were 1.1 (0.6, 2.1), 1.6 (0.9, 2.7), and 1.9 (1.1, 3.2) for the 3rd, 2nd and 1st quartiles respectively. **Conclusions:** Findings suggest that lower mid-life PA measured at least 12 years prior to diagnosis is associated with higher risk of Parkinson's disease among men.

Poster 27 (PD)

Statin Use and the Risk of Parkinson's Disease

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Hydroxy-methylglutaryl-coenzyme A reductase inhibitors (statins) can lower coenzyme Q-10 levels, which may contribute to the pathogenesis of PD. We explored the relationship between statin use and the risk of developing PD through a nested case-control study (case-control study within a cohort) using the British Columbia Linked Health Databases (BCLHD). The BCLHD contain linkable, individual, anonymized health data for four million residents of British Columbia. BCLHD include comprehensive data on prescription drug use, hospitalizations, physician visits, and vital statistics. We created a cohort of individuals who received at least one prescription from 1997-2003. The date of the first prescription was the date of cohort entry. Cohort members were followed to the first diagnosis of PD, termination of the study period, date of emigration from the province, or death. PD was defined as having had a physician visit (ICD-9 code 332), and at least two PD medication prescriptions (all forms of levodopa, bromocriptine, pergolide, selegiline, amantadine, pramipexole, ropinirole) within six months of the physician visit. Incidence cases of PD were identified. We matched a random sample of controls to the cases by age. Conditional logistic regression was used to estimate odds ratios adjusting for antipsychotic use, gender, and comorbidity. We identified 4,957 cases and 19,828 controls. Current users were defined as those using at least one statin prescription within 60 days of index. The relative risk for current statin users was 0.94 (0.82 - 1.09). Our study did not show a statistically significant effect on the risk of PD with statin use.

Poster 28 (PD)

HFE Variants C282Y and H63D Do Not Alter Risk of Parkinson's Disease

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WA; ⁷ Department of Neurology, Oregon Health and Science University, Portland, OR; ⁸ Northwest Parkinson's Disease Research Education and Clinical Center, Portland VA Medical Center, Portland, OR; ⁹Department of Neurology, Albany Medical Center, Albany, NY; ¹⁰Wadsworth Center, New York State Department of Health, Albany, NY; ¹¹Geriatric Research Education and Clinical Center, VA Puget Sound Health Care System, Seattle, WA, USA.

Introduction: In Parkinson's disease (PD), excessive iron deposition frequently occurs within the substantia nigra and might contribute to the loss of nigral neurons by increasing oxidative stress. Hereditary hemochromatosis is a systemic disorder of iron overload caused primarily by two mutations (C282Y and H63D) in the *HFE* gene. Six association studies have examined *HFE* mutations and PD risk with disparate results. We sought to further assess the role of *HFE* as a susceptibility factor for PD in a large case-control sample. **Methods:** We genotyped *HFE* C282Y and H63D in 1,726 PD patients and 1,985 controls of self-defined "white" ancestry using TaqMan assays. All cases were consecutively recruited at clinics across the U.S. (GA, NY, OR, WA) and met UK PD Society Brain Bank clinical diagnostic criteria for PD as determined by a movement disorder specialist. **Results:** There were no significant differences in allele or genotype frequencies between cases and controls for either of the two variants ($p > 0.3$). For C282Y, the unadjusted odds ratio (OR) under a dominant model (C/Y and Y/Y versus C/C) was 0.93 (95% CI, 0.76-1.12). Finally, a meta-analysis combining our data with those from six previous studies revealed no significant association between the 282Y allele and PD (OR, 0.90; 95% CI, 0.79-1.03). **Discussion:** Our data, from the largest case-control sample studied to date, suggest that the *HFE* variants C282Y and H63D do not significantly alter PD risk. Whether functional variation in other genes involved in iron metabolism modifies susceptibility for PD remains to be determined.

