LATE-BREAKING ABSTRACTS,
MDS STUDY GROUP ABSTRACTS AND
GUIDED POSTER TOUR INFORMATION
LBA 1
A randomized trial of creatine monohydrate to impede Parkinson disease (PD) progression

The National Institute of Neurological Disorders and Stroke Exploratory Trials in Parkinson Disease (NET-PD) Investigators

Objective: Long-term Study 1 (LS1) was conducted to determine whether creatine monohydrate (creatine) (10g/day) was more effective than placebo in slowing long-term clinical decline in participants with early PD and on dopaminergic therapy.

Background: In 2001, the NET-PD program was established to evaluate promising compounds for treatment of PD. Creatine was proposed and evaluated according to NINDS CINAPS criteria and hypothesized to impede PD progression through anti-oxidative effects and preservation of mitochondrial function observed in pre-clinical models. A futility trial was conducted. Results indicated that creatine was worthy of investigation in a Phase 3 trial.

Methods: LS1 was a multicenter, double-blind, parallel group, placebo-controlled, randomized Phase 3 trial of creatine. Recruitment goals were successful, with a total enrollment of 1,741 participants with early, stable PD receiving dopaminergic therapy. The primary efficacy outcome measure was the difference in the clinical decline from baseline to five-year follow-up, compared between the creatine and placebo groups. Clinical decline was defined by outcome measures in five domains that reflected motor and non-motor disabilities, quality of life, and cognitive impairment. The five measures were analyzed using a global statistical test (GST).

Results: During a planned interim analysis, LS1 met pre-specified criteria for futility and was stopped in September 2013. At that time, 955 (55%) participants had completed the year five visit. Creatine failed to slow the clinical decline of PD as measured by all five domains in the GST. Creatine was generally well-tolerated and did not negatively impact renal function or weight gain.

Conclusion: LS1 has the largest cohort and the most person years of follow up (>6,000) of any PD study to date. Because of extensive trial planning, incorporation of multiple domains to measure clinical decline, and sufficient retention of a large PD cohort, the investigators concluded that within the context of this trial, 10g/day creatine monohydrate cannot be recommended for clinical decline of PD.

LBA 2
Progressive nigrostriatal neurodegeneration associated with α-synuclein spreading and pathology induced by AAV-mediated overexpression of mutant synuclein in mice, rats and marmosets

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Objective: Animal models are an essential tool for basic pathophysiological research as well as validation of therapeutic strategies of human diseases. The absence of adequate in vivo experimental models has severe repercussions for therapeutic intervention success. Despite unprecedented progress in animals modelling, no mammalian model recapitulates the required age-dependent phenotypes associated with Parkinson’s disease (PD). Both the species and aging differential susceptibility of dopamine neurons was assessed by comparing the extent and pattern of neuronal loss, as well as occurrence of age-dependent intracellular inclusions formation and α-synuclein spreading, in mice, rats and monkeys.
**Methods:** We selected two different mouse strains (C57Bl/6 and senescence-accelerated mouse (SAMP8), as a model of aging), adult rats and young versus aged marmoset monkeys (*Callithrix jacchus*). We used a high-titer adeno-associated virus (AAV) of serotype 9 to express mutant human α-synuclein (A53T) under the neuron specific synapsin promoter including a WPRE enhancer element, injected in the SNpc for 16 weeks. We posit that transfected animals will exhibit species- and age-related differences in term of extent of degeneration and inclusions.

**Results:** Both SNpc and striatum were investigated for dopaminergic function. α-synuclein inclusions and spreading have been assessed in each species with two different antibodies against α-synuclein allowing to distinguish the exogenous human from the endogenous one. According to the species used, we observed differences in the PD-related neurodegeneration progression over time associated with α-synucleinopathy and α-synuclein several in many brain areas.

**LBA 3**

**Targeting of the red nucleus for cerebellar tremor**

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**Key words:** Red nucleus, deep brain stimulation, cerebellar tremor, neuromodulation.

**Conflict of interest:** The authors declare no conflict of interest. There was no financial issue relative to the research or funding sources.

Deep brain stimulation of the thalamus, especially the ventral intermediate nucleus does not significantly improve drug-resistant disabling cerebellar tremor. The dentato-rubro-olivary tract (Guillain-Mollaret triangle, including the red nucleus) is a subcortical loop critically involved in tremor genesis. Red Nucleus is also a key-node along the dentato-rubro-thalamic pathway whose discharges are also associated with tremor. We report the case of a 48 year-old female patient presenting with generalized Cerebellar Tremor due to alcoholic cerebellar degeneration. Resistance to medical therapies and severity of the symptoms led us to investigate the effects of bilateral Red Nucleus –Deep Brain Stimulation. Intra-operative microrecordings of Red Nucleus showed a high background activity with irregular tonic activity, but no rhythmic activity synchronous with upper limb tremor. Insertion of the macro electrodes and in between stimulation conditions led to a complete disappearance of the postural component of Cerebellar Tremor, without any changes in the intentional (kinetic) component. Stimulation by itself (1) did not reduce postural or intentional tremor, and (2) was associated with dysautonomic symptoms (threshold depending of the frequency of stimulation). Our observation supports a role of Red Nucleus as an important centre for tremor genesis and as a possible target for refractory Cerebellar Tremor. Further studies are required to elucidate how the neuromodulation of Red Nucleus should be implemented in these patients.
The Effects of Tyrosine on Orthostatic Hypotension and Autonomic Responses in Parkinson Disease: Randomized, Double-blind, Placebo-Controlled Trial

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Objective: To test the effects of supplementing tyrosine on blood pressure (BP), and norepinephrine (NE) levels in Parkinson’s disease (PD) subjects with orthostatic hypotension (OH).

Background: Individuals with PD can suffer from OH due to reduced levels of NE levels which inhibit the sympathetic nervous system. Orthostatic hypotension is defined as a sustained reduction in systolic blood pressure of at least 20 mmHg or a reduction in diastolic blood pressure of 10 mmHg within 3 minutes of standing (Sharabi 2011). OH symptoms include light headedness, fatigue, dizziness, poor quality of life or falls. Side effects of low NE levels also include reduced HR and BP response to acute exercise stress. Levodopa and dopamine agonists (commonly used to treat PD) reduce NE levels even further leading to a greater decrease in BP and an increase in OH. Tyrosine is a non-essential amino acid that is the major precursor to NE. Tyrosine has been shown to compete with levodopa uptake in the human brain and reduced levels of tyrosine have been shown after administration of levodopa.

Methods: We tested the effect of tyrosine supplements on BP and NE in a randomized, double blind, placebo trial. Thirty four subjects underwent OH testing, and then underwent an exercise stress test. The Tyrosine group received 300 mg of L-tyrosine (150 mg of 2x daily) for 7 days. After 7 days each subject repeated the same testing. The Control subjects underwent the same procedures with a placebo. Systolic and diastolic BP were recorded pre and post OH testing. Fasting plasma samples were taken pre exercise testing for tyrosine levels and NE levels. Heart rate, BP and oxygen consumption were recorded at rest and at peak exercise. At peak exercise plasma NE levels were re-tested. A food diary was kept by all subjects to monitor fluid and salt intake which can impact on BP.

Results: There was a significant increase in plasma levels of tyrosine in our Tyrosine group, and a significant improvement in diastolic BP in the Tyrosine group pre and post intervention (p > .05). We found an improvement in systolic BP after OH testing in both groups post intervention (Tyrosine n=17, Placebo n=19) but failed to show any affect due to Tyrosine. There was no change in HR, BP, and plasma NE pre and post intervention in either group (p > .05).

Conclusion: L-Tyrosine at a dosage of 300 mg (150 mg/2x day) is safe, well tolerated and leads to an increase in plasma tyrosine levels within a normal range. An increase in plasma tyrosine had no effect on plasma NE at rest or under acute exercise stress. An increase in plasma tyrosine had no effect on HR and BP under acute exercise stress. Tyrosine supplementation showed improvement in diastolic BP in OH from pre- to post intervention.

This project was funded by the Michael J. Fox Foundation Rapid Response Innovation Award
Objective: To test dopamine dependency of the age-related decline in motor cortex plasticity in healthy volunteers.

Background: Dopamine has a strong neuromodulatory effect on cortical plasticity. Plasticity of human primary motor cortex that is essential for motor memory and motor skills acquisition is reported to decline with aging. A dose of 100mg levodopa is reported to only prolong and not enhance the level of PAS response in healthy young adults.

Methods: The age-dependency of both motor cortex plasticity and its cerebellar modulation were tested in 40 healthy subjects (20 of each gender; mean age 42.7 ± 14.7 years, range 23-72) spanning six decades of adult life span. Motor cortex plasticity was measured from the response to paired associative stimulation (PAS) of motor cortex alone and its cerebellar modulation was measured from the change in PAS response by theta burst stimulation of cerebellum preceding the PAS. The ability of dopamine to restore deficient plasticity was tested in ten healthy older subjects after a single dose of 100mg of levodopa and compared with a control group of 10 de novo PD patients who had no response to PAS.

Results: There was a substantial decline in motor cortex plasticity with aging (P < 0.002, r = 0.5) but it could be restored in older subjects by a single dose of 100mg levodopa (P < 0.008) and to a similar extent as 100mg levodopa in de novo PD patients, suggesting the dopamine dependency of this age-related deficit. The cerebellar modulation of motor cortex plasticity was less vulnerable to aging and a single session of cerebellar cortical inhibition reinstated the deficient plasticity in older subjects.

Conclusions: The similar loss of plasticity of motor cortex in aging and in PD and its restoration by levodopa, could be the subclinical effect of cortical dopaminergic denervation that is known to exist in both states. Both dopamine supplementation and repeated sessions of cerebellar inhibition are potential interventions that may be tested for their effects on enhancing motor skills acquisition and motor performance in the elderly.

Cerebrospinal fluid neurofilament light chain discriminates multiple system atrophy from Parkinson’s disease

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Objective: To evaluate the diagnostic value of neurofilament light chain (NFL), fms-like tyrosine kinase ligand (FLT3L) and total tau protein (t-tau) in cerebrospinal fluid (CSF) as biomarkers to discriminate Multiple System Atrophy (MSA) from Parkinson’s Disease (PD).

Background: Cerebrospinal fluid biomarkers (CSF) can be useful as an adjunct to clinical assessment for the discrimination of PD from MSA and other atypical parkinsonisms. In previous studies several biomarkers in CSF have been advocated for this clinical application, including the established marker t-tau, but also novel markers like NFL and FLT3L.

Methods: Cohort based study of CSF levels of NFL, FLT3L and t-tau using commercially available enzyme-linked immunosassays (ELISAs). The study was performed in a primary care institutional centre (Radboud UMC Nijmegen). CSF levels of NFL, FLT3L and t-tau were measured in a discovery cohort of 36 PD patients, 27 MSA patients and 57 non-neurological controls and in a validation cohort of 32 PD patients, 25 MSA patients, and 56 non-neurological controls. Clinical diagnoses were defined after 3-years follow-up using internationally accepted criteria. Binary logistic regression models developed from combinations of biomarkers were assessed. Multivariate and
univariate statistical analyses were used to determine differences in CSF parameters between the groups and their significance for distinguishing between MSA and PD. Bootstrapping analysis was used for additional validation.

**Results:** CSF levels of NFL were substantially increased in MSA and discriminated between MSA and PD with a sensitivity of 74% and specificity of 92% (AUC = 0.85) in the discovery cohort. The models and cut-offs defined in the discovery group were applied to the validation cohorts. This resulted in an 80% sensitivity and 97% specificity (AUC = 0.94) in the validation cohort. Bootstrapping analysis resulted in essentially similar results. FLT3L levels in CSF were significantly lower in both PD and MSA compared to controls in the discovery cohort, but not the validation cohort. T-tau levels were significantly higher in MSA than PD and controls. Addition of either FLT3L or t-tau to NFL did not improve discrimination of PD from MSA above NFL alone.

**Conclusions:** Our findings show that increased levels of NFL in CSF offer clinically relevant, high accuracy discrimination between PD and MSA.

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**LBA 7**
Low Muscle Strength in Late Adolescence is Associated with an Increased Risk of Parkinson’s Disease Later in Life: A Nationwide Cohort Study

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**Objective:** To evaluate maximal muscle strength in late adolescence in relation to the risk of Parkinson’s disease (PD) later in life. In addition, associations between subjects’ muscle strength in adolescence and PD diagnoses in their parents were examined.

**Background:** A substantial loss of dopaminergic neurons precede the clinical onset of PD, and the duration of this prodromal phase is uncertain; estimates range from years to decades. Few studies have been longitudinal and based on objective measurements, and attention has mainly been drawn to non-motor symptoms.

**Methods:** We conducted a prospective study based on a nationwide cohort of 1.3 million Swedish men, followed for a mean time of about 30 years after military conscription at 18 years of age. Baseline data included measurements of maximal voluntary muscle strength and physical fitness from highly standardized tests. PD diagnoses in the cohort, and in the 2.6 million parents of the subjects, were acquired from national registries with high validity. Muscle strength in relation to the risk of PD was investigated using multivariate statistical models, unadjusted and adjusted for appropriate confounders.

**Results:** After adjustment for height, weight, age, year of conscription, and PD diagnoses in the parents, subjects diagnosed with PD during follow up had significantly less handgrip [mean difference (MD), −9.9 Newton (N); 95% confidence interval (CI), −15.4 to −4.4] and elbow flexion (MD, −5.6N, 95% CI −10.4 to −0.9) strength, but not knee extension strength (MD, −3.9N, 95% CI −10.4 to 3.6) at 18 years of age, compared to subjects without PD. Men whose parents were diagnosed with PD had less handgrip [mothers: MD, −3.9N, (95% CI −5.8; −2.0; fathers: MD, −4.6N (95% CI −6.1 to −3.1)] and elbow flexion [mothers: MD, −2.7N (95% CI −4.3 to −1.1); fathers: MD, −
3.3N (95% CI –4.7 to –2.0) strength, but not knee extension strength [mothers: MD, 0.9N (95% CI –1.3 to 3.2); fathers: MD, 0.8N (95% CI –1.0 to 2.6)], than those with no such familial history. Adjustment for physical fitness did not substantially change any of the results, and physical fitness itself was not related to the risk of PD.

Conclusion: Maximal upper-extremity voluntary muscle strength was reduced in late adolescence in men diagnosed with PD 30 years later. Deficits were small but highly significant, consistent and may have a genetic component. The findings suggest the presence of subclinical motor deficits three decades before the clinical onset of PD.

LBA 8
Autologous Mesenchymal Stem Cells in patients with Progressive Supranuclear Palsy: results from an open phase first-in-man approach

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Background: Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by early impairment of balance and frequent falls. Bradykinesia, retrocollis, supranuclear gaze palsy, and abnormal vestibulospinal reflexes may be also present. These symptoms are a major cause for impaired quality of life and survival of patients with PSP. No therapy is currently available.

Objective: A pilot study to assess the safety and efficacy of autologous MSC therapy in patients with PSP. Trial NCT01824121 (Italian Ministry of Health).

Patients and Methods: Patients with clinical diagnosis of PSP participated to the study. MSC were isolated from bone marrow under standard procedures in Good Manufacturing Practices (GMP) conditions and administered by micro-catheter in carotid and vertebral arteries. The cell dose was 1.5 ± 0.5x10^6/kg. The UPDRS-III, H&Y, PSP Rating Scales were calculated before the treatment and at follow-up (f.u.) (1, 3, 6, 12 months). Neuropsychological assessment, gait analysis and brain imaging studies (i.e. MRI, FP-CIT SPECT, FDG PET) were also performed before and 1-year f.u..

Results: Nine patients were screened. Four enrolled patients were not able to received the treatment: one died; one patient rapidly worsened and did not further meet the inclusion criteria; MSC growth was inadequate for two other patients. The remaining five patients reached a 3-month f.u. and two of them a 6-month evaluation after treatment. There were no clinical side effects related to MSC therapy in all the patients. We reported one procedure-related adverse event (i.e. ischemic lesion in the territory of posterior cerebral circulation). Clinical evaluation was stable at all f.u.. Anticipatory postural adjustments at gait initiation improved in one subject at 6-month f.u.. Presynaptic dopaminergic uptake at FP-CIT SPECT was reduced meanwhile FDG uptake in the subcortical area was unchanged and increased in prefrontal area at 1 year in one subject.
**Conclusion:** Although preliminary, our results confirm the data previously reported by others on the safety of MSC administration and may suggest some positive effect of MSC treatment in decelerating disease progression. In one patient, we also described an improvement of movement control and planning. Brain Imaging findings obtained in one subject are not univocal interpretation. We hope that these results will be confirmed by the next prospective, randomized, cross-over, sham-controlled and double-blind study.

**LBA 9**
**Severe and reversible Presynaptic Ligand SPECT captation reduction in Akinetic Crisis of Parkinsonism and neuroleptic malignant syndrome**

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**Background:** Akinetic Crisis (AC) is akin to Neuroleptic Malignant Syndrome (NMS) and is the most severe and possibly lethal complication of parkinsonism. Diagnosis is today based only on clinical assessments and often is marred by concomitant precipitating factors. Instrumental evidence of diagnosis has never been presented.

**Methods:** Six patients presented with AC with severe akinesia, five were previously affected by Parkinson’s Disease or Lewy body dementia and the crisis was categorized as AC one developed NMS because of exposure to risperidone. In all presynaptic ligand FP/CIT Single Photon Emission Computerized Tomography (SPECT) was performed in the acute phase. Five patients survived the crisis and SPECT was repeated 3-6 months after the acute event. Quantitative and semi quantitative evaluations were used to assess binding potentials (BP).

**Results:** During AC or NMS, BP values in caudate and putamen was reduced to 1/8-1/15 (noise level) of the 97% inferior confidence limit, established in age matched control population. Follow-up re-evaluation in surviving patients showed a recovery of values by 400-600%.

**Conclusion:** By showing the outstanding binding reduction, presynaptic dopamine transport ligand can provide instrumental evidence of AC in Parkinsonism and of NMS.

**LBA 10**
**The adenosine A2A receptor antagonist, istradefylline enhances anti-parkinsonian effects of dopamine agonists in MPTP-treated common marmosets**

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**Objective:** To investigate whether istradefylline in combination with the threshold dose of the non-ergot dopamine agonist ropinirole or the ergot dopamine agonist pergolide enhances anti-parkinsonian effects in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-treated common marmosets.

**Background:** The adenosine A2A receptor antagonist, istradefylline decreases OFF time in patients with Parkinson’s disease who are already treated with optimal dopaminergic medication. However, the effects of istradefylline in combination with a dopamine agonist have not been studied in detail.
**Methods**: Experiments were performed using eight MPTP-treated common marmosets. On the first day of each experiment, basal locomotor activity was measured and basal motor disability was scored in the marmosets after oral administration of vehicle. On the second day, motor disability and ON time were scored, and locomotor activity was measured in the animals after oral administration of istradefylline (10 mg/kg), a dopamine agonist (threshold dose of ropinirole or pergolide), or a combination of istradefylline and each agonist.

**Results**: Orally administered istradefylline, ropinirole or pergolide to the marmosets showed anti-parkinsonian effects including increases in locomotor activity and ON time, and improvement of motor disability. The combined treatment with istradefylline and a dopamine agonist enhanced the effects of each dopamine agonist alone.

**Conclusion**: These results suggest that additional dosing with istradefylline enhances the anti-parkinsonian effects of a suboptimal dose of dopamine agonists, leading to a reduction in the dosage of a dopamine agonist in the treatment of Parkinson’s disease (PD). Furthermore, istradefylline may be useful for PD patients where a low dose DA agonist treatment is being utilised but where a further improvement in motor function is required. The adenosine A2A receptor antagonist istradefylline will provide a new therapeutic approach to PD as a non-dopaminergic medication.

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**LBA 11**

**Effectiveness and safety of acupuncture and bee venom acupuncture in idiopathic Parkinson’s disease**

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**Objective**: The primary aim of this randomized, controlled, assessor-blind pilot study was to evaluate the effectiveness and safety of bee venom acupuncture (BVA) as an adjunctive treatment in adults with idiopathic Parkinson’s disease (IPD), with a secondary aim of comparing the effectiveness of acupuncture with BVA.

**Background**: In light of the limitations of conventional treatment for Parkinson’s disease (PD), interest is increasing in complementary and alternative therapies. Acupuncture is one of the most popular alternative therapies used by patients with PD. Acupuncture has been used to relieve PD-like symptoms in Asian countries for centuries. In some experimental studies, acupuncture has been demonstrated to possess neurotrophic and neuroprotective effects. Clinically, however, the therapeutic effect of acupuncture in PD remains under debate. BVA is injection of dilute bee venom into acupuncture points. Recently, the anti-neuroinflammatory effect of bee venom has been investigated, and the possibility of its use in the treatment of neurodegenerative disorders has been suggested. To the best of our knowledge, however, there have been no clinical studies on the effectiveness of BVA in PD.

**Methods**: We recruited 43 adults with IPD who had been on a stable dose of antiparkinsonian medication for at least 1 month. They were randomly assigned to 1 of 3 groups: acupuncture, BVA, or control. All participants were assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS), the Parkinson’s Disease Quality of Life Questionnaire (PDQOL), the Beck Depression Inventory (BDI), the Berg Balance Scale (BBS), and the time and number of steps required to walk 30 m. Treatment groups underwent stimulation of 10 acupuncture points (bilateral GB 20, LI 11, GB 34, ST36, and LR 3) using acupuncture or BVA twice a week for 8 weeks. The initial assessment was repeated at the completion of treatment. The control group did not receive any treatment during this period, but subsequently received acupuncture or BVA according to the study protocol twice a week for 8 weeks, followed by an additional full assessment.

**Results**: Participants in the BVA group showed significant improvement on the UPDRS (total score, as well as parts II and III individually), the BBS, and the 30 m walking time. When compared to the control group, the BVA group experienced significantly greater improvement on the UPDRS. In the
In this pilot study, both acupuncture and bee venom acupuncture showed promising results as adjuvant therapies for PD.

LBA 12
Comparative analysis of human iPS cell-derived dopaminergic neurons from monozygotic twins discordant for Parkinson’s disease

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Objective: To use induced pluripotent stem (iPS) cell-derived midbrain dopaminergic (mDA) neurons to examine genetic and epigenetic factors related to the development of Parkinson’s disease (PD) in monozygotic twins who are discordant for PD.

Background: PD is a neurodegenerative disorder that disproportionately affects mDA neurons, and has been attributed to a combination of genetic and epigenetic factors. Recently, we recruited a set of monozygotic twins of Ashkenazi Jewish background who remain discordant for PD after five years of disease in the affected twin.

Methods: Whole exome sequencing was used to perform a comprehensive examination of both twins’ genetic makeup. A Sendai reprogramming kit was then used to generate iPS cells from fibroblasts derived from skin biopsies of the affected twin (PD-twin), unaffected twin (control twin), subjects with sporadic PD, and healthy controls. The iPS cells were subsequently differentiated into neural stem cells (NSCs) and then into mDA neurons in the defined media. Fluorescence-activated cell sorting (FACS) was used to improve the purity of NSCs and mDA neurons, which then underwent biochemical, immunofluorescence, high-performance liquid chromatography (HPLC), and RNA-Seq analysis. Lentivirus 7.2 wild-type glucocerebrosidase (GBA) was used to compensate for the loss-of-function of GBA, and 10 µM of rasagiline was used to inhibit the activity of monoamine oxidase B (MAO-B).

Results: Whole exome sequencing showed that both twins carry the heterogeneous mutation of GBA N370S, suggesting increased genetic susceptibility to PD. No other known PD-related gene variants were identified. In GBA N370S iPS cell-derived mDA neurons from each of the twins, GBA activity was only ~50% of that of controls. In addition, α-Syn protein level – but not mRNA level – was increased by up to 3 fold in iPS cell-derived mDA neurons from both twins, consistent with impaired α-Syn degradation rather than post-transcriptional regulation in neurons with GBA enzyme deficiency.

HPLC analysis demonstrated that mDA neurons from the PD-twin had significantly reduced capacity to synthesize and release dopamine compared to those from the control twin and healthy control. RNA-seq showed that MAO-B expression in neurons derived from the PD-twin was also higher than in those of the control twin. Delivery of lentivirus 7.2 wild-type GBA efficiently reduced α-Syn content in GBA N370S mutated neurons. Both WT GBA viral infection and rasagiline exposure to mDA neurons from the PD twin partially enhanced dopamine yield.

Conclusion: Human iPS cell-derived mDA neurons represent an effective model for examining the contributions of genetic and epigenetic factors in the development of PD.
LBA 13
Cognitive and cortical thinning patterns of subjective cognitive decline in patients with and without Parkinson’s disease

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Background: Subjective cognitive decline (SCD) has gained attention as a predictor of future cognitive decline in neurodegenerative diseases. Based on the hypothesis that different pathologies may distinctly contribute to SCD, we investigated the cognitive profiles and cortical thickness of patients with SCD, with and without Parkinson’s disease (PD).

Methods: In total, 96 patients experiencing SCD were classified as having PD (SCD-PD+, n = 49) or no neurological disease (SCD-PD-, n = 47); cognitively normal subjects without SCD (n = 23) were included as controls. Neuropsychological profiles and cortical thickness were examined using standardized neuropsychological tests and magnetic resonance imaging-based analysis.

Results: No significant differences in demographic characteristics were found among the three groups. Neuropsychological tests demonstrated that the SCD-PD+ patients had lower semantic fluency than SCD-PD- patients and controls, and showed poorer performance in visual memory and confrontational naming than controls, whereas no significant difference in cognitive performance was observed between the SCD-PD+ patients and controls. Cortical thickness analysis revealed that the SCD-PD+ patients had focal cortical thinning in the dorsolateral prefrontal, orbitofrontal, parietal, and parahippocampal areas compared with controls. Compared with SCD-PD- patients, SCD-PD+ patients had cortical thinning in the frontal, parahippocampal, and posterior cortical areas.

Conclusion: Our data show that cortical thinning and cognitive performance in patients with SCD may differ based on the presence of PD, suggesting that SCD in patients with PD reflects disease-related cortical thinning and cognitive dysfunctions more closely than SCD without PD.

LBA 14
Dose Escalation of Oral Octanoic Acid for Treatment of Essential Tremor - A Safety Study

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Objective: To determine the maximum tolerated dose (MTD) of oral OA in patients with Essential Tremor (ET). As secondary outcome, a possible dose-response relationship of safety, pharmacokinetics, and efficacy was investigated.

Background: ET is a common movement disorder. Less than 50% note tremor improvement with pharmacotherapy and there is a high rate of side effects resulting in a strong need for novel treatments. Many patients report significant tremor reduction after consumption of alcohol. Long chain alcohols, such as 1-octanol, have been explored as treatment to achieve the effect of alcohol without intoxication. Octanoic acid (OA) a primary metabolite of 1-octanol might be the active substance mediating tremor-suppression. In a recent study, OA demonstrated safety with a suggestion of efficacy at 4 mg/kg.
Methods: 1) Safety: MTD was studied using a 3+3 dose escalation design, n = 3 at each dose. OA was given to alcohol-responsive patients at steps of 8, 16, 32, 64, and 128 mg/kg. Toxicity was monitored using the Common Terminology Criteria for Adverse Events v4.0. The dose below level at which ≥2 OA-related grade 2 (CTCAE, moderate severity) adverse events (AEs) were observed was defined as MTD. Regular blood laboratory finding, vitals signs and EKG parameters were also examined.

2) Pharmacokinetics: Plasma samples were drawn at 5, 20, 40, 60, 100, 150, 210, 300, and 600 minutes after intake.

3) Efficacy: Tremor of both hands was quantified using accelerometry and digital analysis of spirals drawn at baseline and 20, 40, 60, 100, 150, 210, 300 and 600 minutes. TETRAS, a standard clinical rating scale, was also evaluated.

Results: 1) Safety: Toxicity was not reached even at the highest dose of 128 mg/kg. No serious or study-limiting AEs were observed. There were 10 self-limiting grade 1 AEs. The most frequent AE was mild abdominal pain (n=4). 5 AEs were constitutional and 1 dermatologic. All gastrointestinal AEs and 1 constitutional were considered “definitely related” to OA intake, all others “possibly related.” No tendency was seen in other safety parameters.

2) Pharmacokinetic sampling suggested a dose effect on plasma levels and elimination.

3) Investigations of efficacy were only exploratory due to small cohort size. In this open label design a tendency towards a reduction in tremor was seen for TETRAS, digital spiral analysis, and accelerometry.

Conclusion:
OA as a treatment for ET was safe and well tolerated up to a dose of 128 mg/kg. Therefore, the primary goal of the study to determine MTD was not met. The mainly gastrointestinal AEs are in line with reports on OA in the indication of ketogenic diet. Pharmacokinetics suggested a dose effect on plasma levels. Future studies are needed to further explore the safety in higher dose ranges as well as to confirm any dose depended efficacy in a placebo-controlled design.

LBA 15
Deep Brain Stimulation at short pulse width results in superior therapeutic windows for treatment of Parkinson’s Disease: a randomized, controlled, double-blind neurostimulation trial (CUSTOM-DBS)

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Objective: The primary objective of this study was to demonstrate in patients with Parkinson’s disease (PD) that deep brain stimulation (DBS) at short pulse width (30 µs) results in larger therapeutic windows without compromising efficacy, when compared to DBS at conventional pulse width (60 µs). Therapeutic window was defined as the difference in amplitude of first stimulation-induced side effects (side effect threshold) and amplitude of the lowest setting allowing full rigidity control (efficacy threshold). Efficacy was assessed using UPDRS III score with a non-inferiority margin of 5 points between the short and conventional pulse widths.

Background: Previous researchers have proposed that DBS at short pulse width may decrease the risk of stimulation-related side effects by expanding the therapeutic window (Rizzone et al. 2001; Moro et al. 2002; Volkmann et al. 2002; 2013). However, expectation can lead to placebo effects in PD, and there remains a need to test DBS programming recommendations in a double-blind condition (Mercado et al, 2006; Okun et al 2012; Keitel et al 2013). In this study we performed double-blind assessments of acute stimulation challenges with different parameter combinations, in order to determine which settings best reduce the risk of side effects without sacrificing any significant therapeutic benefit.
**Methods:** Fifteen (15) PD patients implanted with Boston Scientific’s Vercise DBS system for more than 3 months were programmed using test pulse widths of 30 s and control pulse widths at 60 s delivered via single best therapeutic contact. Thresholds for efficacy and side effects as well as UPDRS III were measured in the meds off condition at test and control settings. For all assessments, subject and evaluating neurologist were blinded to the pulse width setting, and statistical analyses were pre-defined. The primary outcome was the width of the therapeutic window (in mA) for the two stimulation conditions.