Poster 29 (PD)

Safinamide Treatment Improves Cognition in Parkinson's Disease

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Background: Cognition is impaired in early idiopathic Parkinson's Disease (PD) with deficits most prominent in reaction time, working memory, and executive functions. **Objective:** We examined the cognitive effects of 100 and 200 mg/day doses of safinamide, a new anti-PD agent combining dopamine (DA) modulation and an effect on the glutamate pathway, compared to placebo as an add-on therapy in non-fluctuating, early idiopathic PD patients receiving a stable dose of a single DA-agonist. **Methods:** 123 PD patients in a Phase III, 24-week, randomised, placebo-controlled trial of safinamide were assessed on selected subtests (Auditory Number Sequencing, Spatial Working Memory, Strategic Target Detection, Tapping Speed, Simple Reaction Time, Choice Reaction Time) of the Cogtest PD battery at baseline, 12 weeks, and 24 weeks. **Results:** Z-scores were generated using

Cogtest's normative database. Baseline to endpoint changes were assessed with repeated measures analysis of variance. At baseline all patients were cognitively impaired, moreover, >50% were impaired in ≥ 1 domain. Statistically significant effects of safinamide were found (vs placebo) for executive function ($p < .05$) and verbal working memory ($p < .05$), while spatial working memory showed a trend ($p = 0.079$). Cognitive effects were seen after 12 weeks of safinamide treatment. *Conclusions:* Significant cognitive deficits were found in early idiopathic PD patients on DA-agonists. Executive function and verbal working memory improved with safinamide, with a trend toward improvement in spatial working memory. These data demonstrated that cognitive deficits are prevalent in PD patients receiving a DA-agonist and that the addition of safinamide to the existing treatment, improved cognition.

Poster 30 (PD)

Evaluation of Olfaction and Personality Traits in 1st Degree Relatives of PD Patients

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Objective: To determine whether an association exists between impaired olfaction and neuropsychological characteristics in relatives of patients with Parkinson's disease (PD). *Background:* Patients with PD may have a pre-morbid personality marked by increased anxiety and depression and reduced novelty seeking. Impaired olfaction has been identified as a non-motor feature that may develop before the cardinal features of PD. *Methods:* We conducted a mail survey of 72 1st degree relatives of PD patients. Respondents completed the 40 item University of Pennsylvania Smell Identification Test (UPSIT) and personality and mood questionnaires including the three-dimensional personality inventory (TPI), State-Trait Anxiety Scale and the CES-D. A sub-set of respondents ($n = 31$) were examined in person with the UPDRS and the MMSE, Hopkins Verbal Learning Test and the Stroop Color Naming Test. *Results:* Mean scores on the personality and affective scales were similar to population norms. There were no significant associations between olfactory impairment and personality parameters. There were non-significant trends for subjects with impaired olfaction (at or below the 10th percentile for age and gender) to have lower scores in the TPI for novelty seeking (OR = 0.88, 95% CI = 0.72, 1.08) and harm avoidance (OR = 0.89, 95% CI = 0.73, 1.09). There were no association between mood or anxiety scores and olfactory performance. Likewise, there was no association between cognitive performance and olfaction. *Conclusions:* The results of this study do not support a strong relationship between abnormal olfaction and a "pre-morbid" parkinsonian personality. Larger and longer duration studies are needed to determine if a modest association exists and whether neuropsychological features can be used to help predict the emergence of clinically manifest PD.

Poster 31 (PD)

The Contribution of Apathy to Global Cognitive Status in Parkinson's Disease

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Background: Recently, attention has focused on apathy as an important factor in Parkinson's disease (PD). It has long been known that emotional states, particularly depression and anxiety, can influence memory and cognitive performance. The purpose of the present study was to examine whether apathy might contribute to the cognitive status of PD patients. *Methods:* To test this hypothesis, we administered the Dementia Rating Scale-2 (DRS-2) as part of a large neuropsychological battery to 121 idiopathic PD patients and examined the contributions of cognitive (executive/memory) and mood measures to overall DRS score. Mood measures included the Beck Depression Inventory-II, Geriatric Depression Inventory, Apathy Evaluation Scale, and State-Trait Anxiety Inventory. *Results:* The PD patients ranged in age from 42 to 87 ($M = 66.5$), were well educated ($M = 14.9$ years), had experienced symptoms for an average of 10 years, and obtained a mean DRS-2 total score of 134.6. An exploratory regression analysis determined the best cognitive predictors of DRS-2 total score were verbal fluency (FAS and Animal Naming), delayed word list recall, and Trailmaking B, which together accounted for 38% of the variance. To examine the influence of mood variables on DRS-2, we performed a hierarchical regression analysis holding the 4 cognitive predictors constant. Results revealed apathy was the only mood variable that made a significant contribution beyond the cognitive model. *Conclusion:* These results indicate an overall association between apathy and DRS-2 performance and suggest apathy has greater influence on global cognitive status than do depression or anxiety.