**Results:** Stimulation at 30 s pulse width resulted in a significantly larger therapeutic window when compared to stimulation at conventional pulse width of 60 s (p = .0009; paired t-test). Efficacy, as measured by UPDRS III score, of short pulse width programming was found to be non-inferior (margin = 5 points, the established minimal clinically important change for UPDRS-III (Schrag et al, 2006)) when compared to conventional programming (p=.0008; paired t-test). Mean efficacy threshold was at a higher current amplitude for short pulse width settings, but the mean total charge delivered per pulse was lower, suggesting that short pulse width settings may require less electrical energy to reach the efficacy threshold (Mean amplitude = 3.05 mA at 30 s, 2.31 mA at 60 s; mean charge per pulse = 91.5 nC/pulse at 30 s, 138.6 nC/pulse at 60 s).

**Conclusions:** This study is the first double-blind assessment comparing stimulation at a pulse width shorter than 60 s to conventional DBS settings at 60 s pulse width. The larger therapeutic window at 30 s suggests that shorter pulse widths may be advantageous for avoiding stimulation-related side effects. This larger therapeutic window was achieved while maintaining efficacy as measured by a non-inferiority comparison of UPDRS III. Importantly, the short pulse width setting required less electrical energy delivered to achieve an efficacy threshold, suggesting there may also be energy efficiency advantages to those settings.

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**LBA 16**
**A Chinese Familial Cortical Myoclonic Tremor with Epilepsy Pedigree Localized on Chromosome 8q22.3-q24.13**

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*Zhidong Cen and Fei Xie contributed equally to this work and should be considered co-first authors*  
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This study was supported by the National Natural Science Foundation of China (Proj. No. 81371266).

**Objective:** To identify the caused gene region of a Chinese familial cortical myoclonic tremor with epilepsy (FCMTE) pedigree.

**Background:** FCMTE is one kind of autosomal dominant epilepsy syndrome with considerable clinical and genetic heterogeneity. Its major clinical manifestations include adult onset, cortical myoclonic tremor, with or without epileptic seizures. Four loci, 8q24 (FCMTE1), 2p11.1-q12.2 (FCMTE2), 5p15.31-p15.1 (FCMTE3) and 3q26.32-3q28 were previously reported with only one gene - α2B adrenergic receptor - be identified in two FCMTE2 pedigrees.

**Methods:** Whole genome scan was performed in a Chinese FCMTE pedigree including five generations and 13 patients alive. Linkage analysis and haplotype analysis were done to identify the caused gene region.

**Results:** Linkage analysis showed 322 peaks covering 26.6 Mb of genomic DNA on chromosome 8 with a two-point LOD score > 3.0 (the range of scores was 3.170–3.766 with a top LOD score of 3.766 at 206 SNPs). Haplotype analysis revealed that all patients share a common haplotype from rs2253336 to rs10093411, about 21.4 Mb on 8q22.3-q24.13.

**Conclusion:** We report the first Chinese FCMTE1 pedigree localized on 8q22.3-q24.13, which shares the same region with Japan’s pedigrees. Whole-exome sequencing and Targeted-genome sequencing need to do to identify the caused gene for FCMTE1.
LBA 17
First 1-year real-life study to assess management of augmentation of restless legs syndrome by switching to rotigotine patch

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Objective: To assess effect of switching to rotigotine (RTG) patch on severity of restless legs syndrome (RLS) in patients who experienced augmentation with prior oral dopaminergics.

Background: Augmentation (worsening of RLS symptoms) can be major complication of long term dopaminergic therapy. Clinical studies indicated low augmentation rates with RTG (only long-acting dopaminergic approved for RLS); transdermal delivery maintains stable plasma levels over 24h.

Methods: Eligibility criteria for this 13-month non-interventional study (AURORA; NCT01386944) in German neurology centers included moderate-to-severe RLS and augmentation with oral dopaminergics (judged by physician). Decision to switch to RTG was made independently by physician according to routine practice. Primary outcome: Clinical Global Impression severity score (CGI-1; 7-point scale). Secondary outcome: treatment regimen for switch assessed to day 28. Other: RLS-6, International RLS Rating Scale (IRLS), Augmentation Severity Rating Scale (ASRS), adverse events (AEs). To evaluate RLS severity and augmentation over time in patients who tolerated RTG, study completers were assessed for effectiveness.

Results: 102 patients were enrolled, 99 (mean age±SD:64.2±11.1 years; female:68) received rotigotine. 46 patients completed ~13 month study; 3 were excluded from effectiveness analyses due to concomitant Parkinson’s disease. Most common reasons for premature withdrawal were AEs (26[mainly application site reactions]) and lack of effectiveness (14); 8 patients lost to follow-up. Among 43 study completers (~13 months), prior dopaminergics were: benserazide/l-dopa (19); pramipexole (19); ropinirole (7); carbidopa/l-dopa (2); l-dopa (1). At final visit, median change in CGI-1 (Hodges Lehman estimate [95%CI]) was -2.0(-2.5,-1.5)(baseline mean±SD:5.3±0.7). 16/43 patients were CGI-1 responders (≥50% improvement). 5 patients switched to RTG after >1-day drug holiday, 23 switched overnight, 9 had overlapping switch, and 6 received ongoing oral dopaminergics with RTG on day 28. IRLS and RLS-6 decreased with RTG (Table 1). At final visit, patients had median ASRS of 0=no worsening/occurrence of augmentation (mean±SD:1.2±2.7). AEs shown in Table 2.

Conclusion: In first long term study of augmentation management, switching to 24h therapy with RTG patch (continuous dopaminergic stimulation) was effective in improving RLS severity among severely affected patients who tolerated RTG and remained on this therapy for 13 months.

Study Support: UCB Pharma, Monheim am Rhein, Germany

<table>
<thead>
<tr>
<th>Table 1: CGI-1, RLS-6 and IRLS scores</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>CGI-1</td>
</tr>
<tr>
<td>RLS-6 items</td>
</tr>
<tr>
<td>Item 1: Satisfaction with sleep</td>
</tr>
<tr>
<td>Item 2: Severity when falling asleep</td>
</tr>
<tr>
<td>Item 3: Severity during night</td>
</tr>
<tr>
<td>Item 4: Severity during day when at rest</td>
</tr>
</tbody>
</table>
Item 5: Severity during day when active
2.3±2.5 0.9±1.6 -1.4±2.2

Item 6: Daytime sleepiness/tiredness
5.9±2.6 3.2±2.8 -2.7±2.9

IRLS
29.2±5.4 16.6±9.7 -12.7±7.5

*No washout of prior dopaminergic medications was performed.

Table 2: Adverse events

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Patients (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events reported by ≥5 patients</td>
<td></td>
</tr>
<tr>
<td>Application site reaction*</td>
<td>33</td>
</tr>
<tr>
<td>Nausea</td>
<td>13</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9</td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>9</td>
</tr>
</tbody>
</table>

*MedDRA high-level term “application and instillation site reactions”; data are number of patients reporting at least 1 AE.

LBA 18
DPI-289, a novel bi-functional delta agonist / mu antagonist (DAMA) therapy for Parkinson’s disease

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Objectives: To assess whether DPI-289, a novel benzhydrylpiperazine with dual delta opioid receptor agonist and mu opioid receptor antagonist (DAMA) properties could provide anti-parkinsonian effect without eliciting motor complications (abnormal involuntary movements; AIMs), compared to L-DOPA, in the 6-hydroxydopamine (6-OHDA)-lesioned rat model of Parkinson’s disease (PD).

Background: Delta agonists are validated as an approach to alleviate parkinsonian symptoms in pre-clinical animal models of PD. Unfortunately, delta agonist benefits are likely limited by a propensity to elicit / exacerbate L-DOPA-induced dyskinesia (LID). However, mu antagonists are validated as an approach to reduce LID. By combining both anti-parkinsonian and anti-dyskinetic mechanisms within the same molecule, DPI-289 provides a novel opportunity to develop a single treatment that might be employed to control parkinsonian symptoms and dyskinetic side effects across the natural history of the disease.

Methods: The study assessed the propensity of acute and repeated DPI-289 treatment as monotherapy to provide anti-parkinsonian benefits and to lead to the development of AIMs. These actions were compared to those of L-DOPA. Three groups of animals (Groups A-C; each N=8), all bearing unilateral 6-OHDA-lesions of the nigrostriatal tract (12.5 mcg, mfb), received once-daily treatment for 15 days. Animals received either vehicle (Group A), L-DOPA (Group B, 6 mg/kg i.p.) or DPI-289 (Group C, 3 mg/kg, p.o.). Animals had received no prior dopaminergic treatments. AIMs and reversal of forelimb asymmetry (a measure of anti-parkinsonian response) were assessed on Days 1, 4, 8, 11 and 15. At the end of the Study, animals were killed and brains removed for confirmation of the extent of the 6-OHDA-lesion via assessment of striatal dopamine transporter (DAT) binding levels.

Results: In treatment-naïve, 6-OHDA lesioned animals, DPI-289 (3 mg/kg, p.o.) produced a robust anti-parkinsonian response as evidenced by a significant reduction in forelimb asymmetry. This effect was present after acute administration, on Day 1, and was maintained throughout the fifteen-day repeat-treatment period (all P<0.05 cf. vehicle). The extent of anti-parkinsonian effect of L-DOPA (6 mg/kg, i.p.) on Day 1 was equivalent to that of DPI-289. However, following repeat-treatment across the remainder of the study period, the quality of anti-parkinsonian response to L-
DOPA, unlike that of DPI-289, was compromised by the emergence of AIMs. DPI-289 evoked no AIMs either acutely or across fifteen days of once daily repeated treatments. In contrast, once-daily L-DOPA evoked significant levels of AIMs by the fourth day of treatment (median score = 5.5) increasing to mild-moderate levels by day fifteen (median score = 7.5, all P<0.001 cf. vehicle).

**Conclusion:** The current study provides support for an ability of DPI-289 to deliver effective anti-parkinsonian action as monotherapy with a much lower propensity to evoke dyskinesia, compared to L-DOPA. Bi-functional delta agonist / mu antagonist (DAMA) strategies offer a novel approach for the symptomatic treatment of PD.

**Support:** Michael J. Fox Foundation

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**LBA 19**

**AbobotulinumtoxinA (Dysport®), improves disease-specific quality of life in patients with cervical dystonia, as measured by Patient-Reported Outcomes, in a Phase III, randomized, double-blind, placebo-controlled study**

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**Objective:** To assess the impact of Dysport on disease-specific quality of life in patients with cervical dystonia using Cervical Dystonia Impact Profile (CDIP)-58, Subject’s VAS for Pain and symptoms and Toronto Western Spasmodic Torticollis Rating Scales (TWSTRS).

**Background:** This is the first report of the effects of BoNT-A on disease-specific quality of life in patients, measured by CDIP-58 in a double blind study.

**Methods:** This was a Phase III, prospective, randomized, placebo-controlled, double-blind, international study conducted at 61 sites in 11 countries. Patients diagnosed with cervical dystonia were randomized to abobotulinumtoxinA 500 U dry form (n=159) and placebo (n=54). These arms were compared (both arms were embedded within a three-arm trial investigating a liquid formulation of abobotulinumtoxinA). Patients received a single treatment cycle of abobotulinumtoxinA (500 U) or placebo. Disease-specific quality of life was assessed by CDIP-58 (including eight subscales: head and neck symptoms, pain and discomfort, sleep, upper limb activities, walking, annoyance, mood and psychosocial functioning), Subject’s VAS (0–100) for Pain and symptoms and TWSTRS.

**Results:** Baseline patient characteristics were similar between abobotulinumtoxinA and placebo in terms of age (49 and 50 years, respectively), gender (female, 64% and 63%, respectively), time since diagnosis of cervical dystonia (7 vs. 6 years) and treatment history (botulinum toxin naïve 25% vs. 26%). Disease characteristics at baseline were also similar between arms; CDIP-58 score was 60.9 for both arms and TWSTRS score was 46 for the abobotulinumtoxinA arm and 47 for the placebo arm. Total CDIP-58 score was significantly improved with abobotulinumtoxinA compared to placebo at Week 4 (mean change from baseline to Week 4: -11.2 vs -0.9; p<0.0001) as were all eight CDIP-58 subscales (p<0.0003). Subject’s VAS for pain and symptoms was significantly improved with abobotulinumtoxinA vs. placebo at Week 4 (Least Squares [LS] mean VAS for pain: -19.2 vs -3.4; LS mean VAS for symptoms: -23.6 vs -3.3; p<0.0001 for both parameters), as were LS mean change from baseline to Week 4 in TWSTRS total score (-14.0 vs -3.9; p<0.0001).
Conclusions: This study is the largest placebo-controlled, double blind abobotulinumtoxinA study conducted in patients with cervical dystonia. One single injection of abobotulinumtoxinA 500 U was shown to significantly improve disease-specific quality of life as measured by CDIP-58 and Subject’s VAS for pain and symptoms, as well as TWSTRS score.

LBA 20
Targeting muscarinic receptor subtypes as a therapeutic approach in dystonia

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Objective: To establish the optimal muscarinic receptor subtype selective antagonist for the treatment of dystonia using experimental animal models.

Background: Anticholinergics are the first line of oral treatment particularly in juvenile dystonia. However, they elicit peripheral and central side effects which reduce compliance. M4 muscarinic receptors are specifically located in the striatum and they may form a target for the treatment of dystonia without the associated side effects. For this reason we investigated the central and peripheral activity of antagonists with differing selectivities for muscarinic receptor subtypes, using pilocarpine-induced perioral movement and salivation as indices of central and peripheral muscarinic activity.

Methods: Rats were treated with pilocarpine (0.1 – 32 mg/kg ip) and the number of purposeless chewing movements was recorded. Additionally, the M3 mediated saliva secretion test was performed by administration of pilocarpine (0.1 – 8 mg/kg ip) and oral introduction of a weighted cotton bud. Subsequently, the effect of the non-selective antimuscarinics: trihexyphenidyl (THP; 0.3 – 5 mg/kg ip) and benztropine (BNZ; 0.3 – 5 mg/kg ip), and relatively selective antimuscarinics: pirenzepine (PIR; 50 – 200 µg ICV; M1), darifenacin (DAR; 0.75 – 24 mg/kg ip; M3) and tropicamide (TRP; 1.25 – 20 mg/kg ip; M4) was investigated on pilocarpine (3.4 mg/kg ip)-induced chewing and saliva production.

Data were analysed by non-linear regression (ED$_{50}$ and ID$_{50}$) or Friedman test followed by Dunn’s test.

Results: Systemic administration of pilocarpine, dose-dependently induced purposeless chewing movements was recorded. Additionally, the M3 mediated saliva secretion test was performed by administration of pilocarpine (0.1 – 8 mg/kg ip) and oral introduction of a weighted cotton bud. Subsequently, the effect of the non-selective antimuscarinics: trihexyphenidyl (THP; 0.3 – 5 mg/kg ip) and benztropine (BNZ; 0.3 – 5 mg/kg ip), and relatively selective antimuscarinics: pirenzepine (PIR; 50 – 200 µg ICV; M1), darifenacin (DAR; 0.75 – 24 mg/kg ip; M3) and tropicamide (TRP; 1.25 – 20 mg/kg ip; M4) was investigated on pilocarpine (3.4 mg/kg ip)-induced chewing and saliva production.

Data were analysed by non-linear regression (ED$_{50}$ and ID$_{50}$) or Friedman test followed by Dunn’s test.

Results: Systemic administration of pilocarpine, dose-dependently induced purposeless chewing behaviour (EC$_{50}$ = 3.4 mg/kg). The chewing was significantly inhibited by peripheral and central administration of antimuscarinics (IC$_{50}$ in mg/kg: THP, 2.9; BNZ, 1; DAR, 9.5; TRP, 9.3; PIR, 0.09 µg). Finally, pilocarpine stimulated sialorrhea was also reduced by all antimuscarinics, except pirenzepine (IC$_{50}$ in mg/kg: THP > 5; BNZ > 5; DAR, 0.2; TRP, 3.27).

Conclusions: Pilocarpine induced purposeless chewing and enhanced saliva secretion as previously reported. The ICV administration of pirenzepine inhibited chewing behaviour but had no effect on suppression of salivation, suggesting involvement of centrally located muscarinic receptor in the expression of chewing behaviour. All peripherally administered anticholinergics inhibited pilocarpine-induced chewing, while darifenacine and tropicamide were more effective in inhibition of salivation than trihexyphenidyl and benztropine. The order of potency, based on the systemic administration for inhibition of chewing was BNZ > THP > TRP > DAR. Since none of the compounds were highly selective for the M4 receptor, further studies with more selective compounds are needed to elucidate the role of M4 muscarinic receptor in the production of involuntary movements.
LBA 21
ULTRA-MICRONIZED PALMITOYLETHANOLAMIDE ULTRA-MICRONIZED IN PARKINSON’S DISEASE

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Objective: The aim of this study was to evaluate the efficacy of ultra-micronized palmitoylethanolamide (PEA) in patients with advanced Parkinson’s disease (PD).

Background: Idiopathic Parkinson’s Disease is the most prevalent neurodegenerative movement disorder, and is characterized by the progressive degeneration of dopaminergic neurons. However, increasing evidence also shows a conspicuous glial reaction together with neuroinflammatory processes in Parkinson’s disease.

Recent data suggest neuroprotective activities of PEA in animal models of Parkinson's disease. In particular, chronic treatment with PEA protects against loss of tyrosine hydroxylase-positive neurons in the substantia nigra pars compacta induced by the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, as well as toxin-induced microglial activation.

Methods: Thirty outpatients with advanced Parkinson’s disease, assessed according to UK Parkinson’s Disease Society Brain Bank criteria were recruited at our Movement Disorder Center. Clinical evaluations were performed by MDS-UPDRS new version (July 1, 2008) and Hoehn & Yahr Scale.

The following scores were evaluated: Non-Motor aspects of Experiences of Daily Living (Part I and Part II), Motor Examination (Part III), Motor Complications (Part IV).

Each patient was evaluated over a period of 12 months. In particular, each patient had taken the same L-dopa therapy without any modification for at least 4 consecutive weeks. Moreover, all patients were also evaluated at the time T0 (basal time), T1 (one month after T0), T3 (three months after T0), T6 (six months after T0) and T12 (one year after T0). Patients received ultra-micronized PEA (600 mg sublingual sachets x 2/day) for at least 3 months, followed sublingual 1 sachet/day for up to 12 months.

All data were analyzed using a repeated measures analysis of variance (ANOVA).

Results: At the end of the follow up period analysis showed a statistically significant improvement ($P<0.0001$) of all the parameters considered, motor- and non-motor symptoms. In particular, there was a significant reduction of dyskinesias and prolonged therapeutic effect of L-dopa therapy.

Conclusion: Our data suggest that ultra-micronized PEA might play an important role in the pharmacological treatment of Parkinson's disease by modulating the interaction between the dopaminergic pathways and glia.

LBA 22 - Withdrawn

LBA 23
THE CAUDAL ZONA INCERTA DOES NOT PROVE SUITABLE AS A TARGET FOR DEEP BRAIN STIMULATION IN PARKINSON’S DISEASE

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¹ Charité University Medicine, Department of Neurology, Berlin, Germany
² Charité University Medicine, Department of Neurosurgery, Berlin, Germany
³ Parkinson-Fachklinik Beelitz, Beelitz, Germany
⁴ Universitätsklinik Otto-von Guericke-University, Department of Neurology & Stereotactic Neurosurgery, Magdeburg, Germany
Objective: To evaluate the effects of a new target (caudal zona incerta, cZI) for Deep Brain Stimulation (DBS) therapy in idiopathic Parkinson’s Disease (PD) vs. subthalamic nucleus (STN-proper) DBS as a standard.

Background: DBS is an established treatment option in PD patients with complications of long-term dopaminergic medication. At present, STN-DBS is favoured for this patient group to reduce motor symptoms of PD along with pronounced reductions of dopaminergic medication. However, different targets have been discussed in PD. DBS of the caudal zona incerta (cZI) has been proposed to show superior benefit for motor control in retrospective and uncontrolled studies.

Methods: This two-arm double-blind RCT for the first time aims to prospectively evaluate the effects of bilateral cZI-DBS in comparison to STN-DBS in otherwise comparable groups of PD patients (NCT 00888095). The study was designed to confirm the effects seen in retrospective trials with 80% power. Patients were randomized to receive DBS in either cZI or STN, stratified for age, sex and motor severity. Throughout the observation period of 12 months, adjustments of DBS settings and medication were performed as necessary to achieve maximal effects with tolerable side effects by clinical investigators blinded to the DBS target. Main outcome parameter is the between-group difference in DBS effect on UPDRS motor score after 1 year. A planned interim analysis was performed after the first 20 out of 70 planned subjects completed the study.

Results: With respect to the main outcome parameter UPDRS III motor score, the two targets differed with larger effects seen in the STN group: scores decreased StimON vs. StimOFF in medOFF condition at 12 months by 59% in STN vs. 36% in cZI group (p=0.0371, two-sided Wilcoxon test). Furthermore, at 12 months follow-up, the mean reduction of equivalent levodopa daily dose compared to pre-surgery baseline was 53% in STN and 13% in cZI group (p=0.0412). Overall SAE rates were comparable to previous large DBS trials and not subject to the present interim analysis. Quality of life data is presently analysed.

Conclusion: In this first prospective trial on cZI stimulation in PD, previous reports on its superiority over STN DBS could not be corroborated by the present interim analysis at one year in 20 patients. Rather, the effects on PD motor symptoms seem to be less pronounced - although with variability within group – and medication could not be reduced in most cZI cases. The present results clearly suggest that cZI-DBS is not superior in comparison to STN-proper-DBS although final analysis of all primary and secondary study outcome parameters is pending.

LBA 24
Neurologist Care Prevents of 4,500 Deaths Annually in Patients with Parkinson’s Disease in the US: A Meta-Analysis

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Objective: While several studies have analyzed the benefit to individuals of neurologist care to patients with Parkinson’s, the magnitude of the problem has not previously been determined.

Background: Previously, studies of patients with Parkinson’s disease covered by Medicare in the US have been shown to have a 22% lower risk of death if treated by a neurologist [1]. The total number of deaths of people with Parkinson’s can be calculated from the published death statistics for 2011 from the US Center for Disease Control [2] together with research on the frequency at which Parkinson’s is mentioned on death certificates among patients with the condition [3].

Methods: Using the method of empirical Bayes, the fraction of the population treated by a neurologist was combined with the relative risk of death for individuals with Parkinson’s treated by a neurologist versus those managed in primary care. Based on these results, the total number of deaths prevented by neurologist care and the number expected should every patient receive neurologist care were computed.

Results: Of the projected 48,139 annual deaths of patients with Parkinson’s disease in the US, approximately 34% (16,469) were managed by a neurologist, versus 40% of total patients who are
managed by a neurologist. Based on the model, improved survival for patients receiving neurologist care prevented 4,645 deaths in 2011 and the extension of neurologist care to patients not currently receiving it would have further reduced overall mortality by another 6,967 patients.

**Conclusions:** Approximately 6,967 patients with Parkinson’s disease die annually due to lack of access to a neurologist. Further study could provide insight into translatable factors that confer this survival benefit or models of care that could provide increased access at scale.


**LBA 25**

Spastic movement disorder treated by AbobotulinumtoxinA (Dysport®) in the hemiparetic upper limb: a randomized, double-blind, placebo-controlled, Phase III study


**Objective:** To assess modifications of movement with abobotulinumtoxinA (Dysport®) in the spastic upper limb

**Background:** Few studies have explored the effects of botulinum toxin A on movement in adults with post-stroke/traumatic brain injury spastic hemiparesis.

**Methods:** This was a Phase III, prospective, double-blind, placebo-controlled study on 243 patients (from 34 sites in 9 countries) randomized (1:1:1) to abobotulinumtoxinA 500 or 1000 units (U) or placebo. In addition to the assessment of passive movements (passive range of motion and spasticity using the Tardieu Scale), active movements were assessed using active range of motion and the ease of applying a splint.

**Results:** Four weeks after injection of abobotulinumtoxinA 500 U and 1000 U, patients who were injected in the finger flexors with abobotulinumtoxinA 500U/1000U gained 27.3°(5.9)/29.5°(5.9) in mean (SEM) Tardieu spasticity angle (p=0.005/p=0.002 versus placebo) and 23.9°(3.6)/17.6°(4.4) in mean (SEM) active finger extension (p<0.001/p<0.001). For the elbow flexors, the mean (SEM) gain was 17.5°(3.2)/24.7°(4.2) in spasticity angle (p=0.011/p<0.001) and 12.6°(4.4)/15.8°(5.1) in active elbow extension (NS/p=0.041). For wrist flexors, the mean (SEM) gain was 16.4°(4.5)/22.5°(3.9) in spasticity angle (p<0.001/p<0.001) and 15.7°(6.0)/26.4°(7.7) in active wrist extension (NS/p=0.024). This was associated with an improvement in the ease of applying a splint. The safety profile was as expected.

**Conclusion:** In addition to being the first large scale study reporting true spasticity reduction (Tardieu scale), this trial shows that abobotulinumtoxinA 500 and 1000 U injected in overactive upper limb muscles produced tangible benefit for active movements and meaningful clinical benefit in hemiparesis.
**Objective:** The objective was to introduce a new treatment concept in Parkinson’s disease (PD), using dispersible microtablets containing levodopa/carbidopa 5/1.25 mg (LC-5), and an automatic dose dispenser.

**Background:** Most patients with PD eventually reach a stage where the therapeutic window becomes narrow and on-off fluctuations start to occur. One proposition to prevent these complications is continuous drug delivery. Dose fractionation is difficult to achieve with current levodopa tablet strengths, but becomes possible with LC-5 and could improve the treatment in patients with PD that experience fluctuations with their current medication.

**Methods:** Seven patients have so far been started on the treatment with LC-5 microtablets, Flexilev® (Sensidose AB, Uppsala, Sweden), since January 2014 on special permissions (Table 1).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age* (y)</th>
<th>Sex</th>
<th>PD** duration (y)</th>
<th>Levodopa dosage</th>
<th>LC-5 dosage</th>
<th>Concomitant medication</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td>73</td>
<td>M</td>
<td>12</td>
<td>4000¹</td>
<td>6-7</td>
<td>3800</td>
</tr>
<tr>
<td>C</td>
<td>68</td>
<td>M</td>
<td>9</td>
<td>675²</td>
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<tr>
<td>D</td>
<td>63</td>
<td>M</td>
<td>23</td>
<td>2000¹</td>
<td>16</td>
<td>1815</td>
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<td>67</td>
<td>M</td>
<td>8</td>
<td>775³</td>
<td>8</td>
<td>1100</td>
</tr>
</tbody>
</table>

* Age at start of LC-5 treatment
** From diagnosis
*** 2400 mg from levodopa/benserazide
¹ Levodopa/benserazide
² Levodopa/carbidopa/entacapone

Abbreviations: F, female; M, male; Rop, Ropinirole; Pra, Pramipexole; Ras, Rasagiline; Ama, Amantadine; Rot, Rotigotine

The LC-5 microtablets are dispensed with an electronic device, MyFID® (My Flexible Individual Dosing) and allow more individualized doses and dose fractionation. The device has a memory and alarm function to facilitate the treatment and could help the patients come closer to mimicking a continuous drug administration due to more stable levodopa concentrations with dose fractionation. Data on the use of the dose dispenser is automatically stored so that for example drug adherence may be studied.

The patients visited their clinic to receive the dispenser and information on how use it. The new dosage was translated from the patient’s previous levodopa therapy. The first dose in the morning was set to be higher than the rest and the dosing interval was determined according to the patient’s requirements.

**Results:** Fine-tuning – either increased or decreased dosage – was applied in some of the patients, in steps of 5 mg for each dose. A few of the patients also utilized the opportunity of being able to increase fractionation. Patient A, who was the first patient to initiate the treatment with LC-5, experienced unexpected complications when the switch was made. The switch from levodopa/benserazide (LB) to LC-5 caused mostly “OFF” state despite of similar initial levodopa
dose and the same fractionation. Due to this the LC-5 dose had to be gradually increased to 750 mg daily (Table 1).

Conclusion: All patients were able to handle the device in a clinical routine setting. The patients were positive to the treatment despite of the potential technical difficulties with the device and the possible need for dose adjustments. The first results obtained suggest that levodopa/carbidopa (LC) and LB are not equivalent. A difference in pharmacokinetics has been observed in previous studies including a comparative study between LB, LC and LC-5 where the LB preparation resulted in a higher peak plasma concentration and shorter half-life. It has been suggested to occur due to the greater potency of benserazide. This is important to consider when switching between LB and LC.

Further observations and their implications on the fine-tuned treatment for the patients started on the LC-5 treatment concept will be presented and discussed.

LBA 27
White matter involvement may explain phenotypic pleiotropy amongst genes involved in episodic movement disorders

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Objective: To identify possible relationships between known episodic movement disorder (EMD) and episodic hemiplegia (EH) genes using genome-wide gene expression data generated from control human brain in order to obtain novel insights into the pathophysiology of these conditions.

Background: The discovery of genes involved in various episodic movement disorders (EMD) has revealed a significant and unexpected phenotypic pleiotropy amongst causative genes, with overlapping spectrums including episodic ataxia, episodic dystonia (paroxysmal dyskinesia and benign paroxysmal torticollis), epilepsy and episodic hemiplegia (EH).

Methods: We used genome-wide gene expression data generated from 788 adult human brain samples originating from 101 neurologically and neuropathologically normal individuals (10 distinct brain regions each) as part of the UK Human Brain Expression Consortium (UKBEC) to study the expression of the following genes: ATP1A2, SCN1A, SLC1A3, ATP1A3, KCNMA1, CACNB4, CACNA1A, KCNA1, GCH1, SLC2A1, PNKD and PRRT2. Weighted gene co-expression network analysis (WGCNA) was used to group all expressed genes into modules in an unsupervised manner (Langfelder and Horvath, 2008; Oldham et al., 2006; Zhang and Horvath, 2005). The overrepresentation of EMD/EH transcripts in modules was assessed using chi-squared tests with Yates correction. Gene ontology (GO) and KEGG pathway enrichment analysis was performed to infer the functions and molecular pathways of genes in biologically relevant modules.
Results: We identified a single white matter gene co-expression module, which was statistically enriched in EMD/EH transcripts (blue module, \( p = 0.0001 \)) with 8 of the 12 EMD/EH genes studied present. This module was significantly enriched for genes related to synaptic transmission (Bonferroni-corrected \( p = 4.02 \times 10^{-44} \)) and more specifically the glutamate signalling pathway (Bonferroni-corrected \( p = 4.89 \times 10^{-6} \)) amongst other terms. We also identified significant enrichment for genes related to a number of KEGG pathways with the longterm potentiation (Bonferroni-corrected \( p = 7.47 \times 10^{-8} \)) and axon guidance (Bonferroni-corrected \( p = 1.17 \times 10^{-7} \)) pathways being most significant.