Poster 32 (PD)

Dystonia in Parkinson's Disease

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Objective: To study Dystonia in L-Dopa treated Parkinson patients. *Background:* Dystonia can be the earliest manifestation of motor dyskinesias and L.J.Currie suggested that early morning dystonia occurs primarily in high doses of levodopa therapy. Professor Marsden observed that low doses of L-Dopa at frequent intervals produced diphasic dystonia. *Design/Methods:* This is a prospective three year study on thirty Parkinson patients with more than five year duration of illness. They were divided into: Group -A -15 patients-low dose 275mg (55mg 5 times daily) and Group -B-15 patients-high dose 550mg (110mg-5 times daily). Patients were assessed at three monthly intervals. A statistical test for difference in proportion was employed to compare high and low doses of L-Dopa therapy. *Results:* 53% of Group A patients developed a Diphasic dystonia within one year of therapy. While 80% of the patients developed early morning foot dystonia, only 27% developed peak dose dystonia. In Group B, 20% of the patients developed a diphasic dystonia within three years of therapy. 66% of the patients developed early morning foot dystonia and 60% developed peak dose dystonia. Diphasic dystonia occurred both in the morning and evening in both the groups. The statistical test for difference of proportions was significant at 5% level in diphasic and peak dose dystonia (statistic value $z = 2$). Early morning foot dystonia was not statistically significant (statistic value $z = 0.8$). *Conclusion:* 1) While low dose of L-Dopa caused early diphasic dystonia, peak dose dystonia was seen in high dose group; 2) Early morning foot dystonia occurred in both groups.

Poster 33 (PD)

The Relationship between Depression and Incident Dementia in Parkinson's Disease

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Previous studies have proposed depression as a risk factor for the development of dementia in Parkinson's disease (PD). However, different assessment methods have been used to define depression and dementia, yielding conflicting results. This analysis investigated the relationship between a depressive diagnosis versus depressive symptoms and incident dementia. From a sample of 142 patients with idiopathic PD followed for up to 8 years in a longitudinal study, 56 participants were assessed for incident dementia during the observation period [37M/19W; mean (SD) age=64.0 (10.2), PD duration=10.7 (7.4) years]. Dementia and depressive diagnoses were based on DSM-IV-TR criteria. Depressive symptom severity was evaluated using the 17-item Hamilton Depression Rating Scale (HDRS). The association between depression and incident dementia was examined using conditional logistic regression. 30 subjects had a current, past or remitted depressive disorder at baseline or during follow up, corresponding to an 8-year prevalence rate of 536 per 1000 (95% CI: 397 to 670). 24 participants developed dementia, corresponding to an incidence rate of 429 per 1000 persons (95% CI: 297 to 568). Incident dementia was comparable among patients with and without a depressive diagnosis at any time point. After controlling for age, a higher HDRS score was associated with incident dementia ($p < 0.05$). The odds ratio of dementia associated with a ten point increase in HDRS score at time of incidence was 2.3 (95% CI: 1.1 to 4.8). These results support previous studies, and suggest a relationship between incident dementia and depressive symptoms, but not a depressive disorder *per se*.

Poster 34 (PD)

Improvements over 24 Months in Patients with Moderate to Severe Idiopathic Restless Legs Syndrome Treated with a Rotigotine Transdermal Patch: Results from a Multi-National, Multi-Centre, Open-Label, Follow-Up Trial

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The aim of this trial is to determine safety, tolerability and efficacy of long-term application of transdermal rotigotine in subjects with moderate to severe idiopathic RLS. Upon completion of a six-arm, double-blind, prospective, placebo-controlled, 7 week, dose-finding study, patients could enter an open-label extension. After the optimal-dose titration period, rotigotine (up to 4mg/24hours) was administered with dose-adjustments allowed at anytime to maintain optimal treatment. Data are presented for the 24 months following titration. Efficacy variables included IRLS total score, CGI, and RLS-6 scales. A total of 295 patients entered the open-label extension trial, and 191 completed 2 years of treatment. The baseline IRLS score was 27.8 ± 5.9 , and optimal dose rotigotine treatment resulted in a reduction of 17.2 ± 9.2 points. A similar response was observed, when the RLS-6 scales were analyzed (reductions of -4.0 ± 3.1 , -4.9 ± 3.0 , -4.3 ± 3.3 , and -2.4 ± 2.7

for the items "at bedtime falling asleep," "during the night," "sleep satisfaction," and "daytime tiredness and sleepiness," respectively). Compared to baseline, the CGI Item 1 (severity of illness) score was reduced (-2.8 ± 1.19). Item 2 (change of condition) showed a sustained improvement (1.4 ± 0.6). The most common adverse events ($>10\%$) were application site reactions (50%), nasopharyngitis (12%), back pain (11%), and nausea (11%). No clinical signs and symptoms of augmentation were reported. Treatment with the rotigotine patch was well tolerated, safe and showed clinically relevant improvement in the IRLS, CGI, and RLS-6 scores. All improvements were observed in the titration period and were sustained during the 24-month follow-up.