Conclusion: Our data suggests that white matter might play a pathophysiological role in episodic diseases and be a unifying factor which would explain the overlap between phenotypes classically considered to be cortical (HM, epilepsy, AHC), subcortical (PKD, BPT) or cerebellar (episodic ataxia) in origin. In addition, it provides additional evidence to suggest that PRRT2 and PNKD, which are relatively unknown genes, play a role in synaptic transmission. Understanding the biological functions of these genes in the brain is of paramount importance to understand the clinical manifestations of mutations, identify new candidate genes and propose novel therapeutic interventions in EMD/EH.

LBA 28
Targeting impulsivity in Parkinson’s disease using atomoxetine

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9. Department of Psychology, University of Cambridge

Objective: To investigate the effects of atomoxetine, a selective noradrenaline reuptake inhibitor, on impulsivity and attention in Parkinson’s disease.

Background: Noradrenergic dysfunction may play a significant role in cognition in Parkinson’s disease (PD), due to the degeneration of the locus coerules, the main source of cortical noradrenaline (NA), which is known to predate nigrostriatal degeneration. The effects of enhancing noradrenergic neurotransmission on parkinsonian cognition have not to date been addressed.

Methods: Atomoxetine (40 mg) was administered in a double blind, randomised, placebo controlled design to directly investigate the impact of noradrenergic augmentation on parkinsonian cognition. The neuropsychological test battery assessed impulsivity in the context of response inhibition (Stop Signal Task; SST), decision making in the context of reward and risk (Cambridge Gambling Task; CGT) and reflection during information sampling (Information Sampling Task; IST). We also assessed sustained attention (Rapid Visual Information Processing; RVIP). Tests of planning (One Touch Stockings of Cambridge; OTS) and working memory (forward and backward digit span) were also administered.

Results: In patients with PD, atomoxetine improved motor inhibitory success [SST: \( P = 0.047 \)], and reduced risk taking [CGT: \( P = 0.01 \)]. Atomoxetine conferred an improvement on reflection impulsivity [CGT: \( P = 0.02 \)], and this effect was also seen as a function of the drug’s measured blood plasma concentration [IST: \( P = 0.03 \)]. A similar plasma level effect was observed on problem solving [OTS: \( P = 0.01 \)]. Target sensitivity on the RVIP was also enhanced [\( P = 0.046 \)] and patients reported feeling more alert [\( P = 0.03 \)]. There were no effects on working memory.
Conclusions: These results support the hypothesis that enhancing noradrenergic function may represent a new avenue of adjunctive therapy for some of the cognitive and behavioural deficits seen in Parkinson’s disease.

LBA 29
A Panel of 9 Cerebrospinal Fluid Biomarkers May Aid in the Differential Diagnosis of Parkinsonian Disorders: A Prospective Cohort Study

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\(^4\)Clinical Neurochemistry Laboratory, Institute of Neuroscience and Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden
\(^5\)Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London

Objective: To assess the discriminatory power of 9 cerebrospinal fluid (CSF) biomarkers in the diagnosis of Parkinsonian disorders.

Background: Progressive supranuclear palsy (PSP), corticobasal syndrome (CBS) and multiple system atrophy (MSA) are also known as atypical parkinsonian syndromes (APS). APS are frequently misdiagnosed due to their overlapping clinical presentations. Early and accurate diagnosis is very important, especially with the emergence of disease modifying drugs. However, an accurate diagnostic test to distinguish these parkinsonian disorders remains elusive.

Methods: A prospective, cohort of patients were recruited from specialist movement disorders and cognitive clinics at the National Hospital of Neurology and Neurosurgery, Queen Square, London. Patients were clinically diagnosed according to current consensus criteria and monitored periodically for at least two years to improve diagnostic accuracy. CSF samples were obtained from 150 patients with clinical diagnoses of Parkinson’s disease (PD) (n=31), PSP (n=33), CBS (n=14), MSA (n=30), Alzheimer’s disease (AD) (n=26) and frontotemporal lobar degeneration (FTLD) (n=16). Healthy, age-matched controls (n=30) were also studied. 10 diseased participants had pathological confirmation of their diagnosis and 3 were genetically defined. Total tau (t-tau), phosphorylated tau (p-tau), β-amyloid 1-42 (Aβ42), neurofilament light chain (NFL), α-Synuclein (α-Syn), amyloid precursor protein soluble metabolites α and β (APPα, APPβ) and two neuroinflammatory markers (MCP1 and YKL40) were measured in the CSF of patients and controls using commercial enzyme linked immunoassays according to manufacturers’ protocols. Multivariable logistic regression analysis was used to study the diagnostic accuracy using all 9 biomarkers simultaneously. We acquired area under the curve (AUC) using receiver operating characteristic analysis.

Results: Together, these 9 biomarkers could differentiate patients with PD from APS (PSP, CBS, MSA) with an AUC of 0.93 (95% CI, 0.87-0.99). NFL and APPα/β contributed the most to the diagnostic accuracy with an AUC of 0.85 and 0.74 respectively. The same panel of biomarkers could discriminate between PD and PSP (AUC 0.95), PD and CBS (AUC 0.99) and PD and MSA (0.96). PSP could be differentiated from MSA with an AUC of 0.81. There was very good discriminatory power between all parkinsonian groups (PD, PSP, CBS, MSA) and healthy and dementia (AD/FTLD) controls with an AUC of 0.89 and 0.97 respectively. In particular, CBS could be differentiated from AD and FTLD with an AUC of 0.93.

Conclusion: This panel of 9 CSF biomarkers shows considerable promise in differentiating PD from between APS, and subtypes of APS from one another. Levels of NFL and APPα/β contribute most to the diagnostic accuracy. There is good discriminatory power between parkinsonian groups and healthy and dementia controls.
Figure 1: Diagnostic accuracy of CSF biomarkers in Parkinson’s disease vs Atypical Parkinsonian Syndromes (multivariable logistic regression analysis performed; receiver operating characteristic curve using all analytes)

Figure 2: Diagnostic accuracy of CSF biomarkers in Parkinson’s disease vs Atypical Parkinsonian Syndromes (receiver operating characteristic curves for each analyte)
Getting ‘personal’ with rasagiline therapy in early Parkinson’s disease: A retrospective pharmacogenetic study of the ADAGIO trial

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3 Neurogenetics Section, Centre for Addiction and Mental Health, Toronto, Canada
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Objective: To identify candidate gene polymorphisms associated with peak motor benefit to rasagiline at 12 weeks and associated with sustained benefit over a 36-week evaluation period.

Background: Rasagiline, a selective irreversible monoamine oxidase-B (MAO-B) inhibitor, has been shown to be safe and effective for the treatment of Parkinson’s disease (PD). As with all drugs, there is variability among individuals in their clinical benefit to rasagiline. The study of pharmacogenetics, the role of heredity in person-to-person differences in drug effects, may help to elucidate the genetic mechanisms underlying this inter-individual variability.

Methods: We performed a retrospective genetic association study using clinical data from the ADAGIO trial. Candidate genes encoding proteins involved in catecholamine synthesis and metabolism, rasagiline metabolism, as well as those reported in genome wide association studies (GWAS) of PD susceptibility were selected. Tag and functional single nucleotide polymorphisms (SNPs), as well as variable number tandem repeats (VNTR) were genotyped. The first analysis examined the association between genetic polymorphisms and peak change in UPDRS score from baseline to 12 weeks, using a linear model. The second analysis examined the association between genetic polymorphisms and change in UPDRS score from baseline over 12, 24, and 36 weeks, using a mixed effects linear model. Both models controlled for placebo response.

Results: 204 SNPs and 5 VNTRs from 28 candidate genes were successfully genotyped. After quality control procedures, clinical and genotype data from 694 consenting patients were included in the analyses (59% of trial participants). A priori power was estimated at >80% for each analysis. Analysis 1: Two SNPs in strong linkage disequilibrium within the dopamine D2 receptor gene (DRD2) were found to be significantly associated with peak change in UPDRS scores at 12 weeks (rs1076560 and rs2283265, False Discovery Rate [FDR]-corrected p=0.045 for each). A third SNP within the gene for the Norepinephrine Transporter (SLC6A2) was also found to be associated with this endpoint (rs36023, FDR-corrected p=0.045). Analysis 2: No allelic associations were identified in the model assessing longitudinal change in UPDRS score from baseline over 12, 24, and 36 weeks, using a mixed effects linear model. Both models controlled for placebo response.

Conclusions: To our knowledge, this is the largest pharmacogenetic study of an anti-Parkinsonian drug conducted to date. The association between these DRD2 and SLC6A2 SNPs and clinical response to rasagiline may indicate improved benefit during the first 12 weeks of treatment for individuals possessing the associated alleles. This is the time at which the mean peak improvement in UPDRS scores was observed, based on ADAGIO results. The D2 receptor is a major target of dopamine and its stimulation relates to motor benefits in PD. Prior literature indicates that the two associated SNPs alter transcriptional processing of DRD2. Together with the dopamine transporter, the norepinephrine transporter is involved in the pre-synaptic reuptake of catecholamines, including dopamine. While the results are interesting they should be interpreted with caution given the significance level and the lack of a replication sample; further investigation is clearly warranted.
**LBA 31**

**Development of L-745,870, a selective D4 receptor antagonist, for the treatment of L-DOPA-induced dyskinesia**

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**Objectives:** To assess the ability of L-745,870, a D4 receptor antagonist to reduce established L-DOPA-induced dyskinesia in the MPTP-lesioned macaque model of Parkinson’s disease.

**Background:** Treatment of L-DOPA-induced dyskinesia (LID), the principal motor complication associated with chronic dopamine replacement therapy in Parkinson’s disease (PD), remains a major unmet clinical need. We have previously suggested that L-745,870 has potential as an anti-dyskinetic therapy (Huot et al. 2012, JPET, 342(2):576-85). L-745,870 was originally developed as a potential therapy for psychosis in schizophrenia. However, clinical trials were unable to demonstrate anti-psychotic efficacy. This notwithstanding, that L-745,870 received an IND to enter clinical studies and was well-tolerated in healthy volunteers as well as schizophrenia patients, suggests that it has good drug-like characteristics and might be revitalised as a development candidate with, compared to a novel chemical entity, a relatively low chance of failure for safety or toxicology reasons. This study was conducted to confirm and extend our previous findings.

**Methods:** Seven cynomolgus macaques (*Macaca fascicularis*) were administered MPTP until the emergence and stabilisation of moderate-marked parkinsonism. Animals were then treated daily with L-DOPA (25 mg/kg as Madopar™) over a period of at least 3 months to elicit established, reproducible dyskinesia. In an acute challenge design, animals were administered L-DOPA (median ± range; 30 ± 5 mg/kg, p.o.) in combination with either vehicle or L-745,870 (0.01-0.1 mg/kg, p.o.). Immediately following treatments, animals were transferred to individual environment-enriched observation cages and monitored via HD-video recording for a period of 6 h. Levels of parkinsonian disability (comprising measures of range of movement, bradykinesia, posture and alertness) and dyskinesia were determined by post-hoc analysis of footage by a movement disorder neurologist blinded to treatment.

**Results:** L-745,870 dose-dependently decreased levels of established LID in the MPTP-lesioned macaque. The effect was evident following all three doses assessed (0.01, 0.03 and 0.1 mg/kg) but was maximal in response to the 0.1 mg/kg dose whereby a 75% reduction in median levels of dyskinesia was observed during the period of peak expression, 2-3 hour following treatment (P<0.05). At no time, did treatment with L-745,870 compromise the anti-parkinsonian benefit of L-DOPA.

**Conclusions:** L-745,870 represents a promising therapeutic candidate for the treatment of LID in PD.

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**LBA 32**

**Gait disorders and freezing in patients with ephedrine parkinsonism**

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Jan Rusů
Michael Okujava
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**Background:** Gait disorders were described among main symptoms in patients suffering from ephedrone-induced parkinsonism (EP). Most often, dystonic cock-gait was observed with a particular difficulty when walking backwards. Freezing and start hesitation were rarely mentioned. An objective assessment of gait in EP has not been reported so far.

**Objective:** The aim of this study was to objectively assess gait in EP patients, compared with healthy subjects, relate gait with other clinical parameters and finally compare patients with and without freezing of gait (FOG).

**Methods:** We studied 28 Caucasian men from Georgia, mean age 39.9 ± SD 4.9 (range 28-48) years, with a history of former ephedrone use and 28 healthy controls, mean age 39.0 ± 4.6 (28-48) years. The pull-test, Timed gait speed at 6 m, walking backwards, turning, the Short Falls Efficacy Scale-International (FES-I), the Freezing of Gait Questionnaire (FOGQ), Mini Mental State Examination (MMSE), Frontal Assessment Battery (FAB), and Neuroprotection and Natural History in Parkinson’s Plus Syndromes (NNIPPS) scale were performed in all patients.

**Results:** Gait impairment appeared as an initial symptom in twelve (43%) patients and was present in 27/28 at the time of study, showing hypokinetic and dystonic features with high postural instability and tendency to fall. Most of patients were unable to walk backwards without assistance. 15 patients (54%) demonstrated FOG. Correlation were found between gait speed and axial bradykinesia \((r=0.59, p=0.001)\) and FES-I score \((r=0.64, p=0.003)\).

No differences between patients with and without FOG were found in gait speed, in NNIPPS subscores of bradykinesia, dystonia, and in the scores of FES, MMSE and FAB.

**Conclusion:** Assessment of gait in EP showed combination of slow hypokinetic gait with severe postural instability and dystonia. FOG was present in more than 50% of patients, with no relationship with other symptoms.


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**LBA 33**

**VANTAGE trial:** Twelve month (12 mo.) follow up of a prospective, multi-center trial evaluating Deep Brain Stimulation with a new multiple-source, constant-current rechargeable system (Vercise™) in Parkinson’s disease

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**Objective:** The VANTAGE study assessed motor improvement in moderate-to-severe Parkinson’s disease (PD) up to 12 months following bilateral subthalamic nucleus deep brain stimulation (DBS) using an implantable, rechargeable, multiple-source, 8-contact, constant-current DBS System, Boston Scientific’s Vercise System.

**Background:** Several randomized controlled trials (Deuschl 2006, Weaver 2009, Okun 2012) have demonstrated that DBS is an effective treatment for patients with Parkinson’s disease. Motor improvement following DBS is sustained up to 10 years (Castrioto 2011). We sought to characterize the benefit of STN-DBS for PD patients using a recently-approved multiple-source, constant-current system that permits a well-defined distribution of applied current. We report here the 12-month results of the first clinical trial for multiple independent current control (MICC) DBS in the treatment of Parkinson’s disease.
**Methods:** VANTAGE is a monitored, prospective, multi-center, non-randomized, open-label interventional trial, sponsored by Boston Scientific Corporation. 40 subjects with idiopathic Parkinson’s disease (PD) were implanted bilaterally in the subthalamic nucleus (STN). Subjects were followed at 3, 6 and 12 months post lead placement. Motor improvement was evaluated using UPDRS III scores in stim ON/meds OFF as compared with pre-operative scores. Other assessments such as CAPSIT motor tests, Tremor Rating Scale, Dyskinesia Rating Scale, PDQ-39, SF-36, Schwab and England, and resource utilization were administered. Patient motor diaries were collected over 3 days. Adverse events were recorded.

**Results:** A highly significant improvement of 62% in UPDRS III scores at 12 months post implant in stim on/meds off condition was reported. Medication usage, as calculated using levodopa equivalents, was reduced by 53% at 6 months and 58% at 12 months compared to pre-operative usage. Highly significant improvement was also demonstrated in overall quality of life as reported using PDQ-39, Schwab and England and motor diaries.

**Conclusion:** Highly significant motor improvement, as evaluated using UPDRS III, was demonstrated at 6 months that was further sustained up to 12 months post lead placement in 40 subjects implanted with Vercise system. Subjects overall quality of life also improved significantly. The VANTAGE trial is the first reported trial of a multiple-source, constant-current rechargeable system (Boston Scientific’s Vercise System) in PD up to 12 months.

**LBA 34 Evolution of sleep disturbances in early Parkinson’s disease: a longitudinal study**

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**Objective:** To assess whether sleep characteristics in an early Parkinson’s disease (PD) cohort change over a two-year period.

**Background:** Sleep disturbances are recognised as a common non-motor complaint in PD. We recently reported that sleep complaints were present in almost half of newly-diagnosed PD patients and that these patients had abnormal sleep architecture compared to controls (increased sleep latency, reduced sleep efficiency and reduced REM sleep).¹ This relates to alterations in circulating melatonin profile and may be linked to differences in clock gene expression. No studies have longitudinally studied sleep characteristics in a cohort of PD patients over time.

**Methods:** We invited all patients to take part in a follow-up sleep study, two years after their baseline assessment. Patients repeated a variety of assessments including sleep questionnaires, 14-day actigraphy and polysomnography. Sleep recordings were scored visually by trained raters using the American Academy of Sleep Medicine guidelines. Primary sleep diagnoses were made according to recognised criteria. Statistical differences between baseline and follow-up assessments were analysed using SPSS version 16.

**Results:** 22 of the original 30 PD patients agreed to participate. Patients exhibited a similar proportion of primary sleep disorders at follow-up compared to baseline assessment - five patients (23%) had REM sleep behavior disorder, seven patients (32%) had periodic limb movements of sleep and five patients (23%) had excessive daytime sleepiness. Two patients (9%) had central sleep apnoea. No patients had moderate or severe obstructive sleep apnoea (although two had been started on nocturnal BiPAP following their baseline assessment). We observed no significant differences in sleep architecture between baseline and follow-up assessments when we studied sleep efficiency, total sleep time, slow wave sleep and REM sleep. We will present the effect of sleep characteristics on quality of life, mood and cognitive.
Conclusion: PD patients exhibit persistent sleep disturbances in early disease which may reflect fundamental pathology in the circadian system.

References
MDS study group validation of MDS criteria for mild cognitive impairment in Parkinson's disease

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Objective: Dementia in Parkinson's disease (PD) is a serious health issue and a major concern for many patients and caregivers. In most cases mild cognitive impairment (MCI) is considered a transitional stage between normal cognitive functioning and dementia. Mild cognitive impairment in Parkinson's disease (PD-MCI) is of potential importance in the early identification and management of those at risk for the development of dementia. A clear definition of PD-MCI is essential for future research on etiology, disease course, and disease modifying or causative treatment. In 2012 a task force of The Movement Disorder Society (MDS) proposed diagnostic criteria for PD-MCI (Litvan et al., 2012). These criteria comprise two operationalizations: Level I (based on an abbreviated assessment) and Level II (based on comprehensive neuropsychological evaluation permitting MCI subtyping). The next step is to investigate the feasibility and validity of these criteria (Geurtsen et al., 2014). This will be done by the MDS Validation of PD-MCI Study Group.

Background: The combined databases from the 24 Study Group sites contain more than 5,500 PD patients, of whom 89% are participating in longitudinal studies. Level I criteria will be applied to all patients. Level II criteria will be applied to approximately 1,600 patients. Just over 1,200 (75%) of those Level II patients are followed longitudinally with measurements at one and two years, just over 300 are followed for 5 years, and just over 120 for 8 years. To assess validity, we will determine whether PD-MCI predicts further cognitive decline, dementia in particular. Moreover, since in the proposed criteria the details for determining PD-MCI are not completely specified, we will study which method best predicts conversion to dementia.

Results: Since the MDS Validation of Mild Cognitive Impairment in Parkinson Disease Study Group started by the end 2013, the work plan and some preliminary results will be presented.

References
Objective: We examined in a multicentric setting, which plani- or volumetric measures on 3D MRI are best to identify progressive supranuclear palsy (PSP) in a case mix of healthy controls and patients with Parkinson's disease (PD) and multiple system atrophy of the cerebellar and parkinsonian type (MSA-C and MSA-P).

Background: The identification and differential diagnosis of atypical parkinson syndromes on purely clinical grounds is of limited precision, particularly in the early disease stages, but important to predict individual prognoses. As supportive examination, MRI is of particular importance in clinical routine, but insufficiently validated. Several quantitative parameters have been proposed for this purpose, but it is not clear which of these is most useful for diagnosis of PSP and its differentiation from PD, MSA-C and MSA-P.

Methods: Patients with PSP (n=63), MSA-P (n=29), MSA-C (n=12), PD (n=110) and healthy controls (n=47) from 3 German academic centers were measured with 3D MP-RAGE sequences on 3T MRI scanners. Plani- and volumetric parameters described in literature were quantified manually. A standardized neurological exam was used for the clinical assessment.

Results: The analysis of the scans demonstrated that the mid-sagittal midbrain area in PSP was reduced (P<0.0001) in contrast to all other groups. The midbrain AP diameter was also highly reduced in PSP vs. healthy controls, PD and MSA-P (P<0.0001 each), but less vs. MSA-C (P<0.05). The pons area was only reduced in MSA-C (P<0.01), but not in MSA-P compared to PSP patients; however, pons area was significantly reduced in MSA-C, MSA-P and PSP compared to both PD patients and healthy controls (P<0.0001). The pons/midbrain area ratio was higher in PSP (P<0.0001) compared to all other groups; and in MSA-C and MSA-P lower also than in PD and PSP (P<0.001). However, the width of SCP and MCP and their ratio provided less distinction between the groups.

Conclusions: The most reliable single measure to identify PSP patients against healthy controls in our cohort was the midsagittal midbrain area. The pons/midbrain area ratio differentiated PSP patients best from MSA and PD. This information might be helpful to optimize differential diagnosis of PSP in clinical routine. To increase reliability, data from further centers are presently analyzed.

SG 3
Co-pathology and clinical correlation in progressive supranuclear palsy

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Objective: This study assessed whether the co-occurrence of other neurodegenerative diseases influences the clinical presentation or the pathological features of 100 clinically well-characterized and neuropathologically confirmed PSP cases.

Background: Progressive supranuclear palsy (PSP) is a neurodegenerative disease with neuronal and glial cytoplasmic inclusions of tau-proteins and is clinically characterized by vertical gaze palsy, unexplained falls and levodopa non-responsive Parkinsonism. Its heterogeneous clinical picture and its overlap with other neurodegenerative diseases like Parkinson's disease, corticobasal degeneration and frontotemporal dementia makes the correct diagnosis during lifetime difficult. Moreover, the co-occurrence of Alzheimer disease (AD) associated pathology; Lewy body (LB)
pathology and agyrophilic grain disease (AGD) possibly changes the clinical picture of PSP and complicates the clinical diagnosis.

**Methods:** 100 autopsy-confirmed PSP cases were systematically screened for co-pathology. Clinical data, histology and deposits of tau-protein were correlated with these findings.

**Results:** AD associated alterations are the most frequently co-occurring pathology in PSP followed by AGD and less frequently LB pathology. A large proportion of PSP cases displayed even features of more than one neurodegenerative disease, mostly AD associated lesions in combination with AGD. Preliminary results indicate that the duration of disease is longer in PSP cases with additional features of other neurodegenerative diseases than in PSP cases without co-pathology. Cases without co-pathology are more likely to have intracellular deposits of tau-protein in the diencephalon, mesencephalon and pons.

**Conclusions:** The co-occurrence of AD associated pathology, AGD and LB pathology is frequent in PSP and has an impact on the clinical presentation. This renders the clinical diagnosis even more complicated. This study underlines the need to develop biomarkers that can predict the underlying neuropathology in vivo and the need to develop effective treatment options for patients with features of multiple neurodegenerative diseases.

**SG 4**

**Clinical predictors of survival in patients with progressive supranuclear palsy**

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**Objective:** To identify early clinical predictors of disease duration in patients with Progressive Supranuclear Palsy (PSP).

**Background:** The published median disease duration of PSP ranges between 5 years (De Bruin et al, 1994) and 8.6 years (Birdi et al., 2004); however, these and other studies on neuropathologically confirmed PSP cases reported a high variability of disease duration with individuals who survived considerably longer than 10 years. An accurate prognosis is relevant for patients and caregivers. Recognition of prognostic factors may also become important for stratification of patients in interventional trials.

**Methods:** In a cohort of 100 autopsy-confirmed patients with PSP, demographic and clinical data were collected by chart review. For recognition of factors possibly affecting disease duration, we performed a multivariate linear regression analysis with disease duration as quantitative dependent variable, and presence or absence of 33 clinical features during the first 3 years of disease, age at disease onset and gender as independent variables. In addition, logistic regression analyses were conducted with the same independent variables and with disease duration dichotomized at ≤5 and >5 years as well as ≥10 years and <10 years.
Results: In our cohort, the mean disease duration was 8.7±0.4 [2–28] years. In 33 cases, disease duration was ≥10 years and in 16 cases ≤5 years. Multivariate linear regression showed a significant association of age at disease onset, supranuclear gaze palsy, cognitive dysfunction, cortical sensory loss, tremor, and freezing of speech with disease duration. Independent predictors of shorter survival during the first 3 years of disease were older age at onset, presence of supranuclear gaze palsy, cognitive dysfunction and freezing of speech. Independent predictors of longer survival during the first 3 years of disease were the presence of tremor and cortical sensory loss. The absence of supranuclear gaze palsy and/or cognitive dysfunction during the first 3 years of disease had a significant effect on the probability of a disease duration ≥10 years. The presence of supranuclear gaze palsy and/or frontal lobe dysfunction during the first 3 years of disease had a significant effect on the probability of disease duration ≤5 years.

Conclusions: The age at onset and the identification of early clinical features allow clinically relevant prognostic predictions for disease duration in PSP.

Non-motor dominant profiles in Parkinson’s disease: First analysis from an international naturalistic study


Objective: In this ongoing study we have analysed data from a non-motor symptoms (NMS) naturalistic study to characterize the severity of NMS using cutoff scores (>8 = severe) on specific items of the NMS Scale (NMSS) and assigning these “cases” to specific NMS “dominant” profiles.

Background: Recent interest has focused on non-motor subtypes of Parkinson’s disease (PD) complementing motor subtypes.

Methods: Database analysis identified 6 specific subsets of NMS which independently registered scores of >8 on specific NMSS items, with other NMSS items being normal or non-severe. We named these Park-Autonomic, Park-Sleep, Park-Cognitive, Park-Pain, Park-Mood and Park-Fatigue. We sought correlation of these dominant profiles with, overlapping NMS, motor, and other variables.

Results: A total sample of 686 patients (males=425; mean age 66.8±11.0 yrs; PD duration 5.5 ±5.8 yrs) has been investigated so far, and in 367 (53.5% of total sample; males=229; mean age 67.1±11.0 yrs; mean PD duration 4.5±4.5 yrs) specific NMS profiles could not be assigned as there was NMS overlap and NMS registered <8 on NMSS. However, in 153 patients (22.3% of total sample; males=97; mean age 68.4±10.9 yrs; mean PD duration 6.9±8.0 yrs) had one of the observed NMS profiles (45.5%-Park Autonomic, 22.7% -Park Sleep, 11%-Park Cognitive, 9%-Park Pain, 6.5%-Park Mood, and 5.2%-Park Fatigue). A further subgroup had two or three dominant NMS profile. There were no differences between the groups in terms of age, duration of PD, sex, Hoehn and Yahr stage, NMSS total scores and SCOPA motor scores.

Conclusions: Based on the analysis of a large cross-sectional sample of patients, approximately one quarter of PD patients may have a specific NMS dominant profile, with autonomic and sleep symptoms together representing over two-thirds of cases.
Non-motor symptoms in drug naïve versus long-term Parkinson’s disease patients: Results from an UK multicenter study

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Objective: The aim of this ongoing study was to describe the holistic non motor profile of drug naïve PD (DNPD) patients compared to long-term PD patients (LTPD), arbitrarily defined as disease duration of 15 years or more.

Background: Recent studies have demonstrated that, contrary to common perception non-motor symptoms (NMS) occur in early and untreated stage of Parkinson’s disease (PD) and not just advanced PD.

Methods: Cross sectional UK data of a multicenter (16 sites) collaboration were obtained and specifically NMS dataset from validated scales were analysed in DNPD and LTPD patients. The PD NMS scale (NMSS) was used as the primary outcome variable.

Results: Out of a current database of 468 PD patients, 76 (65% males) were DNPD [mean age 64.2±13.9 yrs, mean age at diagnosis 62.9±13.50 yrs, median Hoen and Yahr (HY) stage 1] and 21 (57% males) were LTPD (mean age 67.0±9.5 yrs, mean age at diagnosis 47.4±8.9 yrs, median HY stage 3). For the DNPD patients, the mean NMSS score was 42.1±33.6 (range 1 – 160). Using NMS cutoff scores, 31.6% had mild, 27.6% moderate, 25.0% severe and 15.8% very severe burden of NMS [1]. The number of NMS per patient was high at 9.5±4.8 (range 1-22). The dominant NMS reported were fatigue (61.8% of patients), depression (55.3%), lightheadedness (53.9%), urinary urgency (48.7%) and nocturia (48.7%). As expected, LTPD patients had a younger age at diagnosis of PD and their mean NMSS score was significantly higher (p<0.001) at 81.1±37.5 (range 12 – 158). Using NMS cutoff scores, 4.8% had mild, 9.5% moderate, 23.8% severe and 61.9% very severe burden of NMS [1]. The number of NMS per patient was also significantly higher (p<0.001) at 13.8±4.6 (range 3-23). The most reported problems were fatigue (81.0% of patients), depression (61.9%), light-headedness (61.9%) and dribbling of saliva (61.9%).

Conclusions: Both DNPD and LTPD showed similar NMS profiles although the number of NMS reported per patient as well as the overall burden of NMS were significantly higher in LTPD even in this small sample examined. Fatigue, depression/anxiety and lightheadedness appear to complicate DNPD as well as LTPD, while perceptual abnormalities, attention/memory, gastrointestinal and sexual problems dominate LTPD suggesting a progressive natural history of these NMS.