Poster 35 (PD)

Long-Term Safety of Rotigotine Transdermal Patch in Early-Stage Parkinson's Disease

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Rotigotine is a dopamine agonist formulated as a once-daily transdermal delivery system. Upon completion of a double-blind, placebo-controlled trial in which Parkinson's disease (PD) patients treated with rotigotine up to a target dose of 6mg/24h showed significant improvement in UPDRS scores, participants could enter an open-label extension phase assessing long-term safety. Interim results from this study (up to 33 months of rotigotine treatment) are described. Following double-blind treatment, patients were tapered to their starting dose (2mg/24h rotigotine or matching placebo) and (re)titrated over a 3-week period. Rotigotine was limited to $\leq 6\text{mg}/24\text{h}$ the first year, after which doses up to 16mg/24h were allowed as needed. Adverse events (AEs), safety measures, dyskinesia and UPDRS scores were assessed. Two hundred sixteen patients (97% of those completing the double-blind phase) enrolled in the open-label extension ($n=79$ and $n=137$ from placebo and rotigotine groups, respectively). Most participants (73% $^{158}/216$) remained in the study at 33 months of open-label treatment. Discontinuations due to treatment emergent AEs were low (13%), with most withdrawals occurring within the first 12 months. As with any transdermally-delivered drug, application site reactions were among the most frequently reported AEs. Most ASRs (95%) were mild in severity. Fourteen patients (6.5%) experienced dyskinesia, with a mean time-to-onset of 476.0 days; in all but three of those patients (11/14), dyskinesia developed following initiation of L-dopa. The mean time-to-onset of dyskinesia after L-dopa initiation was 251.2 days. Long-term treatment with rotigotine was safe and well tolerated with few AE-related discontinuations and a low incidence of dyskinesia.

Poster 36 (PD)

Longitudinal Pattern of Cognitive Deficits Associated with Psychotic Symptoms in Parkinson's Disease

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Psychotic symptoms (hallucinations and delusions) are a common complication of Parkinson's disease (PD). Although linked with dementia, a specific cognitive profile associated with psychosis has not been well characterized. This study investigated the cognitive profile and rate of cognitive decline associated with hallucinosis (hallucinations with insight, PDH) and psychosis (hallucinations without insight and/or delusions, PDP) using a cohort of 141 participants with idiopathic PD followed for up to six years. Generalized estimating equations and random-effects models were used to explore longitudinal associations between performance on a comprehensive cognitive battery and presence of hallucinosis and psychosis. Participants on average completed 2.8 biennial clinical evaluations (SD=1.1, Range 1-4) for a total of 300 evaluations. Hallucinosis was present at 33 evaluations (11%, 95% CI: 0.08-0.15) and psychosis was present at 77 evaluations (26%, 95% CI: 0.21-0.30). Compared to participants with no psychotic symptoms (PDN), PDP had worse performance on tests of global cognition, verbal learning, spatial learning, visuospatial function, simple attention, psychomotor speed, whereas both PDP and PDH had relative deficits on tests of spatial learning and set shifting. Rate of cognitive decline was comparable across groups. These relationships persisted after adjustment for baseline age, sex, education, and DSM-IV defined dementia. These results suggest that set-shifting and spatial learning deficits are a core feature of psychotic symptoms in PD. The differential cognitive profile across groups in the absence of differential rates of cognitive decline suggests that associated cognitive impairment may be specific to psychotic symptoms and not reflective of progressive disease pathology.