A novel Parkinson's disease pain questionnaire (King’s PD pain quest): The patient’s perspective

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Objective: To develop an "easy to use" novel clinical Parkinson's specific pain questionnaire (complimentary to the Kings PD Pain Scale) which can be completed by patients themselves.

Background: Pain is an under-explored and poorly characterised non-motor symptom of Parkinson’s and a key determinant of quality of life (Wasner G, Deuschl G. Nat Rev Neurol. 2012;17(8):284–294.). Yet there are currently no validated Parkinson’s specific bedside tools to characterise the various types of pain in PD and to allow for focused treatment.

Methods: In a cross-sectional, open, multicentre pilot study we collected data from PD patients with otherwise unexplained pain to validate a specific PD-Pain-Scale (King’s PD Pain Scale). A patient-completed questionnaire (King’s PD Pain Quest) with simple “yes” or “no” answers to 14 questions was then developed based on the PD pain scale and applied, addressing the same items as the scale in simple English understandable by patients. (Figure 1)
Results: So far data from 127 patients (mean age 64.4±11.5 years, duration of disease 5.3±5.0 years, median H&Y 2 [range 1-4], 59.1% male) have been collected. Most frequent types of pain were reported as musculoskeletal pain (joint pain) (83.5%), pain while turning in bed at night (48.0%), dystonic pain (42.5%), radicular pain (37.0%) and RLS related pain (33.9%). The least patient-reported pain modalities were any kind of oro-facial pain (pain while chewing 7.1%, bruxism 6.3%, burning mouth syndrome 0.8%). (Figure 2)

Validation of the Kings PD Pain Quest is under way.

Conclusions: Interim results suggest the PD Pain Quest may be a useful self completed tool complimentary to the PD pain scale for assessment of patient reported pain in PD.

Objective: To validate an "easy to use" novel clinical Parkinson's specific pain scale using internationally accepted methods, with a focus on sub-classification of pain described in literature.

Background: Pain is an under-explored and poorly characterised non-motor symptom of Parkinson's and a key determinant of quality of life (Wasner G, Deuschl G. Nat Rev Neurol. 2012;17(8):284–294). Yet there are currently no validated Parkinson's specific bedside scales to characterise the various types of pain in PD.

Methods: In this cross-sectional, open, multicentre pilot study, we report data from use of a specific PD-Pain-Scale (King's PD Pain Scale). (Figure 1) Acceptability, internal consistency, reliability,
construct validity and precision in 150 PD patients with otherwise unexplained pain and 75 age and gender matched controls is being tested. Test-retest reliability, tested after two weeks (average), is reported in 50 patients, as is inter-rater reliability. Co-morbidity, motor and non-motor symptoms and quality of life are also assessed.

Results: So far 89 PD patients (mean age 64.1±11.5 years, duration of disease 6.4±5.4 years, 47.2% male) with otherwise unexplained pain and 58 controls have been studied. There were no missing data, no floor or ceiling effect, and acceptable skewness in the patient group. Internal consistency was acceptable, inter-rater-reliability and test-retest resulted highly satisfactorily. Correlations between domains were weak-moderate, with other measures of PD or mood disorder moderate-high, and high with quality of life measures. (Figure 2)
Data in 58 controls (mean age 60.5±10.8 years, 36.2% male) showed significantly lower PD Pain total score, as observed in all domains except for domain 5 (oro-facial pain).

Conclusions: These results suggest that the PD Pain Scale is a valid and potentially useful specific tool for assessment of pain in PD.

Previously Presented: Partial results have been presented at the XX World Congress on Parkinson’s disease and Related Disorders 2013.

Non motor symptoms profile in black and south Asian minority ethnic subjects compared to white Caucasians with Parkinson’s disease: A prospective multicentre comparative study between London South and India

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Objective: To assess the non-motor symptoms phenotype in black and south Asian communities with Parkinson's disease (PD).

Background: We had previously reported an atypical motor dominant levodopa resistant phenotype being significantly more prevalent in black and south Asian communities with PD in London [1]. In this ongoing study we report data utilising the PD Non Motor Symptoms (NMS) Scale (NMSS) in black and south Asian subjects with PD and a white Caucasian (WC) group from London versus a cohort from India (IndPD).
Methods: Cases assigned as black/south Asian (BSA) ethnicity with PD (OPCS, UK) from a London and Indian (Mumbai and Kolkata) database developed for a NMS naturalistic longitudinal study were analysed. Cross sectional data is presented.

Results: 33 BSA (mean age 64.8±11.1 years, mean duration of disease 5.4±3.5 years, median Hoehn and Yahr (HY) stage 3 (range 1-4)), 33 compared WC (mean age 68.1±11.2 years, mean duration of disease 7.6±6.7 years, median HY stage 3 (range 1-4)) and 60 PD patients from Mumbai (India) (mean age 67.3±9.1 years, mean duration of disease 7.2±4.6 years, median HY stage 3 (range 1-4)) were compared. NMSS total score (NMSSST) was lower (non significant) in BSA (58.9±46.8 versus 71.0±50.1, p=0.325) and IndPD (52.4±40.1 versus 71.0±50.3, p=0.054) group compared to WC in spite of similar HY stage in all 3 groups. NMSSST scores were similar between UK based south Asian and IndPD group. Pain scores however, were significantly worse in WC subjects (6.0±4.2 versus 2.2±3.2, p<0.001), as well as aspects of cardiovascular (2.6±3.7 versus 1.2±2.1, p<0.05) and sexual domains (3.8±5.9 versus 1.8±3.8, p<0.05) compared to the IndPD group. Cognitive and depression/anxiety domains showed similar impairment across all groups.

Conclusions: Preliminary results from this international ethnicity NMS study suggest that NMS profiles may be different in WC PD versus south Asian PD subjects, possibly regardless of any migration related factors. In particular, aspects of NMS such as pain and dysautonomia are overrepresented in the WC PD. Further work adding natural history, imaging and other biomarkers are currently under way.

Bilateral subthalamic stimulation improves aspects of non-motor symptoms in Parkinson’s disease

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Objective: To study the effects of bilateral subthalamic nucleus (STN) deep brain stimulation (DBS) on motor, non-motor symptoms (NMS), and Quality of Life (QoL) in patients with Parkinson’s disease (PD) using validated composite measures.

Background: STN-DBS is well established for the symptomatic treatment of motor symptoms and QoL in patients with PD 1,2. However, effects of DBS on NMS (apart from neuropsychiatric) have not been systematically studied. Available studies have methodological limitations due to a lack of objective clinician-based assessment 3 and small cohort sizes of 10 subjects 4, 5. We hypothesised that STN-DBS is associated with a reduction of a range of NMS in patients with PD.

Methods: In this multicentre, open, prospective, international study (Cologne, London, Manchester) we investigated non-motor effects of STN-DBS in real life use in patients with PD. We evaluated Non-motor Symptoms Scale (NMSS), Non-motor Symptoms Questionnaire (NMSQ), Unified PD Rating Scale (UPDRS) III and IV, and PD Quality of Life Questionnaire (PDQ-8) preoperatively and at 6 months follow-up (6MFU).
**Results:** Thus far 57 consecutive patients with advanced PD (34 male, mean age: 61.78±8.02 yrs, mean duration of disease: 10.20±3.40 yrs, median Hoehn &Yahr stage: 3) have been enrolled. NMSS, NMSQ, UPDRS-III, UPDRS-IV, and PDQ8 total scores improved significantly at 6MFU (Wilcoxon signed rank-test, respectively Student’s paired t-test when criteria for parametric tests were fulfilled; all p≤0.002). DBS had a small effect size on NMSS, medium effect sizes on NMSQ and PDQ8, and a large effect size on UPDRS-III and IV (see table).

<table>
<thead>
<tr>
<th></th>
<th>Relative change (%)</th>
<th>Effect size</th>
<th>% who improved ≥1/2 SD</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NMSS-T</td>
<td>-27.90</td>
<td>0.46</td>
<td>39.66</td>
<td>2.52</td>
</tr>
<tr>
<td>NMSQ-T</td>
<td>-25.40</td>
<td>0.58</td>
<td>50.00</td>
<td>2.00</td>
</tr>
<tr>
<td>UPDRS-III</td>
<td>-37.15</td>
<td>1.00</td>
<td>70.37</td>
<td>1.42</td>
</tr>
<tr>
<td>UPDRS-IV</td>
<td>-43.93</td>
<td>0.92</td>
<td>58.54</td>
<td>1.71</td>
</tr>
<tr>
<td>PDQ8</td>
<td>-25.82</td>
<td>0.50</td>
<td>50.00</td>
<td>2.00</td>
</tr>
</tbody>
</table>

(Table; Effect size = Cohen’s d; NNT = [1/ % of patients who improved ≥1/2 SD])

**Conclusions:** This multicentre European study provides evidence that bilateral subthalamic DBS improves NMS burden in patients with PD. Our data are in accordance to previously reported effects of DBS in improving motor symptoms and QoL in PD patients. Effects of DBS on specific NMS domains such as sleep, mood and pain are now being studied.

Profile of non-motor symptoms in patients with Parkinson’s disease of 20 years duration: Data from an international collaboration

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Objective: To determine the non-motor characteristics of patients with Parkinson’s disease (PD) duration greater than 20 years.

Background: Although it is perceived that at very long-term there is high non motor symptoms (NMS) load particularly concerning cognition, sleep dysfunction and dysautonomia, such situation is unclear.

Methods: Cross sectional data of a multicenter international (17 countries) collaboration were obtained and NMS dataset were analysed in those with PD ≥ 20 years. The PD NMS scale (NMSS) was used as the primary outcome variable.

Results: Out of a database of 1385 PD patients, 71 (52.1% male) had PD duration ≥ 20 years (mean age 68.78±8.37 yrs, mean age at diagnosis 44.6±8.90 yrs), median HY 3 (interquartile range: 2-4). The majority were on levodopa (97.10%), with 68.12% on dopamine agonists (67.16% of them with levodopa), 18.8% on a MAO-B inhibitor; 10.96% underwent surgery. The mean NMSS score was 86.50±54.33 (range 5 – 229). Using NMS cutoff scores [Ray Chaudhuri et al. PLoS ONE 2013; 8: e57221], 8.22% had mild, 10.96% moderate, 26.03% severe and 54.79% very severe burden of NMS. The number of NMS per patient was 15.45±6.05 (range 4-30). NMSS domains analysis revealed highest burden (standardized score on maximum possible score) for urinary (37.90%), gastrointestinal (28.90%), sexual (25.80%), and miscellaneous dimensions (25.9%), whereas mood/apathy (21.82%), sleep/fatigue (24.11%), and attention/memory (24.66%) showed a lower burden. The five most outstanding problems were nocturia, urinary urgency, loss of taste/smell, fatigue and dribbling saliva (mean scores: 5.20-3.90).UPDRS or SCOPA-Motor standardized scores (from 0%, normal, to 100%, maximum disturbance) were: examination, 38.91%; ADL, 50.39%; dyskinesias and complications, 42.52%. The correlation between total motor and non-motor scores was 0.64 (p<0.0001).

Conclusions: Data come from patients assessed in movement disorder units or neurological departments, a fact recognized as a selection bias given that institutionalized patients are underrepresented in the series. A high burden of NMS is not inevitable in long duration PD. Dysautonomia, mainly affecting urinary functioning, anosmia, fatigue and drooling may be the most troublesome problems at long-term. The mean burden of NMS per patient is higher at 20 years, compared to that reported in PD patients as a whole (8-12 NMS).
Prevalence, severity and correlates of impulse control disorders in Parkinson’s disease patients with dementia

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Objective: To determine the characteristics and predictors of impulse control disorders (ICDs) in a sample of patients with Parkinson's disease dementia (PD-D).

Background: In PD, ICDs are disruptive neuropsychiatric manifestations (NPS) associated with dopamine replacement therapy (DRT). ICD prevalence and correlates have been analyzed in diverse samples with different instruments, but this is the first study comparing ICDs in PD patients with and without dementia, using a recently validated instrument, the Scale for Evaluation of Neuropsychiatric Disorders in PD (SEND-PD) (J Neurol 2012;259:2299-2308).

Methods: A Spanish nationwide series of 529 consecutive PD patients and their caregivers participated in this cross-sectional study. Applied assessments included motor disorder evaluation (SCOPA-Motor), Mini-Mental State Examination, global PD severity scales (Hoehn & Yahr, CISI-PD), lexical fluency test, Pill Questionnaire, and SEND-PD. MDS criteria for diagnosis of PD-D were applied (Mov Disord 2007;22:1689–1707; Mov Disord 2007;22:2314–2324).

Results: Of the 529 participants, 85 (16.1%) met criteria for PDD. They were significantly older, had longer PD duration, and higher levodopa equivalent daily dose (LEDD) than patients without dementia (PD-ND) (815.14±467.44 vs. 638.08±413.86 mg; p=0.0004). Difference between groups for dopamine-agonists LEDD was not significant. Less patients in the PD-D group were on dopamine agonists than in PD-ND group (77.65% vs 82.88%), but the difference was not significant. As a whole, prevalence of ICDs was approximately 50% and severity approximately 66% higher in the PD-D group compared with the PD-ND group (both, p≤0.0002). Correlation between ICD total score and dopamine-agonists LEDD and total LEDD was weak (r<0.25) in both groups. In multivariable models including age, PD duration, motor examination, motor complications, SEND-PD psychotic symptoms and mood/apathy, and LEDD, only psychotic symptoms predicted ICDs in the PD-D group, whereas younger age and psychotic score predicted ICDs in the PD-ND group.

Conclusions: ICDs have not been previously reported to occur in PDD patients, but upon formal assessment in patients prescribed a broad range of PD medications, presence of dementia appears to be a risk factor for ICD development, which co-occur in PDD patients with psychosis, another DRT-linked side effect.
Neuropsychiatric symptoms in Parkinson’s disease (PD): An epidemiological study based on the scale for evaluation of neuropsychiatric disorders in PD

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1Research Unit, Alzheimer Center Reina Sofia Foundation and CIBERNED, Carlos III Institute of Health, Madrid, Spain; 2National Center for Epidemiology, Carlos III Institute of Health, Madrid, Spain; 3National School of Public Health, Carlos III Institute of Health, Madrid, Spain; 4Research Unit, Alzheimer Center Reina Sofia Foundation, and CIBERSAM, Carlos III Institute of Health, Madrid, Spain; 5Research Unit, Alzheimer Center Reina Sofia Foundation, Carlos III Institute of Health, Madrid, Spain and 6National Parkinson Foundation International Centre of Excellence, Kings College University and Kings College Hospital, London, United Kingdom.

Objective: To determine the prevalence and severity of the most relevant neuropsychiatric symptoms (NPS) present in Parkinson’s disease (PD), as well as their associated factors.

Background: NPS have a major negative impact on PD patients, increasing their disability, decreasing their quality of life, and causing their and institutionalization. The Scale for Evaluation of Neuropsychiatric Disorders in PD (SEND-PD) is a specific instrument for evaluation of the NPS (dimensions: psychotic symptoms [0-16 points], mood/apathy [0-20], and impulse control disorders [0-12]) in PD [J Neurol 2012;259:2299–2308].

Methods: A Spanish nationwide cross-sectional study of consecutive patients with diagnosis of PD and a stable caregiver. The interview was primarily addressed to the patient, but the caregiver was allowed to correct or clarify the responses provided by the patient when needed. Other applied assessments were: SCOPA-Motor, SCOPA-Psychiatric complications (SCOPA-PC), MMSE, Hoehn and Yahr staging (HY), and Clinical Impression of Severity Index for PD (CISI-PD).

Results: Data from 615 patient-caregiver pairs were included for analysis. Age of patients, 57.76% men, was (mean±SD) 70.89±10.01 years; PD duration was 8.02±5.49 years; and 16.64% presented dementia as per the clinical judgment. Median HY was 2 (IR: 2-3; range: 1-5); SCOPA-Motor score, 21.80±13.08; SCOPA-PC, 2.77±2.92; MMSE, 25.84±4.48 (range: 5-30), and CISI-PD, 8.77±5.01. SEND-PD scores were: psychotic symptoms, 1.33±2.25; mood/apathy, 4.54±3.67; and impulse control disorders, 0.58±1.32. Most prevalent NPS were in the domain mood/apathy (prevalence, 55%-65% for each item in the domain), followed by psychotic symptoms (16%-37%) and impulse control disorders (5.20%-17.20%). NPS significantly increased with age and PD duration and severity, but were not related with age at PD onset or gender. A high correlation between motor aspects and psychotic and mood disturbances was found. Only 10.57% of patients were asymptomatic for NPS when assessed by the SEND-PD.

Conclusions: The SEND-PD was useful for screening and evaluation of the NPS in PD, and using this instrument a high prevalence of a range of NPS with mild-moderate severity was observed. A thorough evaluation of these disorders is necessary for an appropriate management of patients.
Global MSA Registry (GLOMSAR): Objectives and Methodology

Florian Krismer*1, Lucy Norcliffe-Kaufmann*2, Italo Biaggioni2, Horacio Kaufmann2, Phillip A. Low4, Werner Poewe1, Shoji Tsuji5 and Gregor K. Wenning1 on behalf of the MDS MSA Study Group *contributed equally

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2. Dysautonomia Center, Department of Neurology, Langone Medical Center, New York University, New York, USA
3. Division of Clinical Pharmacology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, USA
4. Department of Neurology, Mayo Clinic, Rochester, USA
5. Department of Neurology, Graduate School of Medicine and Medical Genome Center, University of Tokyo, Tokyo

Objectives: The GLObal Multiple System Atrophy Registry (GLOMSAR) was established with the specific goal of uniting the European MSA Study Group and North American Rare Autonomic Disorders Consortium in an international collaborative effort focused on MSA. GLOMSAR will have two primary objectives: First, to create a patient registry to allow us to contact MSA patients on a worldwide scale and facilitate enrolment in supported clinical trials. Second, to collate longitudinal data at prospective periodic evaluations and define the natural history of MSA.

Methods: Research strategy. We outlined an infrastructure for the registry within the Movement Disorders Society Study Group for MSA program. With the goal of capturing clinical features and their evolution using standardized examinations, in August 2013, we defined a minimal mandatory dataset (table 1) to be collected annually.

Plan for data collection and management. Case report forms and a manual of operations detailing all procedures are currently in development. Each site will be asked to designate a staff member who will be trained in collecting the data for the registry. A framework for existing registry sites in Europe and North America will be established to allow them to contribute data to GLOMSAR. Data collected will be de-identified and managed within the Consortium’s existing secure database (RedCap platform). An oversight committee will perform quality control checks, data mining and analysis tasks, and will govern access to the data contained in the registry.

Conclusions and Outlook: GLOMSAR will unite MSA working groups from Europe and North America to create the first international registry for patients with MSA. The project should facilitate recruitment into clinical trials on a global scale. Careful follow-up of patients will allow us to define and answer remaining questions on the natural history of MSA and should facilitate multi-center research projects.

Acknowledgements: Work for this study is supported by the MSA Coalition, National Institutes for Health (U54NS065736) and the Austrian Science Fund (F04404-B19 and KLI 380)

Table 1: Minimal data set to be collected on an annual basis in the global MSA registry.

<table>
<thead>
<tr>
<th>Domain</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>Country of origin, age, gender, data of birth, examination date</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Sub-type of MSA (predominance of parkinsonian or cerebellar phenotype)</td>
</tr>
<tr>
<td></td>
<td>MSA-diagnostic criteria</td>
</tr>
<tr>
<td></td>
<td>Red flag checklist</td>
</tr>
<tr>
<td>Clinical evolution</td>
<td>Symptom onset, chronology of motor vs. autonomic features</td>
</tr>
<tr>
<td>Family history</td>
<td>Prevalence of key neurological disorders in the family cohort</td>
</tr>
<tr>
<td>Biological specimens</td>
<td>Biobank repository information with including availability of cerebrospinal fluid, serum and DNA</td>
</tr>
<tr>
<td>Treatment history</td>
<td>Current medications, responsiveness to parkinsonian therapies, side effects/complications, clinical benefits</td>
</tr>
<tr>
<td>Motor features</td>
<td>United MSA Rating Scale (UMSARS I and II)</td>
</tr>
<tr>
<td></td>
<td>Hoehn-Yahr rating scale</td>
</tr>
</tbody>
</table>
### Autonomic features
- Supine and standing blood pressure and heart measurements
- Orthostatic hypotension questionnaire
- SCOPA autonomic questionnaire

### Sleep disorder incidence
- Prevalence of insomnia, daytime sleepiness, restless leg syndrome, periodic limb movements, sleep apnea (central or obstructive)

### Cognitive features
- Mini-mental status examination
- Beck Depression inventory

### Quality of life
- SF-36 health survey
- MSA-QoL

### Availability of additional data
- Brain magnetic resonance imaging
- Sleep study
- Detailed autonomic function tests
- Anal sphincter electromyography (EMG)
- Urethral sphincter EMG

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**SG 15**

**Clinical characteristics of long-term survivors in multiple system atrophy: An analysis of the EMSA-SG registry**

*Florian Krismer, Susanne Duerr, Klaus Seppi, Christoph Scherfler, Sylvia Boesch, Karen Ostergaard, Erik Dupont, Eduardo Tolosa, A Cardozo, Thomas Klockgether, Michael Abele, Francois Tison, Farid Yekhlef, Guenther Deuschl, Christine Daniels, Cristina Sampaio, Miguel Coelho, Niall Quinn, Maria Bozi, Anette Schrag, Christopher J Mathias, Clare Fowler, Hakan Widner, Christer F Nilsson, Wolfgang Oertel, Nicole Schimke, Alberto Albanese, Francesca del Sorbo, Paolo Barone, Maria Teresa Pellecchia, Ruth Djaledetti, Carlo Colosimo, Giuseppe Meco, Antonio Gonzalez-Mandly, Jose Berciano, Tanya Gurevich, Nir Giladi, Olivier Rascol, Monique Galtzky, Thomas Gasser, Christoph Kamm, Uwe Siebert, Werner Poeue, Gregor K Wenning and On Behalf of EMSA-SG.*

**Department of Neurology, Innsbruck Medical University, Innsbruck, Austria.**

**Objective:** To characterize the clinical characteristics of long term survivors in multiple system atrophy (MSA).

**Background:** MSA is a rapidly progressive α-synucleinopathy with reduced life expectancy. On average, MSA patients succumb to death after 9 years. Recently, a clinicopathological study has shown that a subgroup of MSA patients may experience a more benign course of the disease with slow progression and prolonged survival of more than 15 years.

**Methods:** In 19 participating EMSA-SG centres across 9 European countries and Israel, all patients with a clinical diagnosis of MSA were recorded in a patient registry. Recruitment lasted from 2001 to 2005. A standardized minimal data set was completed in all patients. It comprised basic demographic data, motor features, autonomic features, neuropsychiatric symptoms and drug treatment. Patients with a disease duration that exceeds the upper boundary of the 95% confidence interval (i.e. 11.2 years) of the survival analysis of the EMSA natural history study were considered long term survivor.

**Results:** 30 of 437 patients (6.9%) recorded in the registry fulfilled our inclusion criterion (i.e. disease duration ≥ 11.2 years). In only 3 patients autonomic failure was the presenting feature. Another 3 patients had both motor and autonomic features at symptom-onset, while the remaining 24 patients first presented with motor symptoms (parkinsonism or ataxia). Latter patients developed autonomic failure with a median latency of 8.0 years (IQR 3.0 – 10.0 years). Overall, at the time of data entry 62.1% of patients had symptomatic orthostatic hypotension, 16.7% suffered from recurrent syncopes and urinary incontinence and incomplete bladder emptying were present in 72.4% and 29.6%, respectively. Parkinsonism was observed in 90% and gait ataxia in 60% of patients.

**Conclusions:** Similar to previous clinicopathological reports, long term MSA survivors in our patient registry were characterized by early motor involvement and relatively late emergence of autonomic failure.
Objectives: To highlight the frequency and importance of cognitive and behavioral features in parkinsonian (MSA-P) and cerebellar variant (MSA-C) of multiple system atrophy (MSA).

Background: Consensus diagnostic criteria for MSA consider dementia as a non-supporting feature, despite emerging evidence suggesting that cognitive impairment is an integral part of the disease.

Methods: We systematically reviewed the existing literature on cognitive dysfunction in MSA searching PubMed for reports published between 1988 and 2013. A total of 21 neuropsychological studies were identified with total 431 MSA, 226 MSA-P and 133 MSA-C patients included.

Results: Estimated mean dementia prevalence rate in MSA is 13-31%, with variably overlapping patterns of cognitive deficits compared to other parkinsonian disorders. Frontal executive dysfunction is prominent, affecting up to half of patients. Memory disturbances, observed in two-thirds of MSA patients, commonly present with impaired verbal learning, immediate and delayed recall, and less often verbal and visual recognition. Visuospatial and constructional functions may also be impaired, while language functions seem to be mostly preserved. While visuospatial impairment may be one of the major difficulties in MSA-C, MSA-P patients seem to exhibit more executive problems. MSA-P patients have more recall deficits, improving with cueing, while learning disturbances are more typical in MSA-C patients, suggesting that distinctive subcortical degeneration patterns (predominant striatonigral or olivopontocerebellar) may differently influence cognition via cortical inputs in MSA. Impaired attention and executive functions impact on all cognitive abilities and behavior. Imaging and neuropathological findings support the concept that cognitive impairment in MSA originates from striatofrontal deafferentation with additional contributions from intrinsic cortical degeneration and cerebellar pathology.

Conclusions: The MODIMSA neuropsychology group will examine the issue of cognitive impairment and dementia in MSA in greater detail, ultimately aiming to revise the current consensus criteria by including operational guidelines for MSA dementia. The latter will serve to better recognize cognitively impaired MSA patients, a prerequisite for further trials.
The Movement Disorder Society-Endorsed PSP Study Group

Günter U. Höglinger*, Kailash Bhatia, Adam L. Boxer, Carlo Colosimo, Lawrence Golbe, Keith A. Josephs, Irene Litvan, Brit Mollenhauer, Huw R. Morris, Ulrich Müller, Christer Nilsson, Wolfgang Oertel, Maria Stamelou, John C van Swieten, Jennifer Whitwell, David Williams, for the MDS PSP Study Group

*German Center for Neurodegenerative Diseases e.V. (DZNE) & Technical University Munich (TUM), Dept. for Translational Neurodegeneration, Max Lebsche Platz 30, D-81377 Munich, Germany

Objectives:
1st To provide an evidence-based revision of the diagnostic criteria for PSP.
2nd To promote cooperative clinical research into PSP.
3rd To promote clinical trials aiming to cure PSP.
4th To raise awareness and spread knowledge about PSP.

Background: PSP is an adult-onset neurodegenerative disorder with cerebral tau pathology leading to an akinetic-rigid syndrome with oculomotor dysfunction, postural instability, frontal lobe and bulbar dysfunction. The diagnostic gold standard is pathological diagnosis (Hauw et al., Neurology. 1994;44:2015-9). The clinical diagnosis remains a challenge. The National Institute of Neurological Disorders and Stroke and the Society for PSP (NINDS-SPSP) criteria have been proposed for the clinical diagnosis (Litvan et al., Neurology 1996; 46:922-930). Validation of these criteria in independent sets of patients demonstrated a high positive predictive value, albeit low sensitivity particularly during the early course of the disease (Osaki et al., Mov Disord. 2004;19;181–189; Respondek et al., Mov Disord. 2013 doi: 10.1002/mds.25327). Particularly, the NINDS-SPSP criteria do not allow the recognition of the recently described variable phenotypic PSP presentations. No curative treatment options are available at present. Clinical research into this rare disorder is limited in power due to its fragmentation.

Aims: We aim to improve the currently available diagnostic criteria, to create collaborative clinical research networks, and to initiate measures facilitating therapeutic clinical trials in PSP.

Methods: We initiated the establishment of international S3-guidelines for the clinical diagnosis of PSP based on published evidence. Particularly, we aim to create new criteria to identify PSP prior to establishment of the full clinical picture with falls and gaze palsy. Therefore, we aim to characterize the earliest clinical signs and symptoms occurring over the disease course of pathologically confirmed PSP. Finally, we are undertaking studies to facilitate clinical trials in PSP, including an improvement of early diagnosis for early recruitment and protocol development and refinement for clinical trials.

Results: Working groups have been created for ‘clinical course’, ‘neuropsychology’, ‘oculomotor dysfunction’, ‘MR imaging’, ‘nuclear medicine’, ‘genetics’, ‘biomarker’. Key questions and search terms have been used for a systematic literature research. A retrospective analysis of original clinico-pathological datasets has been done and is further expanded. Clinical research networks have been initiated in the US, UK, France and Germany. A Continuing Medical Education Course ‘50 years of Progressive Supranuclear Palsy’ to be held in October 2014 in Munich.

Conclusions: The MDS PSP Study Group has set up studies to improve early diagnosis and treatment of PSP.
### 2014 GUIDED POSTER TOUR ABSTRACTS

**GUIDED POSTER TOUR 1 - HUNTINGTON’S DISEASE**

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**GUIDED POSTER TOUR 2 - LEWY BODY DEMENTIA AND OTHER DEMENTIAS IN MOVEMENT DISORDERS**

<table>
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<th>Abstract</th>
<th>Authors</th>
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<td>604 Clinicopathological characteristics of pure type Lewy body disease with dementia (Parkinson’s disease with dementia and dementia with Lewy bodies)</td>
<td>R. Sengoku, H. Sumikura, M. Takao, H. Hatsuta, A. Nogami, A. Uchino, Y. Saito, S. Murayama</td>
<td>Tokyo, Japan</td>
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<td>605 Lower urinary tract function in dementia with Lewy bodies (DLB)</td>
<td>F. Tateno, Y. Tuyusaki, M. Kishi, O. Takahashi, M. Sugiyama</td>
<td>Sakura, Japan</td>
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<td>606 Association of APOE4 and BCHE-K genotypes with diagnosis and cognitive decline in dementia patients</td>
<td>S. Vijayaraghavan, T. Darreh-Shori, A. Rongve, G. Berge, S.B. Sando, L.R. White, D. Aarsland</td>
<td>Stockholm, Sweden</td>
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508 A diary to assess non-motor symptoms in patients with Parkinson’s disease
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500 Prevalence of non-motor symptoms amongst people with Parkinson’s disease compared to controls
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1249 Nutritional profile of dystonic patients submitted to functional surgery
J.R. Meireles, J.A. Guimarães, M.J. Rosas, R. Vaz (Porto, Portugal)

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