Poster 37 (OMD)

LATE-BREAKING RESEARCH

The UHDRS Motor Exam and Speeded Tapping in the PREDICT-HD Cohort

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Background: Identifying clinical outcomes that predict disease onset in pre-manifest HD (pre-HD) is critical for designing preventive therapeutic trials. The UHDRS motor exam is the standard metric for HD diagnosis and disease severity but may not capture subtle motor impairments in pre-HD. *Objective:* To identify UHDRS motor items associated with estimated proximity to disease onset and whether computerized tapping speed improves prediction of estimated onset. *Methods:* Using baseline data from 665 pre-HD individuals from the PREDICT-HD cohort, we performed a multiple regression between proximity to onset (5 year probability of onset, Langbehn et al., 2004) and subscale scores for oculomotor function, bradykinesia, rigidity, dystonia, and chorea (Marder, 2000), controlling for age and gender. We repeated this analysis substituting UHDRS items as the predictors, and evaluated the results both with and without tapping speed as an additional predictor. *Results:* Higher bradykinesia and chorea scores were associated with closer proximity to onset ($p < .003$). Worse performance on saccade initiation, finger tapping, Luria maneuver, gait, tandem gait and chorea items were associated with closer proximity

to onset (all p 's $< .02$). With the addition of tapping speed, gait and chorea were no longer associated with estimated onset; tapping speed was the strongest predictor ($b = .001$, $SE_b = .0001$, $p < .0001$). *Conclusions:* Computerized tapping speed is more strongly associated with estimated disease onset than are individual UHDRS motor items, suggesting quantitative motor tasks maybe useful outcomes in preventive trials. Longitudinal analysis will need to confirm whether changes on these measures are associated with actual disease onset.

Poster 38 (PD)

LATE-BREAKING RESEARCH

Survey of the Parkinson's Disease Registry

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Background: The Parkinson's Disease Registry has over 2000 participants with a self-reported diagnosis of Parkinson disease who have provided background demographic and disease-specific information. The Registry can help investigators evaluate issues affecting individuals with Parkinson disease. *Objective:* To determine the feasibility and limitations of conducting a postal survey of the Parkinson's Disease Registry participants. *Methods:* We mailed a survey to Registry participants to determine their satisfaction with medical care, experience with support groups, and interest in group patient visits. We compared baseline characteristics of respondents and non-respondents using data collected during Registry enrollment between 2003 and 2006. *Results:* Of 2080 surveys mailed, 157 (7.5%) were returned without reply. The reasons for non-reply were incorrect address ($n = 134$) and the registrant had deceased ($n = 23$). A total of 726 registrants (34.9%) completed at least part of the survey. Responders were more likely to be white (94.6% vs. 90.5%), have a college degree (68.2% vs. 55.3%), have health insurance (96.3% vs. 92.7%), be employed (34.0% vs. 21.4%), and report annual household income greater than \$50,000 (44.0% vs. 31.4%). The mean age (64.8 vs. 65.1 years), duration of disease (7.3 vs. 6.8 years), and age at diagnosis (55.5 vs. 57.9 years) of responders and non-responders were similar. *Conclusions:* Surveying the PD Registry is feasible and can generate many respondents with a modest response rate. Consistent with other surveys, responders were more likely to be white and to have a higher socio-economic status than non-responders. Disease specific characteristics were similar between the groups.

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Poster 39 (PD)

LATE-BREAKING RESEARCH

Multi-Center Trial of Tasmar in Parkinson's Disease: Real-World Experience

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Background: Tolcapone was the first catechol-O-methyltransferase inhibitor approved for Parkinson's disease (PD), but

little information is published on its efficacy in a real-world setting. *Methods:* The multicenter Tasmar Adjunctive Study in Parkinson's (TASK) has enrolled PD patients to receive tolcapone 100 mg TID as adjunct to L-dopa and carbidopa for 30 days. The primary endpoint is change in patient-reported quality of life using the PDQ-8 questionnaire. Investigators also rated their Clinical Global Impression of Improvement (CGI-I). *Results:* Forty-eight physicians had enrolled 133 patients at the time of this interim analysis, performed on the first 72 patients (50 men, 22 women) to complete therapy. Two thirds of patients were age ≥ 65 years. Duration of PD was < 5 years in 45.8% and ≥ 5 years in 54.2%. About half (51.4%) of patients took concomitant dopamine agonists. The mean PDQ-8 total score improved from 42.3 at baseline to 34.9 after 4 weeks of tolcapone ($p=0.0001$). Two thirds of patients (67%) were rated as improved on CGI-I: improvement was marked in 7%, moderate in 22%, and mild in 38%. Three patients discontinued due to adverse events of dizziness, insomnia, and disorientation. No adverse events related to the liver were reported. Investigators reported they planned to continue 69.4% of patients on tolcapone after the study. *Conclusion:* Tolcapone demonstrated rapid improvement in patient- and physician-rated parameters in the majority of PD patients studied and was well tolerated with minimal adverse events.